▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

XEVUDY (Sotrovimab) Concentrated injection solution for infusion

1 NAME OF THE MEDICINE

Sotrovimab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg of sotrovimab in 8 mL (62.5 mg/mL).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Sotrovimab is a clear, colourless or yellow to brown concentrated injection solution for intravenous infusion.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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.

4.2 DOSE AND METHOD OF ADMINISTRATION

As part of risk stratification of patients the pivotal consideration is the comorbidities, alongside age, particularly multiple comorbidities.

XEVUDY should not be used in patients hospitalised due to COVID-19.

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.

Method of Administration

XEVUDY is administered as a single intravenous (IV) infusion over 30 minutes (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

It is recommended that XEVUDY is administered within 5 days of onset of symptoms of COVID-19 (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

XEVUDY must be diluted prior to intravenous administration and must not be administered as an intravenous push or bolus injection.

XEVUDY should be administered in healthcare facilities in which patients can be monitored during and for one hour after administration of XEVUDY (see Section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Preparation for Dilution

XEVUDY should be prepared by a qualified healthcare professional using aseptic technique.

1. Remove one vial of XEVUDY from the refrigerator (2°C to 8°C). Allow the vial to equilibrate to ambient room temperature, protected from light, for approximately 15 minutes.

2. Visually inspect the vial to ensure it is free from particulate matter and that there is no visible damage to the vial.
    a. If a vial is identified to be unusable, discard and restart the preparation with a new vial.

3. Gently swirl the vial several times before use without creating air bubbles.
    a. Do not shake or vigorously agitate the vial.

Dilution Instructions for Intravenous Infusion

1. Withdraw and discard 8 mL from an infusion bag containing 50 mL or 100 mL of sodium chloride 9mg/mL (0.9%) solution for injection or 5% dextrose for injection.

2. Withdraw 8 mL from the vial of XEVUDY.

3. Inject the 8 mL of XEVUDY into the infusion bag via the septum.

4. Discard any unused portion left in the vial as the product contains no preservative. The vial is single-use only and should only be used for one patient.

5. Prior to the infusion, gently rock the infusion bag back and forth 3 to 5 times. Do not invert the infusion bag. Avoid forming air bubbles.

The diluted solution of XEVUDY is intended to be used immediately. If immediate administration is not possible, the diluted solution may be stored at room temperature (up to 25°C) for up to 6 hours or refrigerated (2°C to 8°C) for up to 24 hours from the time of dilution until the end of administration.

Administration Instructions

1. Attach an infusion set to the infusion bag using standard bore tubing. The intravenous dosing solution is recommended to be administered with a 0.2-µm in-line filter.

2. Prime the infusion set.

3. Administer as an IV infusion over 30 minutes at room temperature.

Children

The safety and efficacy of XEVUDY have not been established in children less than 12 years of age or weighing less than 40 kg (see Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

Elderly

No dose adjustment is required in patients aged 65 years or older (see Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

Renal impairment

No dose adjustment is required in patients with renal impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

Hepatic impairment

No dose adjustment is required in patients with hepatic impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or any of the excipients (see Section 6.1 LIST OF EXCIPIENTS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions

Hypersensitivity reactions, including serious reactions such as anaphylaxis, have been reported following infusion of sotrovimab. If signs and symptoms of severe hypersensitivity reactions occur, immediately discontinue administration and initiate appropriate treatment and/or supportive care.

If mild to moderate hypersensitivity reactions occur, consider slowing or stopping the infusion along with appropriate supportive care.

Antiviral resistance

Due to the observed decrease in in vitro neutralisation activity against the Omicron BA.2 spike variant, it is uncertain if the approved dose of sotrovimab 500 mg IV will be effective against this variant (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Pharmacodynamic effects).

Use in elderly

Based on population pharmacokinetic analysis, there was no difference in sotrovimab pharmacokinetics in elderly patients when compared with younger patients.

Paediatric use

The safety and efficacy of XEVUDY have not been established in children less than 12 years of age or weighing less than 40 kg (see Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal interaction studies have been conducted with sotrovimab.

Sotrovimab is not renally excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

In *in vitro* pharmacodynamic studies with remdesivir or bamlanivimab, sotrovimab showed additive virologic effect and no antagonism with either agent.

The efficacy and safety of sotrovimab in subjects who have received a COVID-19 vaccine at any time prior to its administration has not been established. The receipt of a COVID-19 vaccine within 48 hours prior to, or 4 weeks following treatment with sotrovimab has not been studied.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effects of sotrovimab on human male or female fertility. Effects on male and female fertility have not been evaluated in animal studies.

Use in pregnancy (Category B2)

There are insufficient data on the effects of sotrovimab on human pregnancy. Effects on embryo-fetal development have not been evaluated in animal studies. In a cross-reactive binding assay using a protein array enriched for human embryofetal proteins, no off-target binding was detected. Since sotrovimab is an engineered human immunoglobulin G (IgG), it has the potential for placental transfer from the mother to the developing fetus. The potential treatment benefit or risk of placental transfer of sotrovimab to the developing fetus is not known.

XEVUDY should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the foetus.

Use in lactation

There are insufficient data on the presence of sotrovimab in human milk. There are no data in lactating animals. A decision must be made whether to discontinue breast-feeding or to abstain from sotrovimab therapy considering the benefit of breast-feeding for the child and the benefit of therapy for the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There have been no studies to investigate the effect of sotrovimab on the ability to perform tasks that require judgement, motor or cognitive skills. A detrimental effect on such activities would not be anticipated from the pharmacology of sotrovimab. The clinical status of the patient and the adverse event profile of sotrovimab should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial data

The safety of the 500 mg dose of sotrovimab was evaluated in a placebo-controlled randomised study in 1049 non-hospitalised patients with COVID-19 (COMET-ICE) (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

Table 1: Summary of common adverse events reported in the COMET-ICE trial at an incidence of ≥ 1%.

MedDRA System Organ Class **Preferred Term**	**Sotrovimab 500 mg (n = 526)** **n (%)**	**Placebo (n = 523)** **n (%)**
Gastrointestinal disorders		
Nausea	5 (<1%)	9 (2%)
Diarrhoea	8 (2%)	4 (<1%)
Infections and infestations		
COVID-19 pneumonia[a]	5 (<1%)	22 (4%)
Nervous system disorders		
Headache	7 (1%)	11 (2%)
Vascular disorders		
Hypertension	6 (1%)	5 (<1%)
Respiratory, thoracic, and mediastinal disorders		
Dyspnoea	2 (<1%)	6 (1%)
Cough	0	6 (1%)

[a]As recorded by the investigator

Adverse reactions are listed below by MedDRA body system organ class (SOC) and by frequency (Table 2). Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000).

Table 2: Clinical trial adverse reactions

System Organ Class	Frequency	Adverse Reactions
Immune system disorders	Common	Hypersensitivity reactions[a] (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

[a]Includes rash, dermatitis contact, skin reaction, hypersensitivity, multiple allergies, infusion-related reaction and bronchospasm

Hypersensitivity including anaphylaxis and infusion-related reactions

In COMET-ICE, hypersensitivity reactions, of grade 1 (mild) or grade 2 (moderate), were reported (7 patients in the sotrovimab arm; 6 patients in the placebo arm). None of the reactions in either study arm led to pausing or discontinuation of the infusions.

One case of anaphylaxis was reported following infusion of sotrovimab in a study in hospitalized patients; the patient received adrenaline (epinephrine) and the event resolved.

Post-marketing data

Table 3: Post-marketing adverse reactions

System Organ Class	Frequency	Adverse Reactions
Immune system disorders	Rare	Anaphylactic reaction (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no clinical experience with overdose of sotrovimab.

There is no specific treatment for an overdose of sotrovimab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antiviral monoclonal antibodies.

ATC code: J06BD05

Mechanism of action

Sotrovimab is an engineered human IgG1 mAb that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2 with high affinity (dissociation constant Kd =31 ng/mL). The Fc domain of sotrovimab includes M428L and N434S amino acid substitutions (LS modification) that extends antibody elimination half-life, but does not impact wild-type Fc-mediated effector functions when compared with the original mAb with LS modification (S309+LS) in cell culture

Pharmacodynamic effects

Immunogenicity

Treatment-emergent anti-drug antibodies (ADAs) to sotrovimab were detected in 13% (65/513) of participants, through week 24 in the COMET-ICE study. None of the participants with confirmed treatment-emergent ADAs had neutralising antibodies against sotrovimab. The clinical relevance of such antibodies has not been fully established.

Antiviral activity

Sotrovimab neutralized SARS-CoV-2 *in vitro* (76.6 – 132.5 ng/mL), and *in vivo* (≥5 mg/kg in SARS-CoV-2 infected hamsters dosed with sotrovimab prior to virus inoculation) and effectively neutralised pseudotyped virus containing the SARS-CoV-2 spike.

Sotrovimab exhibited antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) in cell-based assays.

Sotrovimab demonstrated activity *in vivo* in a hamster model of SARS-CoV-2 infection using sotrovimab as well as VIR-7831-wild type (WT), a mAb that has identical variable regions as sotrovimab but is lacking the LS modification. Intraperitoneal administration of sotrovimab or VIR-7831-WT at ≥ 5 mg/kg prior to inoculation resulted in a significant improvement in body weight loss. Sotrovimab and VIR-7831-WT significantly decreased total viral RNA in the lungs at ≥ 0.5 and ≥5 mg/kg, respectively, and infectious virus levels based on $TCID_{50}$ measurements at ≥ 0.5 mg/kg. Protection was also observed in B.1.351-infected hamsters based on significant reductions in total and infectious virus on Day 4 post-infection in animals receiving a single intraperitoneal dose of 2, 5 or 15 mg/kg sotrovimab compared to isotype control antibody-treated animals.

Antibody Dependent Enhancement (ADE)

The risk that sotrovimab could mediate viral uptake and replication by immune cells was studied in U937 and primary human monocytic dendritic cells and peripheral blood mononuclear cells. This experiment did not demonstrate productive viral infection in immune cells exposed to SARS-CoV-2 at concentrations of sotrovimab from 1-fold down to 1000-fold the EC_{50} value.

The potential for ADE was also evaluated in a hamster model of SARS-CoV-2 using sotrovimab as well as VIR-7831-wild type (WT). No evidence of enhancement of disease

was observed at any dose evaluated, including sub-neutralizing doses down to 0.05 mg/kg. Additionally, a separate hamster study using a modified version of the parental antibody S309 that interacts with hamster FcRs was conducted. There was no evidence of ADE using the modified antibody at neutralising or sub-neutralising doses.

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to sotrovimab.

Cell Culture Studies: Pseudotyped VLP assessments in cell culture and/or in vitro resistance selection with increasing concentrations of sotrovimab were performed using Wuhan-Hu-1, Omicron BA.1 and Omicron BA.2 spike proteins. The epitope sequence polymorphisms at K356T, P337, E340, T345P, and L441N in the Wuhan-Hu-1 spike, conferred reduced susceptibility to sotrovimab. EC50 values against K356T, P337H/K/L/N/R/T and E340A/K/G/I/Q/S/V, T345P, and L441N, increased by 5.1->304 fold relative to the wild type.

Epitope substitutions P337H (>631), K356T (>631), P337S (>609), E340D (>609), and V341F (5.89) in the Omicron BA.1 spike variant, and P337H (>117), P337S (>117), P337T (>117), E340D (>117), E340G (>117), K356T (>117), and K440D (5.13) in the Omicron BA.2 spike variant conferred reduced susceptibility to sotrovimab based on the observed fold-increase in EC50 value shown in parenthesis relative to each spike viral variant.

Table 4. Sotrovimab neutralisation data for SARS-CoV-2 variants

SARS-CoV-2 Variant		Key Substitutions Tested[a]	Fold Reduction in Susceptibility[b]	
Lineage	WHO Nomenclature		Pseudotyped Virus	Authentic Virus
B.1.1.7	Alpha	N501Y	No change	No change
B.1.351	Beta	K417N+E484K+N501Y	No change	No change
P.1	Gamma	K417T+E484K+N501Y	No change	No change
B.1.617.2	Delta	L452R+T478K	No change	No change
AY.1 and AY.2	Delta [+K417N]	K417N+L452R+T478K	No change	Not tested
AY.4.2	Delta [+]	L452R+T478K	No change	Not tested
B.1.427/B.1.429	Epsilon	L452R	No change	Not tested
B.1.526	Iota	E484K	No change	Not tested
B.1.617.1	Kappa	L452R+E484Q	No change	No change
C.37	Lambda	L452Q+F490S	No change	Not tested
B.1.621	Mu	R346K+E484K+N501Y	No change	Not tested
B.1.1.529/BA.1	Omicron	G339D+S371L+S373P+ S375F+K417N+N440K+ G446S+S477N+T478K+ E484A+Q493R+G496S+ Q498R+N501Y+Y505H	No change	No change
BA.1.1	Omicron	G339D+R346K+S371L+ S373P+S375F+K417N+ N440K+G446S+S477N+ T478K+E484A+Q493R+ G496S+Q498R+N501Y+ Y505H	No change	No change
BA.2	Omicron	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ S477N+T478K+E484A+ Q493R+Q498R+N501Y+ Y505H	16[c]	15.7[c]
BA.2.12.1	Omicron	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+L452 Q+S477N+T478K+ E484A+Q493R+Q498R+ N501Y+Y505H	16.6[c]	25.1[c]
BA.2.75	Omicron	G339H+S371F+S373P+ S375F+T376A+ D405N+R408S+K417N+ N440K+G446S+N460K+S477 N+T478K+E484A+ Q498R+N501Y+Y505H	8.3[c]	Not tested

SARS-CoV-2 Variant		Key Substitutions Tested[a]	Fold Reduction in Susceptibility[b]	
Lineage	WHO Nomenclature		Pseudotyped Virus	Authentic Virus
BA.2.75.2	Omicron	G339H+R346T+S371F+ S373P+S375F+T376A+ D405N+R408S+ K417N+N440K+ G446S+N460K+S477N+ T478K+E484A+ F486S+Q498R+N501Y+ Y505H	10	Not tested
BA.3	Omicron	G339D+S371F+S373P+ S375F+D405N+K417N+ N440K+G446S+S477N+ T478K+E484A+Q493R+ Q498R+N501Y+Y505H	7.3[c]	Not tested
BA.4	Omicron	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ L452R+S477N+T478K+ E484A+F486V+Q498R+ N501Y+Y505H	21.3[c]	48.4[c]
BA4.6	Omicron	G339D+R346T+S371F +S373P+S375F+T376A +D405N+R408S +K417N+N440K+L452R+S477 N+T478K+E484A+F486V+Q4 98R+N501Y +Y505H	57.9	Not tested
BA.5	Omicron	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ L452R+S477N+T478K+ E484A+F486V+Q498R+ N501Y+Y505H	22.6[c]	21.6[c]
BF.7	Omicron	G339D+R346T+S371F+ S373P+S375F+T376A+ D405N+R408S+ K417N+N440K+L452R+S477 N+T478K+ E484A+F486V+Q498R+N501 Y+Y505H	74.2	Not tested
BQ.1	Omicron	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+ N440K+K444T+L452R+N460 K+S477N+ T478K+E484A+F486V+ Q498R+N501Y+ Y505H	28.5	Not tested

SARS-CoV-2 Variant		Key Substitutions Tested[a]	Fold Reduction in Susceptibility[b]	
Lineage	WHO Nomenclature		Pseudotyped Virus	Authentic Virus
BQ.1.1	Omicron	G339D+R346T+S371F+ S373P+S375F+T376A+ D405N+R408S+ K417N+N440K+ K444T+L452R+N460K+ S477N+T478K+ E484A+F486V+Q498R+N501 Y+Y505H	94	Not tested
XBB.1	Omicron	G339H+R346T+L368I+ S371F+S373P+S375F+ T376A+D405N+R408S+K417 N+N440K+ V445P+G446S+N460K+ S477N+T478K+E484A+ F486S+F490S+ Q498R+N501Y+Y505H	6.5	Not tested
XD	None[d]	G339D+S371L+S373P+ S375F+K417N+N440K+ G446S+S477N+T478K+ E484A+Q493R+G496S+ Q498R+ N501Y+ Y505H	Not tested	No change

[a] Substitutions in the spike receptor binding domain are listed.
[b] Based on EC_{50} fold change compared to wild-type. No change: ≤5-fold change in EC_{50} compared to wild-type.
[c] The clinical relevance of the fold reductions in susceptibility >5 is unknown.
[d] Variant has not been named by the WHO.

Clinical Studies: SARS-CoV-2 variants of concern or variants of interest (VOC/VOI) were detected in participants enrolled in COMET-ICE (Table 5).

Table 5. SARS-CoV-2 VOC/VOI detected at ≥2% prevalence in sotrovimab-treated participants

Clinical Study	VOC/VOI	Prevalence, % (n/N)[a]	Participants Meeting Primary Clinical Endpoint[b]
COMET-ICE	Alpha (B.1.1.7)	10.4% (35/338)	1
	Epsilon (B.1.427/B.1.429)	4.7% (16/338)	1
	Gamma (P.1)	2.7% (9/338)	0

[a] n = number of sotrovimab-treated participants with the designated VOC/VOI; N = total number of sotrovimab-treated participants with SARS-CoV-2 spike sequence results.
[b]The primary clinical endpoint for progression was defined as hospitalisation for >24 hours for acute management of any illness or death from any cause through Day 29.

SARS-CoV-2 viruses with baseline and treatment-emergent substitutions at amino acid positions associated with reduced susceptibility to sotrovimab in vitro were observed in COMET-ICE (Table 6). Of the 32 sotrovimab-treated participants with a substitution detected at amino acid positions 337 and/or 340 at any visit baseline or post-baseline, only 1 met the primary endpoint for progression of hospitalisation for >24 hours for acute management of any illness or death from any cause through Day 29. This participant had E340K detected post-baseline and was infected with the Epsilon variant of SARS-CoV-2.

Table 6. Baseline and treatment-emergent substitutions detected in sotrovimab-treated participants at amino acid positions associated with reduced susceptibility to sotrovimab when tested in vitro.

Clinical Study	Baseline[a]		Treatment-Emergent[b]	
	Substitutions	Frequency, % (n/N)	Substitutions	Frequency, % (n/N)
COMET-ICE	P337H, E340A	1.3% (4/307)	P337L/R, E340A/K/V	14.1% (24/170)

[a] n = number of sotrovimab-treated participants with a baseline substitution detected at spike amino acid positions 337 or 340; N = total number of sotrovimab-treated participants with baseline sequence results

[b] n = number of sotrovimab-treated participants with treatment-emergent substitutions detected at spike amino acid positions 337 or 340; N = total number of sotrovimab-treated participants with paired baseline and post-baseline sequence results

The clinical impact of these variants is not yet known.

Clinical trials

Study 214367 (COMET-ICE) was a Phase II/III randomised, double-blind, placebo-controlled study which evaluated sotrovimab as treatment for COVID-19 in non-hospitalised patients at high risk of medical complications of the disease. Patients included were aged 18 years and older with at least 1 of the following comorbidities: diabetes requiring medication, obesity (BMI>30), chronic kidney disease (eGFR< 60 mL/min), congestive heart failure (NYHA ≥ 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 were aged 55 years and older. The study included symptomatic patients with SARS-CoV-2 infection, as confirmed by local laboratory tests and/or point of care tests. The study was conducted when the wild-type Wuhan-Hu-1 virus was predominant, with the highest frequency of variants being Alpha and Epsilon (see 5.1 PHARMACODYNAMIC PROPERTIES, Pharmacodynamic effects). Patients with severe COVID-19 requiring supplemental oxygen or hospitalization and patients who have received a COVID-19 vaccine were excluded from the trial. Patients were randomised to receive a single 500 mg infusion of sotrovimab (N = 528) or placebo (N = 529) over 1 hour (Intent to Treat [ITT] population at Day 29).

A total of 46% of randomised participants were male. The median age of the overall randomised population was 53 years (range: 17 to 96). A total of 20% of participants were aged 65 years or older and 11% were over 70 years of age. The majority of participants

were of White race (87%); 8% were Black or African American and 4% were Asian. The ethnicity of the majority of participants was Hispanic or Latino (65%). Fifty-nine percent of participants received sotrovimab or placebo within 3 days of COVID-19 symptom onset and 41% within 4-5 days. The four most common pre-defined risk factors or comorbidities were obesity (63%), 55 years of age or older (47%), diabetes requiring medication (22%) and moderate to severe asthma (17%). Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

Enrolment to COMET-ICE was halted for overwhelming efficacy following a pre-specified interim analysis (IA) of the primary endpoint. The primary endpoint, progression of COVID-19 at Day 29, was reduced by 79% compared with placebo (adjusted relative risk reduction) in recipients of sotrovimab (p<0.001) in the final intention to treat (ITT) population. This reduction is consistent in magnitude to that previously reported for ITT (IA) population. Tables 7 and 8 below, provides the results of the primary endpoint and key secondary endpoints of COMET-ICE.

Table 7: Results of primary and secondary endpoints in the ITT population at Day 29 (COMET-ICE)

	Sotrovimab (500 mg IV infusion) N= 528	**Placebo N= 529**
Primary endpoint		
Progression of COVID-19 as defined by hospitalisation for >24 hours for acute management of any illness or death from any cause (Day 29)		
Proportion (n, %) [a]	6 (1%)	30 (6%)
Adjusted relative risk reduction (95% CI)	79% (50%, 91%)	
p-value	<0.001	
Secondary endpoints		
Progression of COVID-19 as defined by visit to a hospital emergency room for management of illness or hospitalisation for acute management of illness or death from any cause (Day 29)		
Proportion (n, %)	13 (2%)	39 (7%)
Adjusted relative risk reduction (95% CI)	66% (37%, 81%)	
p-value	<0.001	
Progression to develop Severe and/or Critical Respiratory COVID-19 (Day 29) [b]		
Proportion (n, %) [c]	7 (1%)	28 (5%)
Adjusted relative risk reduction (95% CI)	74% (41%, 88%)	
p-value	0.002	
All-cause mortality		
Up to Day 29		
Proportion (n, %)	0	2 (<1%)
Up to Day 90		
Proportion (n, %)	0	4 (<1%)

	Sotrovimab (500 mg IV infusion) N= 528	Placebo N= 529
[a] No participants required intensive care unit (ICU) stay in the sotrovimab arm versus 9 participants in the placebo arm. [b] Progression to develop severe and/or critical respiratory COVID-19 defined as the requirement for supplemental oxygen (low flow nasal cannulae/face mask, high flow oxygen, non-invasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation [ECMO]). [c] No participants required use of high flow oxygen, non-rebreather mask or mechanical ventilation in the sotrovimab arm versus 14 participants in the placebo arm.		

Table 8: Summary of Nasal SARS-CoV-2 Viral Load in log 10 copies/mL on Day 8 in the Virology Population (secondary endpoint)

	Sotrovimab (500 mg IV infusion)	Placebo
Baseline (log 10 copies/mL)		
n	369	385
Mean (standard deviation)	6.535 (1.6331)	6.645 (1.6632)
Day 8 (log 10 copies/mL)		
n [a]	316	323
Mean (standard error)	3.968 (0.0593)	4.219 (0.0589)
Day 8 change from baseline (log 10 copies/mL)		
Mean (standard error)	-2.610 (0.0593)	-2.358 (0.0589)
95% CI	-2.726, -2.493	-2.474, -2.243
Least Squares Mean Difference (standard error)	-0.251 (0.0835)	
95% CI	-0.415, -0.087	
p-value	0.003	

[a] Number of participants with available data at Day 8.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic profile of sotrovimab is consistent with a half-life extended IgG.

Based on population PK analyses, the PK of sotrovimab were not affected by age, sex, renal impairment, or mild or moderate hepatic impairment; body weight and BMI were significant covariates. Over the range from 40 to 160 kg, the effect of body weight on exposure was not considered clinically relevant and dose adjustment is not recommended.

Absorption

Based on noncompartmental analyses, following a 1 hour, 500 mg intravenous infusion, the geometric mean Cmax was 165 µg/mL (N = 360 CVb% 36.2), and the geometric mean Day 29 concentration was 40.3 µg/mL (N = 469, CVb% 39.7) from all participants with an available Day 29 sample.

Distribution

Following a 500 mg intravenous infusion, based on noncompartmental analysis, the mean steady-state volume of distribution of sotrovimab was 7 L.

Metabolism

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

Excretion

Following a 500 mg intravenous infusion, based on noncompartmental analysis, the mean systemic clearance (CL) was 90.3 mL/day, with a median terminal half-life of approximately 56.5 days.

Special patient populations

Children

The pharmacokinetics of sotrovimab in children under the age of 18 years have not been evaluated. However, the recommended dosing regimen in patients aged 12 years and older weighing at least 40 kg is expected to result in comparable serum exposures of sotrovimab as those observed in adults, based on an allometric scaling approach which accounted for effect of body weight changes associated with age on clearance and volume of distribution.

Elderly

Based on population pharmacokinetic analysis, there was no difference in sotrovimab pharmacokinetics in elderly patients when compared with younger patients.

Renal impairment

Sotrovimab, like other immunoglobulins, is too large to be excreted renally, thus renal impairment is not expected to have any effect on the elimination of sotrovimab. Furthermore, based on population pharmacokinetic analyses there was no difference in sotrovimab pharmacokinetics in patients with mild, moderate or severe renal impairment (eGFR <30 mL/min/1.73m2). There are limited data available in subjects with severe renal impairment.

Hepatic impairment

Sotrovimab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue; therefore, changes in hepatic function are unlikely to have any effect on the elimination of sotrovimab. Furthermore, based on population pharmacokinetic analyses there is no difference in sotrovimab pharmacokinetics in patients with mild and moderate hepatic impairment. There are limited data available in patients with severe hepatic impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies have not been conducted with sotrovimab.

Carcinogenicity

Carcinogenicity studies have not been conducted with sotrovimab.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Histidine

Histidine hydrochloride monohydrate

Sucrose

Methionine

Polysorbate 80

Water for injections

6.2 INCOMPATIBILITIES

XEVUDY concentrated injection solution for infusion must not be mixed with other medicinal products except those mentioned in section 4.2 DOSAGE AND METHOD OF ADMINISTRATION, Method of administration.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

The expiry date can be found on the vial and packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened packs

Store refrigerated at 2°C to 8°C in the original carton. Do not freeze. Protect from light.

Opened packs (in-use storage conditions)

The diluted solution of XEVUDY is intended to be used immediately. If immediate administration is not possible, the diluted solution may be stored at room temperature (up to 25°C) for up to 6 hours or refrigerated (2°C to 8°C) for up to 24 hours from the time of dilution until the end of administration (see Section 4.2 DOSAGE AND METHOD OF ADMINISTRATION, Method of Administration).

6.5 NATURE AND CONTENTS OF CONTAINER

10 mL Type I clear glass vial, with a rubber stopper and flip-off aluminium over-seal.

XEVUDY is supplied as a single-use vial. Use in one patient on one occasion only. Contains no antimicrobial preservative.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Not relevant

CAS number

2423014-07-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

GlaxoSmithKline Australia Pty Ltd

Level 4, 436 Johnston Street,

Abbotsford, Victoria, 3067

9 DATE OF FIRST APPROVAL

20 August 2021

10 DATE OF REVISION

22 March 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
5.1	Immunogenicity, and antiviral resistance data updated. Clinical trial all-cause mortality data updated
5.2	Absorption and excretion data updated
All	Editorial amendments

Version 4.0