Date: 3 November 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

XEVUDY

International non-proprietary name: sotrovimab

Pharmaceutical form: concentrate for solution for infusion

Dosage strength(s): 500 mg

Route(s) of administration: intravenous

Marketing Authorisation Holder: GlaxoSmithKline AG

Marketing Authorisation No.: 68471

Decision and Decision date: temporary authorisation in accordance with Art. 9a TPA approved on 14 January 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

ACE2	Angiotensin-converting enzyme 2
ADA	Anti-drug antibody
ADE	Antibody-dependent enhancement
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BMI	Body mass index
CE-SDS	Capillary electrophoresis sodium dodecyl sulfate
cIEF	Capillary isoelectric focusing
CI	Confidence interval
CL	Apparent total body clearance of the drug
C_{max}	Maximum observed plasma/serum concentration of drug
COVID-19	Coronavirus Disease 2019
CYP	Cytochrome P450
DDI	Drug-drug interaction
eGFR	Epidermal Growth Factor Receptor
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration (USA)
FIH	First in Human
GLP	Good Laboratory Practice
HPLC	High performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
ICU	Intensive care unit
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
IV	Intravenous
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MDRD	Modification of Diet in Renal Disease
Min	Minimum
MRHD	Maximum recommended human dose
mRNA	messenger Ribonucleic Acid
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
NYHA	New York Heart Association
PBPK	Physiology-based pharmacokinetic
PD	Pharmacodynamics
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetic

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PSP	Pediatric Study Plan (US-FDA)
qRT-PCR	Quantitative reverse-transcription polymerase chain reaction
RMP	Risk Management Plan
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SE-HPLC	Size exclusion high-performance liquid chromatography
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
USP	United States Pharmacopeia
VOC	Variant of concern
VOI	Variant of interest
Vss	Volume of distribution at steady state

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance sotrovimab of the medicinal product mentioned above.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Art. 9a TPA.

Authorisation for a COVID-19 medicinal product
Connected with the COVID-19 pandemic, the applicant requested a rolling submission procedure.

OPEN project EMA
Swissmedic has been participating in the EMA's OPEN project. Further information at: *EMA COVID-19 assessments 'OPEN' to non-EU regulators | European Medicines Agency (europa.eu).*

2.2 Indication and Dosage

2.2.1 Requested Indication

For the treatment of patients with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19 (see "Clinical Studies").

2.2.2 Approved Indication

Xevudy is indicated for the treatment of confirmed coronavirus disease 2019 (COVID-19) in adults and adolescents (from the age of 12 years and with a body weight of at least 40 kg) who do not require oxygen therapy or hospitalisation for COVID-19 and who are at risk of developing a more severe COVID-19 course (see *"Properties/Effects"*).
Xevudy should be used according to the official recommendations and taking into account local epidemiological data on circulating SARS-Cov-2 variants.

2.2.3 Requested Dosage

Summary of the applied standard dosage:

Adults and adolescents (aged 12 years and over and weighing at least 40 kg):
The recommended dose is a single 500 mg intravenous (IV) diluted infusion.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	6 May 2021
Formal control completed	11 May 2021
Rolling submission	11 May 2021 – 12 July 2021
List of Questions (LoQ)	19 August 2021
Answers to LoQ	15 September 2021
Predecision	19 November 2021
Answers to Predecision	17 December 2021
Labelling corrections	23 December 2021
Answers to Labelling corrections	6 January 2022
Final Decision	14 January 2022
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical Context

Coronavirus Disease 2019 (COVID-19) is a pandemic disease that started in Wuhan, China, in December 2019. It is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The COVID-19 clinical spectrum ranges from asymptomatic infection to severe disease. The majority of patients present non-severe (flu-like syndrome) or mild symptoms. However, up to 20% of patients develop severe (important lung involvement leading to impairment of gas exchange function) or critical disease (including respiratory failure, thrombosis, multiorgan failure) that might ultimately lead to death. Patients with risk factors (e.g. obesity, older age, chronic lung, kidney or heart disease, active cancer or immunosuppression, diabetes) are especially at higher risk of a severe course and death.

Vaccines based on various technologies (mRNA, viral vectors, protein-based) have been developed and are the major component of the prevention of severe COVID-19.

For the treatment of COVID-19, apart from the usual standard of care techniques, several drugs have been approved throughout the course of the pandemic for the management of hospitalised patients, and are used depending on the state of the disease and patient characteristics.

Monoclonal antibody-based therapies exhibit virus neutralising properties principally by targeting epitopes such as the receptor-binding domain of the SARS-CoV-2 spike protein, inhibiting virus binding to the angiotensin-converting enzyme 2 (ACE2) receptor and therefore preventing viral entry into the target cells.

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4 Quality Aspects

4.1 Drug Substance

Sotrovimab is a recombinant human monoclonal antibody (IgG1κ) that is directed against a highly conserved epitope on the spike protein receptor-binding domain of SARS-CoV-2. Sotrovimab consists of two heavy and two kappa light chains connected by interchain disulfide bonds. Both heavy chains contain one oligosaccharide chain in the conserved Fc site (Asn307).

Sotrovimab is expressed in a Chinese hamster ovary (CHO) cell line, and is manufactured using a fed-batch production process in a production bioreactor. The cell culture fluid is harvested, and the antibody is purified by several chromatographic and filtration steps, including virus inactivation and virus removal steps. The drug substance manufacturing process is performed by WuXi Biologics Co., Ltd., Wuxi, China.

The fermentation and purification process was validated on three batches, demonstrating a consistent manufacturing process that effectively reduces process-related impurities. The impurity clearance validation studies are supported by the impurity levels measured in the drug substance and/or spiking studies. The physicochemical and biological properties of the drug substance and its impurities were characterised using state-of-the-art methods.

The specifications for release include relevant tests and limits, e.g. for appearance, identity, pH, several purity/impurity tests (e.g. SE-HPLC, non-reduced CE-SDS, reduced CE-SDS, cIEF), protein concentration, and potency assays (Binding ELISA and, in future, pseudovirus neutralisation assay). Specifications are based on clinical data, batch analysis (release and stability data) and are in conformance with current compendial or regulatory guidelines.

Batch analysis data from development, clinical and process validation batches were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release. All specific analytical methods are described and are fully validated.

The drug substance is stored frozen. No changes were observed within the proposed storage conditions. A shelf-life of 12 months has been accepted.

4.2 Drug Product

The finished product Xevudy is available as 500 mg product, which is supplied as sterile liquid in a single-use vial. It is intended for intravenous infusion together with normal saline or 5% dextrose for injection. All excipients used comply with the European Pharmacopoeia.

The finished product manufacturing process consists of dilution of the drug substance, sterile filtration, aseptic filling, capping and inspection steps, and is conducted at GlaxoSmithKline Manufacturing S.p.A., Parma, Italy. Process validation studies were executed at commercial scale using three validation batches.

The release and stability specifications include relevant tests and limits, e.g. for appearance, identity, pH, osmolality, purity and impurity tests (SE-HPLC, non-reduced CE-SDS, reduced CE-SDS, cIEF), potency assays (binding ELISA and, in future, pseudovirus neutralisation assay), protein concentration, particles, sterility and bacterial endotoxins. All specific methods are validated in accordance with ICH guidelines.

Batch analysis data from development, clinical and process validation batches were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release.

The drug product is stored in 10 mL Type I clear glass vials at 2-8°C, protected from light. Each vial is closed with a chlorobutyl rubber stopper. The stoppered vial is sealed with an aluminium closure with a flip-off cap. All components are compliant with Ph. Eur. and USP. A shelf-life of 12 months has been accepted.

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4.3 Quality Conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf-life of the drug substance and drug product is supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk of adventitious agents is minimised.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for a temporary authorisation of Xevudy (sotrovimab), Swissmedic Division Nonclinical Assessment relied on the assessment of the nonclinical studies by the foreign reference authority, the Therapeutic Goods Administration of Australia (TGA).

Some pharmacology study reports that were submitted at a later stage of the procedure were evaluated by Swissmedic; there was no impact on the overall assessment.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

ADME

Biopharmaceutical Development
Sotrovimab is administered intravenously. No clinical biopharmaceutical studies were conducted. Two sotrovimab presentations were developed. The Gen 1 presentation contained 25 mg/mL sotrovimab in a delivery volume of 10 mL. This presentation was used in the COMET-ICE Study. The proposed commercial Gen 2 product contains 62.5 mg/mL sotrovimab in a delivery volume of 8 mL. The main difference between both drug products is the content of sotrovimab and sucrose. Furthermore, the Gen 2 material is produced by a different cell line than the Gen 1 material. Extensive non-clinical comparisons have been done for the Gen 1 and Gen 2 material, but at this time, no final clinical data (PK, efficacy, safety) are available for the Gen 2 material. Potential pharmacokinetic differences between Gen 1 and Gen 2 material are currently under investigation (*Clinical requirement)*.

Dose Proportionality
Only one fixed dose of 500 mg IV has been administered so far to humans.

Pharmacokinetics after multiple dosing
Only a single dose has been administered so far to humans.

Distribution
The sotrovimab central volume of distribution in a typical patient was estimated to be 4.3 L, and Vss was 11.5 L.

Metabolism
No studies regarding the metabolism of sotrovimab have been conducted considering the biological nature of the molecule.

Elimination
The sotrovimab CL in a typical patient was estimated to be 0.192 L/day, and the terminal half-life was 44 days. The long half-life of sotrovimab is due to a modification of the molecule.

Special Populations

The effect of demographic and disease-related factors on sotrovimab PK was investigated in a preliminary popPK analysis. The dataset included 476 COVID-19 patients participating in the COMET-ICE study. The overall age range of the patients was 18 to 96 years. The majority of the patients (80.5%) were between 18 to 64 years, 18.5% were ≥ 65 to 84 years of age and 1.05% were ≥ 85 years of age. The overall weight range of the patients was between 49 and 183 kg.

The majority of the patients (88.5%) had normal hepatic function. There were 9.4 % of patients with mild hepatic impairment, 8 patients with moderate and 1 patient with severe hepatic impairment. The majority of the patients (63.6%) had normal renal function. The dataset included 31.6% of patients with mild renal impairment, 4.4% of patients with moderate renal impairment and 2 patients with severe renal impairment. The baseline viral load at baseline was > log 107 in the majority of the patients (31.1%).

Only 9 of the 476 (1.9%) patients were ADA positive. This may be due to the single dose administration and/or the drug tolerance of the ADA assay, which might have allowed the ADA to be detected at the later sampling times only.

The final model was a 2-compartment model with i.v. bolus input and first order elimination. It included fixed allometric weight scaling of volume and clearance terms, as well as a factor to account for the

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about 46% higher exposure in the lead-in phase compared to the extension phase (see clinical section for further details on the design of the COMET-ICE study). The body weight-related covariates were the only ones with a statistically significant impact on sotrovimab PK. Age, renal or hepatic function or ADA directed against sotrovimab had no meaningful effect on sotrovimab PK.

Because of the excess of sotrovimab administered, the fully linear model described the data reasonably well, i.e. the sotrovimab PK was in the linear range. The simulated sotrovimab tissue concentrations exceeded the tissue-adjusted IC_{90} for 196 days post-dose and the 10-fold IC_{90} for at least 56 days post-dose.

Interactions

An effect of sotrovimab on CYPs, UGTs or transporters by its metabolism, chemical properties or mechanism of action appears unlikely. No *in vitro* or clinical interaction studies were done.

6.2 Dose Finding and Dose Recommendation

No formal dose finding, dose-response study was conducted. The pivotal study (COMET-ICE) was also an FIH study using the proposed 500 mg dose.
The 500 mg dose was selected based on the following considerations. Sotrovimab neutralised SARS-CoV-2 live virus with an average 90% effective concentration (EC_{90}) value of 186.3 ng/mL (range: 125.8 – 329.5 ng/mL). The selected dose is expected to ensure that sotrovimab concentrations in the lung are maintained well above levels anticipated to be neutralising for the first 28 days after administration. 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, 25x lung-tissue adjusted EC_{90} for 28 days in 50% of participants and at, or above, 15x 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.
Only the selected 500 mg dose was used in clinical studies.

The company proposed the same dose for adolescents over 12 years or weighing at least 40 kg. No clinical data were available to support the efficacy in this age group, and the dose recommendation was based on an allometric scaling approach.

6.3 Efficacy

A single pivotal clinical study (COMET-ICE) was submitted in support of the marketing authorisation application.
Several further studies are currently ongoing with sotrovimab.

COMET-ICE was a Phase II/III randomised, multi-centre, double-blind, placebo-controlled study to assess the safety and efficacy of sotrovimab for the early treatment of COVID-19 in non-hospitalised patients.
The study enrolled non-hospitalised participants with early, mild/moderate COVID-19 who were at risk of progression of disease in 57 centres (45 in the USA, 6 in Brazil, 3 in Spain, 2 in Canada, and 1 in Peru). The study consisted of a lead-in phase that served as the first-in-human assessment (20 participants [planned 20, actual 21 as 1 subject withdrew on D5 and was replaced] 1:1 randomisation sotrovimab vs. placebo) followed by an expansion phase (1340 patients, 1:1 randomisation sotrovimab vs. placebo).

The study population included non-hospitalised ≥ 18 year-old patients who tested positive for SARS-CoV-2, oxygen saturation ≥ 94% on room air (i.e. no supplemental oxygen required), ≤ 5 days from onset of symptoms AND at high risk of progression of COVID-19 based on presence of one or more of the following risk factors:

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- diabetes (requiring medication)
- obesity: BMI (>30-original protocol) >35 kg/m2 (Amendment 1)
- chronic kidney disease (i.e., eGFR <60 by MDRD)
- congestive heart failure (NYHA class II or more),
- chronic obstructive pulmonary disease (history of chronic bronchitis, chronic
- obstructive lung disease, or emphysema with dyspnoea on physical exertion)
- moderate to severe asthma (participant requires an inhaled steroid to control symptoms or has been prescribed a course of oral steroids in the past year)

The primary efficacy endpoint was the proportion of participants who have progression of COVID-19 through Day 29 as defined by (i) hospitalisation > 24 hours for acute management of illness OR (ii) death. Other relevant secondary efficacy endpoints at the Day 29 analysis included time to symptom alleviation using a self-reporting symptom questionnaire (FLU-PRO Plus) questionnaire, 29-day 60-day and 90-day all-cause mortality and change from baseline in viral load in nasal secretions by quantitative reverse-transcription polymerase chain reaction (qRT-PCR) at Day 8. Of note, the testing of secondary endpoints was adjusted for multiplicity by using a pre-defined hierarchy strategy.

A total of 1351 participants were screened, and 1057 (ITT set) participants 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). Participants in the sotrovimab arm received a single infusion of 500 mg sotrovimab. Of the 1049 participants, 1037 participants were followed for >29 days.

Demographics and baseline characteristics were well balanced between the treatment arms. Median age was 53 years. 20% of the studied population were ≥ 65 years old and 11% ≥ 70 years old. The main conditions considered as risk factors were obesity with a BMI >30 kg/m^2 (ca. 65% of study population), age ≥ 55 years (ca. 50%) and diabetes (ca 20%).

The Day 29 analysis for the primary endpoint has been conducted on the ITT analysis set (N=1057). 6/528 (1%) participants met progression criteria for the primary endpoint in the sotrovimab arm vs. 30/529 (6%) in the Placebo arm. The adjusted risk reduction is 79%. Of note, according to the applicant, 3 of the 6 participants in the sotrovimab arm were hospitalised for events potentially unrelated to COVID-19, whereas all participants in the Placebo arm were hospitalised due to events potentially related to COVID-19. Results for the primary endpoint were consistent with those reported in the ITT population when, as a sensitivity analysis, participants with missing primary endpoint data (n=7 for sotrovimab, n=5 for placebo) were analysed as treatment failures, with a calculated adjusted risk reduction of 62%. In subgroup analyses, as might be expected, the data generally show a higher proportion of progressions in the higher age group (participants >70 years) in both treatment arms, but the sotrovimab arm maintained an advantage. In those ≤ 70 years, the proportions of participants who have progression were <1% and 5% in the sotrovimab and placebo groups, respectively, and in those ≥ 70 years, the proportions of participants who have progression were 4% and 13% in the sotrovimab and placebo groups, respectively.

For the all-cause mortality assessment by Day 29, 2 participants in the placebo arm had died of respiratory complications (COVID-pneumonia and pneumonia), and no participants in the sotrovimab arm had died at Day 29. Because of the small number of death events, statistical significance cannot be determined. Nevertheless, the 2 death events at the Day 29 assessment occurred in the placebo group and were linked to respiratory complications (COVID-pneumonia and pneumonia). Of note, because of the data cut-off, not all participants could be evaluated for 60-day and 90-day mortality.

Clinical data linked to exploratory endpoints indicated that, compared to placebo, sotrovimab reduced the number of participants who were admitted to hospital and, amongst those who required hospitalisation, resulted in a reduction in the duration of hospitalisation, reduced the incidence of an

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ICU stay (no participants in the sotrovimab arm required an ICU stay), and no participants in the sotrovimab arm required mechanical ventilator support.

The study was performed at a time when the current variant causing the vast majority of infections in Europe (Delta) was not present. Therefore, the clinical efficacy of sotrovimab against this variant is not established. However, *in vitro* data (pseudotyped virus-like particle neutralisation assays) indicate that sotrovimab retains *in vitro* activity (i.e. < 5-fold change in IC_{50}) against the variants of concern Omicron, Delta (Indian), Beta (South African), Gamma (Brazil), Alpha (UK) and against Epsilon, Kappa and Iota.
The COMET-ICE Virology report (representing sequencing data for 38% of the total participants) states that the amino acid variants were reported at consensus level (≥15% allelic fraction). Variants at position E340 were the most frequently observed variants in the epitope. Variants at two positions, E340 and P337, resulted in significant EC_{50} shifts, indicating reduced susceptibility to sotrovimab. Sequence and phenotypic analysis for all qualifying participants in COMET-ICE is ongoing, and the final version of the Virology report will need to be submitted when available (*Clinical requirement*).
The applicant is required to further monitor the in vitro activity of sotrovimab against VOCs, VOIs and to conduct pseudovirus and authentic virus assays.

6.4 Safety

Over 900 participants have received sotrovimab as part of ongoing clinical trials investigating sotrovimab as monotherapy or in combination with bamlanivimab.
Most of the safety data come from the interim analysis (Data cut-off: 27 April 2021) of the pivotal study COMET-ICE including 523 subjects receiving (Gen1) sotrovimab. Further supportive safety data are derived from the following 3 studies: (1) COMET-PEAK study provided blinded safety data from 116 subjects who received sotrovimab (N:30 Gen1 or Gen2, N:86 Gen2 i.v. or i.m.), (2) ACTIV-3 TICO study provided unblinded safety data from 182 hospitalised subjects who received (Gen1) sotrovimab and (3) BLAZE-4 study provided data from 101 subjects who received Gen2 sotrovimab in combination with bamlanivimab.

The overall rate of AEs was similar in those treated with sotrovimab compared to placebo (sotrovimab: 114 [22%]; placebo: 123 [23%]).
SAEs and Grade 3 to 4 AEs were more common in participants treated with placebo than participants treated with sotrovimab, reflecting that most SAEs were likely related to COVID-19 disease and progression.
No deaths and no SAEs considered related to treatment by the investigator were reported in the sotrovimab arm of the study. There were 4 fatal SAEs in the placebo arm, and 2 SAEs deemed related to study drug (placebo).
Furthermore, the proportion of participants with infusion-related reactions (IRRs) was comparable in the two arms.
No events suggestive of ADE were identified during a review of renal/pulmonary/cardiac AEs.
To date, treatment-emergent anti-sotrovimab antibody responses have been low, with no detectable impact on safety and efficacy.
Changes in laboratory parameters and vital signs were consistent with underlying disease and were similar in both treatment arms.
Numerically more participants in the sotrovimab arm met laboratory criteria for hepatocellular injury ([(ALT/ALT ULN)/(ALP/ALP ULN)]) ≥5 and ALT ≥3xULN) (3/511 [<1%] in the placebo arm vs. 6 /516 [1%] in the sotrovimab arm).

The incidence of AEs was similar between both the treatment arms for each renal impairment category. Overall, AEs were more common in participants with moderate or severe renal impairment. Due to the small numbers of participants with an impaired baseline hepatic function, a meaningful comparison based on baseline hepatic function was not possible.

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As in the COMET-ICE study, Gen 1 materials were used. Since no clinical safety data were available for the to-be-marketed Gen 2 material, uncertainties remain regarding the safety profile of sotrovimab. Furthermore, PK and safety data from ongoing clinical studies using the Gen 2 material were requested as a *Clinical Requirement*.

Hypersensitivity reactions were deemed as an identified risk (adverse drug reaction). Although anaphylaxis was not reported in COMET-ICE, there was one report of a severe immediate hypersensitivity reaction in a hospitalised patient with COVID-19 in the ACTIV-3-TICO study. This case met the criteria for an anaphylactic reaction. Furthermore, one case of cytokine release syndrome related to sotrovimab was also observed in the ACTIV-3 TICO study.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Vaccines are available and widely used for the prevention of COVID-19, and some therapeutics provide a potential benefit in the later stages of the disease. The early administration of monoclonal antibodies is an attractive option to prevent a severe course of the disease, especially in patients with risk factors. Currently, various monoclonal antibodies (used alone or in combination) have been engineered to that aim and might also be modified depending on the emergence of virus variants to preserve their efficacy.

Sotrovimab is a human SARS-COV-2 neutralising monoclonal antibody. It binds to a highly conserved epitope on the receptor-binding domain (RBD) of SARS-CoV-2 spike protein, outside of the receptor-binding motif (RBM).
For single antibodies, there is a theoretical concern of promoting the emergence of treatment-resistant variants. This might be less likely with a combination product.
A single pivotal study, COMET-ICE (VIR-7831-5001 GSK-214367), was submitted in support of this marketing authorisation application.
COMET-ICE is an ongoing randomised, double-blind, multi-centre, placebo-controlled trial of sotrovimab for the early treatment of COVID-19 in non-hospitalised participants. The data submitted are based on the planned day 29 analysis with all randomised participants (N=1057).

Beneficial Effects

Sotrovimab has the typical PK profile of an IgG monoclonal antibody with an extended half-life. The sotrovimab PK was in the linear range after the administered single dose of 500 mg. Apart from weight, none of the covariates investigated (including age, gender, hepatic and renal function) had a clinically relevant impact on sotrovimab PK. The simulated sotrovimab tissue concentrations exceeded the tissue-adjusted IC_{90} for 196 days post-dose and the10-fold IC_{90} for at least 56 days post-dose.

When used in high-risk patients, sotrovimab treatment was associated with a significant reduction in hospitalisation for the main COVID-19-related morbidities, that is progression of infection in the respiratory tract leading to severe pneumonia and the need for supplemental oxygen and hospitalisation.

In the COMET-ICE study, the primary efficacy endpoint was the proportion of participants who have progression of COVID-19 through Day 29 as defined by (i) hospitalisation > 24 hours for acute management of illness OR (ii) death. In the ITT analysis (N=1057, 528 patients in the sotrovimab arm and 529 patients in the placebo arm) 1% in the sotrovimab treatment group showed progression of COVID-19 vs. 6% in the placebo group, corresponding to a 79% risk reduction. Other relevant secondary efficacy endpoints at the day 29 analysis (time to symptom alleviation using a self-reporting symptom questionnaire, change from baseline in viral load, all-cause mortality) were also in favour of the sotrovimab treatment.

Based on *in-vitro* data, sotrovimab retains activity against the Delta and Omicron variants.

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Uncertainties regarding the Beneficial Effects

The popPK dataset included only a small number of patients with moderate or severe hepatic or severe renal impairment. Potential pharmacokinetic differences between Gen 1 and Gen 2 material are currently under investigation. Therefore, the available PK data of the COMET-ICE study should be regarded as preliminary.

No formal clinical assessment was conducted to exclude the possibility that the differences between Gen 1 (used in the pivotal study) and Gen 2 (to-be-marketed) sotrovimab do not have an effect on efficacy. Data from clinical studies using the Gen 2 material (as study COMET-PEAK) will be able to provide further information.
Clinical efficacy or PK data for adolescents were not available.

Based on in vitro pseudotyped virus-like particle neutralisation assays, sotrovimab retains activity against the variants of concern: Omicron, Delta (and Delta Plus AY.1 and AY.2), Beta, Gamma, Alpha, and against Epsilon, Kappa and Iota. Based on an authentic virus assay, sotrovimab is active against Beta, Gamma and Delta variants, but no data are yet available for the Delta plus and Omicron variants.
Furthermore, no clinical data are available regarding efficacy against the Delta variant, as none of the subjects included in the study had a Delta variant infection. The rate of subjects infected with the Alpha variant was also low (4%).
Nor are there any clinical efficacy data against the Omicron variant that rapidly became the predominant variant in Switzerland by the end of December 2021. However, based on the currently available in-vitro (pseudovirus assay) data, Xevudy is expected to be active against the newly emerged Omicron variant.
The applicant will monitor the presence and emergence of VOCs/VOIs and assess the in vitro activity of sotrovimab using a pseudotyped virus system and, when possible, authentic virus. The applicant will also sequence participant samples in ongoing sotrovimab clinical trials and assess sotrovimab efficacy in a clinical setting.

Unfavourable Effects

The available PK data were obtained after administration of Gen 1 drug material only. Potential pharmacokinetic differences between Gen 1 and Gen 2 material are currently under investigation.

The safety findings from the pivotal COMET-ICE study were supplemented by safety data from studies in which sotrovimab was utilised in different populations and/or in combination with other monoclonal antibodies.
In the review of the totality of the safety data, hypersensitivity reactions were deemed as an identified risk (adverse drug reaction). Although anaphylaxis was not reported in COMET-ICE, there was one report of a severe immediate hypersensitivity reaction in a hospitalised patient with COVID-19 in the ACTIV-3-TICO study meeting the criteria for an anaphylactic reaction. Furthermore, one case of cytokine release syndrome related to sotrovimab was also observed in the ACTIV-3 TICO study.

Uncertainties regarding the Unfavourable Effects

No safety data are available for adolescents over 12 years of age.
No formal clinical assessment was conducted to exclude the possibility that the differences between Gen 1 (used in the pivotal study) and Gen 2 (to-be-marketed) sotrovimab have an effect on safety. Higher exposure at day 29 for Gen 2 was observed, although the pharmacovigilance on the emergency use and marketed use of the Gen 2 material did not identify new safety findings. The safety results from ongoing studies using the Gen 2 material needs to be submitted when available (*Clinical Requirement*).

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Benefit –Risk Assessment Clinic

The overall benefit-risk of sotrovimab for the treatment of mild/moderate COVID-19 to prevent progression to severe COVID-19, the need for oxygen therapy, hospitalisation or death in SARS-CoV-2 infected high-risk patients is positive.
The available sotrovimab PK data did not raise any concerns. However, due to the still ongoing evaluation of possible differences between Gen 1 and Gen 2 material, they should be regarded as preliminary.
Efficacy against the currently most prevalent Omicron variant is clinically not established. However, based on in-vitro pseudotyped virus-like particle neutralisation assays, sotrovimab retains activity - among others - against the previously predominant Delta variant and also against the currently predominant Omicron variant.
The clinical efficacy of sotrovimab against emerging new VOCs remains to be determined and must be actively monitored.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Xevudy was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Xevudy is authorised for a temporary period; see the *"Properties/Effects"* section.

XEVUDY

Composition

Active substances

Sotrovimab produced from genetically modified Chinese hamster ovary (CHO) cells.

Excipients

L-histidine, L-histidine monohydrochloride, saccharose, polysorbate 80, L-methionine, water for injection purposes.

Pharmaceutical form and active substance quantity per unit

Concentrate for making a solution for infusion (i.v.).

A vial with 8 mL concentrate contains 500 mg sotrovimab (62.5 mg/mL).

Clear, colourless or yellow to brown solution in a single-use vial.

Indications/Uses

Xevudy is indicated for the treatment of a confirmed 2019 coronavirus disease (COVID-19) in adults and adolescents (from the age of 12 years and with a body weight of at least 40 kg) who do not require oxygen therapy or hospitalisation for COVID-19 and who are at risk of developing a more severe COVID-19 course (see *"Properties/Effects"*).
Xevudy should be used according to the official recommendations and taking into account local epidemiological data on circulating SARS-Cov-2 variants.

Dosage/Administration

Treatment should be initiated and monitored under the supervision of a qualified physician. Treatment should be given under conditions where treatment of an infusion reaction/allergic reaction is possible (see *"Warnings and precautions"*).

Xevudy should be given as soon as possible after a positive virus test for SARS-CoV-2 (see *"Properties/Effects"*).
For confirmation of Covid-19, a nucleic acid amplification technique (NAT) test is preferred.
In order to ensure the traceability of biotechnological medicinal products, it is recommended that the trade name and batch number be documented for each treatment.

Usual dosage

Adults and adolescents (from the age of 12 years and with a body weight of at least 40 kg)

The recommended dose is a single dose of 500 mg, administered as an intravenous infusion (see *"Undesirable effects"*, *"Properties/Effects"*, *"Pharmacokinetics"*).
Special dosage instructions

Patients with hepatic disorders

The dose does not need to be adjusted for patients with hepatic disorders (see *"Pharmacokinetics – kinetics in specific patient groups"*).

Patients with renal disorders

The dose does not need to be adjusted for patients with impaired renal function (see *"Pharmacokinetics – kinetics in specific patient groups"*).

Elderly patients

The dose does not need to be adjusted for patients aged 65 years or older *(*see *"Pharmacokinetics – kinetics in specific patient groups").*

Children and adolescents

Dose adjustment is not recommended in children and adolescents aged ≥12 years and weighing ≥40 kg (see sections *"Undesirable effects"*, *"Properties/Effects"* and *"Kinetics in specific patient groups"*).
The safety and efficacy of sotrovimab have not yet been demonstrated for children under 12 years of age or weighing less than 40 kg *(*see *"Pharmacokinetics – kinetics in specific patient groups").*

Mode of administration

The instructions for diluting sotrovimab can be found under *"Instructions for handling"*.

Sotrovimab is administered as a single intravenous (i.v.) infusion over a period of 30 minutes.

Sotrovimab needs to be diluted prior to administration and may not be administered as an intravenous push or bolus injection.

Contraindications

Hypersensitivity to the active substance or one of the excipients as per composition.

Warnings and precautions

Patients should be monitored during dose administration and observed for at least 1 hour after administration of the intravenous infusion is complete.

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of sotrovimab (see *"Undesirable effects"*). If there are signs and symptoms of a clinically significant hypersensitivity reaction, administration needs to be suspended immediately and suitable supportive treatment needs to be initiated.

Mild to moderate hypersensitivity reactions were observed in a study of non-hospitalised COVID-19 patients. If mild to moderate hypersensitivity reactions occur, slowing or discontinuation of the infusion should be considered along with appropriate supportive treatment.

Infusion-related reactions

Infusion-related reactions (IRRs) have been observed with intravenous administration of sotrovimab. IRRs observed in clinical studies were mostly mild to moderate in severity and were typically observed within 24 hours post infusion. Commonly reported symptoms of these reactions included pyrexia, chills, dizziness, dyspnoea, pruritus, and rash. However, IRRs may present as severe or life-threatening events and may include other signs and symptoms. If an IRR occurs, the infusion should be interrupted, slowed or stopped.

Interactions

So far, there have been no studies of interactions with sotrovimab.

Sotrovimab does not undergo renal elimination or metabolism by cytochrome P450 (CYP) enzymes. This means the likelihood of any interactions with concomitant medications that undergo renal elimination is small, and the same applies to substrates, inductors or inhibitors of CYP enzymes.

Sotrovimab showed additive virological activity in *in vitro* pharmacodynamic studies with remdesivir or bamlanivimab and no antagonism with either agent.

A potential interference with a COVID-19 vaccine following treatment with sotrovimab was not assessed and cannot be excluded. The official guidelines for the administration of SARS-CoV-2

vaccine and advice on the risks associated with the administration of SARS-CoV-2 vaccine should be taken into account.

Pregnancy, lactation

Pregnancy

There are no data on the effects of sotrovimab on pregnancy in humans. In animal studies, the effects on embryofoetal development have not been studied so far. No off-target binding was identified in a cross-reactive binding test using a protein array enriched with human embryofoetal proteins. As sotrovimab is a genetically produced human immunoglobulin G (IgG), there is a possibility of placental transfer from the mother to the developing foetus. The potential benefit of treatment or the risk of placental transfer of sotrovimab to the developing foetus are not known.

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

Lactation

There are no adequate data regarding the transfer of sotrovimab to human milk. A risk to the infant cannot be excluded. A decision needs to be taken on whether to interrupt breastfeeding or not to provide sotrovimab therapy. It is a case of weighing the benefit of breastfeeding for the child against the benefit of therapy for the mother.

Fertility

There are no data on the effects of sotrovimab on male or female fertility. In animal studies, the effects on male and female fertility have not been studied so far.

Effects on ability to drive and use machines

No studies have been conducted on how sotrovimab might affect a person's ability to perform certain activities that require judgement and motor or cognitive abilities. No adverse effect on such activities is to be expected from the pharmacology of sotrovimab. An assessment should be made of whether a patient is capable of mastering tasks requiring judgement and motor or cognitive abilities, taking into account the patient's clinical status and the side effect profile of sotrovimab.

Undesirable effects

Data from clinical trials

The safety of sotrovimab was investigated in a placebo-controlled, randomised study of 1,049 non-hospitalised adult patients with COVID-19 (COMET-ICE) *(see “Clinical trials”)*. Safety data is

not available for adolescents 12 years of age and older.

The most common adverse reactions were hypersensitivity reactions (2%) and infusion-related reactions (1%). The most common serious adverse reaction was anaphylaxis (0.05%).

Undesirable effects are listed below according to the MedDRA system organ class (SOC) and by frequency (Table 1). Frequencies are defined as follows: *"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 1: Undesirable effects

System organ class (SOC)	Frequency	Undesirable reaction
Immune system disorders	common rare	Hypersensitivity reaction* Anaphylaxis
Injury, poisoning and procedural complications	common	Infusion-related reactions

*such as skin rash and bronchospasm. Pruritus may also occur as a manifestation of hypersensitivity reactions.

Hypersensitivity reactions

In COMET-ICE, there were reports of grade 1 (mild) or grade 2 (moderate) hypersensitivity reactions (9 patients in the sotrovimab arm; 5 patients in the placebo arm). None of the reactions in either arm caused the infusions to be interrupted or discontinued. One case of anaphylaxis requiring hospitalization was reported following sotrovimab infusion in a study in patients with COVID-19; the event occurred 21 minutes after the start of the infusion, the infusion was immediately discontinued, the patient was treated with epinephrine and recovered.

Infusion-related reactions

Infusion-related reactions occurring within 24 hours post infusion have been reported in the COMET-ICE study with similar frequency (1%) in patients treated with sotrovimab and placebo. All IRRs were mild to moderate in severity and none led to discontinuation of infusion. Reported symptoms of these reactions were pyrexia, chills, dizziness, dyspnoea, pruritus, and rash.

Changes in laboratory chemistries

Numerically more participants in the sotrovimab arm met laboratory criteria for hepatocellular injury ([(ALT/ALT ULN)/(ALP/ALP ULN)]) ≥5 and ALT ≥3xULN) 6/516 [1%] in the sotrovimab arm vs 3/511 [<1%] in the placebo arm).

Data after market launch

No relevant data exist.

Immunogenicity

Consistent with the potentially immunogenic properties of protein- or peptide-based therapeutics, patients may develop antibodies to sotrovimab following treatment. The clinical relevance of anti-sotrovimab antibodies is not known. The incidence of anti-drug antibodies (ADAs) depends significantly on the sensitivity and specificity of the test. Furthermore, the observed incidence of antibody positivity (including neutralising antibodies) in a test may be affected by several factors, e.g. the test method, the handling of samples, the time the samples were taken, concomitant medication and the underlying disease. For this reason, the comparison of the incidence of anti-sotrovimab antibodies with the incidence of other anti-drug antibodies may be misleading.

A preliminary interim analysis of available immunogenicity data in subjects receiving sotrovimab in COMET-ICE (single dose by intravenous infusion of 500 mg sotrovimab) showed an incidence of antibodies to sotrovimab of 3% (10/391 participants) by day 29 of the study.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS (Electronic Vigilance System) portal. You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

There is no clinical experience of overdose with sotrovimab.

Treatment

There is no specific treatment for overdose with sotrovimab. After an overdose, the patient should be treated with appropriate supportive measures and monitored accordingly.

Properties/Effects

ATC code

Not yet assigned.

Mechanism of action

Sotrovimab is a human IgG1 mAb that binds to a highly conserved epitope on the spike protein receptor binding domain of SARS-CoV-2 with a dissociation constant Kd = 0.21 nM. The Fc

domain of sotrovimab contains the amino acid substitutions M428L and N434S (LS modification), which extend the antibody's elimination half-life, but without inhibiting the wild-type-Fc-mediated effector functions in the cell culture.

In vitro, sotrovimab showed FcγR activation when Jurkat reporter cells, which express FcγRIIa (high-affinity H131 allele), FcγRIIIa (high-affinity V158 allele) and FcγRIIb, were used. In cell-based assays, sotrovimab showed antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP).

Pharmacodynamics

Antiviral effect

Sotrovimab neutralised the SARS-CoV-2 virus (USA WA1/2020) *in vitro* (EC_{50} 76.6-132.5 ng/mL) and *in vivo* (≥5 mg/kg in hamsters treated with sotrovimab prior to SARS-CoV-2 infection).

Antibody-dependent enhancement (ADE)

The risk that sotrovimab might mediate viral uptake and replication through immune cells was studied for U937 cells, primary human monocytic dendritic cells and mononuclear cells from peripheral blood. The experiment in question did not show any productive viral infection or any increased cytokine production in immune cells exposed to SARS-CoV-2 at sotrovimab concentrations from 1- to 1,000-fold the EC_{50} value.

The potential for ADE was also studied in a hamster model for SARS-CoV-2 using sotrovimab and the VIR-7831 wild type (WT). There was no indication at any of the doses studied – including subneutralising doses down to 0.05 mg/kg – of any increase in disease. There was also a separate hamster study involving a modified version of the parental antibody S309, which interacts with hamster Fc receptors (FcRs). There was no indication of ADE when the modified antibody was used at neutralising or subneutralising doses.

Antiviral resistance

Given the development of viral variants resistant to sotrovimab, there is a potential risk that treatment may fail. No viral breakthrough was identified after 10 serial passages with the virus (34 days) at a fixed antibody concentration, including at the lowest concentration tested (~10x EC_{50}). During forced generation of resistant variants via a selection method at increasing concentration, E340A was identified as a sotrovimab-mAb-resistant mutant (MARM). During cell culture selection of resistant viruses, an E340A substitution occurred that showed a >100-fold reduction of activity in an assay with pseudotyped virus-like particles (VLPs).

A study of pseudotyped VLPs in a cell culture showed that the epitope sequence polymorphisms at K356T, P337H/L/R/T/K and E340A/K/G/Q/V show reduced sensitivity to sotrovimab. The EC_{50} values increased by 5.1- to >304-fold compared with the wild type.

The pseudotyped VLP and authentic SARS-CoV-2 neutralisation data for sotrovimab are summarised in the following table (Table 2).

Table 2. Neutralization activity of sotrovimab against SARS-CoV-2 variants

Variant/Lineage with spike protein substitutions	Key substitutions tested	Fold change in susceptibility[a] (authentic virus)	Fold change in susceptibility[a] (pseudovirus)
Alpha (B.1.1.7)	del69-70, del144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H	3.0	2.3
Beta (B.1.351)	L18F, D80A, D215G, K417N, E484K, N501Y, D614G, A701V	1.2	0.6
Gamma (P.1)	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F	1.6	0.35
Delta (B.1.617.2)	T19R, G142D, E156G, del157-158, L452R, T478K, D614G, P681R, D950N	0.4	1.0
Delta Plus (AY.1)	T19R, T95I, G142D, E156G, del157-158, W258L, K417N, L452R, T478K, D614G, P681R, D950N	ND	1.1
Delta Plus (AY.2)	T19R, V70F, G142D, E156G, del157-158, A222V, K417N, L452R, T478K, D614G, P681R, D950N	ND	1.3
Epsilon (B.1.427/B.1.429)	S13I, W152C, L452R, D614G	ND	0.7
Iota (B.1.526)	L5F, T95I, D253G, E484K, D614G, A701V	ND	0.6
Kappa (B.1.617.1)	T95I [b], G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H	0.9	0.7
Lambda (C.37)	G75V, T76I, del246-252, L452Q, F490S, T859N	ND	1.5
Omicron (B.1.1.529)	A67V, del69-70, T95I, G142D, del143-145, del211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F	ND	2.7

ND = not determined, del = deletion, ins = insertion

[a] Fold change calculated relative to wild type authentic virus (2019-nCoV/USAWA1/2020) or wild type pseudovirus (sequence YP_009724390)

[b] Present in the pseudovirus but not in the live virus.

The COMET-ICE clinical trial showed epitope variants in 20 participants in the sotrovimab arm after baseline (A344V [6.2%]; R346G [5.2%]; K356R [7.5%]; E340A [99.0%]; E340V [73.1%]; P337L/E340K [49.4%/54.8%]; 2 patients with S359G [12.2% and 8.3%]; 5 patients with E340K [8.0%-99.9%]; 7 patients with C361T [5.0%-15.7%]). As regards the variants identified at and after baseline in both treatment groups, the phenotypes of L335F, L335S, P337L, G339C, E340A, E340K, A344V, R346I, R346G, K356N, K356R, R357I, I358V and S359G were studied using a pseudotyped VLP system. Sotrovimab activity is maintained for L335F, L335S, G339C, A344V, R346I, R346G, K356N, K356R, R357I, I358V and S359G (0.7- to 1.7-fold change in the EC_{50} value). P337L, E340A and E340K cause reduced sensitivity to sotrovimab (>180-fold, >100-fold or >297-fold change in the EC_{50} value). Data gathering and analysis are still ongoing.

Clinical efficacy

Trial 214367 (COMET-ICE) is an ongoing randomised, double-blind, placebo-controlled phase II/III trial that studied the use of sotrovimab for the treatment of COVID-19 in non-hospitalised adult patients at a high risk of complications from the disease. Patients with a laboratory-confirmed SARS-CoV-2 infection who had been exhibiting symptoms for a maximum of five days and who did not require any form of oxygen supplementation at baseline were included in the trial. The patients included in the trial were 18 years or older and showed at least one of the following comorbidities: diabetes, obesity (BMI >30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, moderate to severe asthma or age 55 years or over regardless of comorbidities. Patients who had received a COVID-19 vaccine were not included in the trial. The patients were randomised, with some being given 500 mg sotrovimab (n = 528) and others a placebo (n = 529) as a single infusion for 1 hour (intention-to-treat [ITT] population on day 29).

In total, 46% of the randomised participants were male. The median age for the overall randomised population was 53 years (range: 18 to 96). In total, 20% of participants were 65 years or older, with 11% older than 70 years. Most participants were of European origin (87%), with 8% Black or African-American and 4% Asian. The ethnicity of most participants was Hispanic or Latin American (65%). 59% of participants were given sotrovimab or a placebo within 3 days of the onset of COVID-19 symptoms, with 41% being given this within 4-5 days. The 4 most common predefined risk factors or comorbidities were obesity (63%), an age of 55 years or over (47%), diabetes requiring medication (22%) and moderate to severe asthma (17%). Overall, demographic data and disease characteristics were balanced between treatment arms.

The primary endpoint, the progression of COVID-19 on day 29, was reduced by 79% ($p < 0.001$)

for patients given sotrovimab compared with those treated with placebo (adjusted relative risk reduction). Table 3 below shows the results for the primary endpoint and the main secondary endpoints for the COMET-ICE trial.

Table 3: Results for the primary and secondary endpoints in the ITT population on day 29 (COMET-ICE trial)

	Sotrovimab (500 mg via i.v. infusion) n = 528	Placebo n = 529
Primary endpoint		
Progression of COVID-19, defined as time in hospital >24 hours for acute treatment of disease 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 in terms of development of 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	

[a] One participant in the sotrovimab arm needed to spend time on an intensive care unit (ICU), as compared with 9 participants in the placebo arm.
[b] Progression in terms of development of severe and/or critical respiratory COVID-19, defined as the need for additional oxygen (low-flow nasal cannula/face mask, high-flow oxygen, non-invasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation [ECMO]).
[c] No participant in the sotrovimab group needed high-flow oxygen, a non-rebreather mask or mechanical ventilation, as compared with 14 participants in the placebo group.

Temporary authorisation

Given that clinical data were incomplete at the time the application for authorisation was assessed, the medicinal product Xevudy is only authorised for a temporary period (Art. 9a of the Swiss Therapeutic Products Act). Temporary authorisation is strictly conditional on the timely meeting of requirements. Once these are met, temporary authorisation may be superseded by regular authorisation.

Pharmacokinetics

The pharmacokinetic profile of sotrovimab corresponds to an IgG with an extended half-life. Serum

concentrations on day 29 showed little variability (22%), irrespective of any potential intrinsic factors.
Based on a preliminary population pharmacokinetic analysis, the geometric mean for C_{max} following a 1-hour i.v. infusion for all subjects for whom a sample was available on day 29 was 117.6 µg/mL (n = 290, CV% 46.5) and the geometric mean for the concentration on day 29 was 24.5 µg/mL (n = 372, CV% 42.4)

Absorption

No studies have been conducted on absorption.

Distribution

Based on a non-compartmental analysis, the steady-state volume of distribution for sotrovimab was 8.1 L.

Metabolism

Sotrovimab is a genetically produced human IgG1 monoclonal antibody and is degraded by proteolytic enzymes that are widely distributed in the body and not restricted to hepatic tissue.

Elimination

Based on a non-compartmental analysis, the median systemic clearance (CL) was 125 mL/day, with a mean terminal half-life of around 49 days.

Kinetics in specific patient groups

Based on the population PK analyses, the pharmacokinetics of sotrovimab were not influenced by age or sex; body weight and BMI were significant covariates.

Hepatic disorders

Sotrovimab is degraded by widely distributed proteolytic enzymes that are not restricted to hepatic tissue, so changes in liver function are unlikely to affect the elimination of sotrovimab. In addition, there is no difference, based on preliminary population pharmacokinetics analyses, in the pharmacokinetics of sotrovimab in patients with mild to moderate elevations in alanine aminotransferase (1.25 to <5 x ULN). There are no data available for patients with severe elevations in alanine aminotransferase (5 to <10 x ULN). .

Renal disorders

Like other immunoglobulins, sotrovimab is too large for renal elimination. Therefore, renal impairment is not expected to affect the elimination of sotrovimab. In addition, there was no difference, based on preliminary population pharmacokinetics analyses, in the pharmacokinetics of sotrovimab in patients with mild or moderate renal disorders. There are insufficient data available for patients with severe renal impairment.

Elderly patients

Based on a preliminary population pharmacokinetics analysis, there were no differences in the pharmacokinetics of sotrovimab in elderly patients compared with younger patients.

Children and adolescents

The pharmacokinetics of sotrovimab in children under 18 years have not been studied so far. It is to be expected, however, that the recommended dosage schedule for patients aged 12 years and over and weighing at least 40 kg would lead to similar serum exposure levels for sotrovimab as identified in adults. This is based on an allometric scaling approach that takes account of the effects of age-related changes in body weight on clearance and the volume of distribution.

Preclinical data

Based on a two-week study of toxicity in monkeys, which also studied safety pharmacology parameters, the preclinical data do not indicate any particular risks for humans.

Carcinogenicity, mutagenicity

No studies of genotoxicity or carcinogenicity have been performed for sotrovimab.

Reproductive toxicity

No non-clinical studies of reproductive or development toxicity have been performed for sotrovimab.

Other information

Incompatibilities

Sotrovimab concentrate for making a solution for infusion may not be mixed with other medicinal products, apart from those stated under *“Instructions for handling”*.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Shelf life after opening

The diluted sotrovimab solution is intended for immediate use. If immediate administration is not possible, the diluted solution may be stored at room temperature (20 °C to 25 °C) for up to 6 hours or cooled (2 °C to 8 °C) for up to 24 hours from the time of dilution until administration is complete *(*see *“Instructions for handling”)*.

Special precautions for storage

Store in the refrigerator (at 2 °C to 8 °C) in the original packaging. Protect from light.

Do not freeze.

Store out of the reach of children.

Instructions for handling

Sotrovimab concentrate for making a solution for infusion needs to be prepared by a qualified health professional in aseptic conditions.

Preparation for dilution

1. Take a vial with sotrovimab from the refrigerator (2 °C to 8 °C). Leave the vial to stand for around 15 minutes at room temperature, ensuring it is protected from light.
2. Inspect the vial to ensure it does not contain any particles and there are no visible signs of damage.

   If a vial cannot be used, discard it and start preparation again using a new vial.
3. Prior to using the vial, gently sway it a few times without creating any air bubbles.

   Do not shake the vial or subject it to any violent movements.

Dilution instructions for intravenous infusion

1. Remove 8 mL from an infusion bag containing 50 or 100 mL sodium chloride 9 mg/mL (0.9%) or dextrose 5% solution for injection.
2. Remove 8 mL from the vial with sotrovimab.
3. Inject 8 mL sotrovimab via the septum into the infusion bag.
4. Discard anything left unused in the vial as the medicinal product does not contain any preservatives. The vial is only intended for single use and may only be used for one patient.
5. Gently sway the infusion bag back and forth 3 to 5 times before proceeding with the infusion. Do not turn the infusion bag over once it is ready. It is important not to let air bubbles form.

The diluted sotrovimab solution is intended for immediate use. If immediate administration is not possible, the diluted solution may be stored at room temperature (20 °C to 25 °C) for up to 6 hours or cooled (2 °C to 8 °C) for up to 24 hours from the time of dilution until administration is complete.

Instructions for use

1. Use a tube with a standard diameter to connect the infusion set to the infusion bag. It is recommended to use a 0.2 µm inlet filter when administering the intravenous infusion.
2. Fill the infusion set.
3. Administer the solution as an i.v. infusion over a period of 30 minutes at room temperature.

Disposal

Any unused medicinal product or waste material is to be disposed of in accordance with national requirements.

Authorisation number

68471 (Swissmedic).

Packs

Xevudy, vial with 500 mg/8 mL: 1 [A]

Marketing authorisation holder

GlaxoSmithKline AG, 3053 Münchenbuchsee

Date of revision of the text

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