EMA/CHMP/16919/2024
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMEA/H/C/005676/II/0026

Invented name: Xevudy

International non-proprietary name: sotrovimab

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	12 Dec 2023	12 Dec 2023
☐	CHMP Rapporteur Assessment Report	15 Jan 2024	15 Jan 2024
☐	PRAC Rapporteur Assessment Report	22 Jan 2024	22 Jan 2024
☐	PRAC members comments	26 Jan 2024	26 Jan 2024
☐	CHMP members comments	29 Jan 2024	29 Jan 2024
☐	Updated PRAC Rapporteur Assessment Report	30 Jan 2024	n/a
☐	Updated CHMP Rapporteur Assessment Report	01 Feb 2024	n/a
☐	PRAC endorsed relevant sections of the assessment report	06 Feb 2024	06 Feb 2024
☐	Start of written procedure	06 Feb 2024	06 Feb 2024
☐	Request for supplementary information	08 Feb 2024	08 Feb 2024
	Submission deadline	13 Feb 2024	13 Feb 2024
☐	CHMP Rapporteur Assessment Report	21 Feb 2024	22 Feb 2024
☐	PRAC Rapporteur Assessment Report	n/a	n/a
☐	PRAC members comments	26 Feb 2024	26 Feb 2024
☐	CHMP members comments	26 Feb 2024	26 Feb 2024
☐	Updated PRAC Rapporteur Assessment Report	n/a	n/a
☐	Updated CHMP Rapporteur Assessment Report	29 Feb 2024	n/a
☐	PRAC endorsed relevant sections of the assessment report	n/a	n/a
☐	Start of written procedure	05 March 2024	05 March 2024
☒	Opinion	07 March 2024	07 March 2024

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Glaxosmithkline Trading Services Limited submitted to the European Medicines Agency on 16 November 2023 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

To update sections 4.2, 4.8 and 5.2 of the SmPC in order to update information on paediatric population based on final results from study COMET-PACE (215226), a category 3 study in the RMP; this is an open-label, non-comparator, multicentre study to describe the pharmacokinetics (PK), pharmacodynamics (PD; viral load) and safety following a single intravenous or intramuscular dose of sotrovimab in paediatric participants with mild to moderate COVID-19 at high risk of disease progression. The updated RMP version 1.1 has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).

2. Abbreviations:

ADA (anti-drug antibodies): Antibodies developed against sotrovimab in sotrovimab-treated patients.

AESI: Adverse events of special interest

AE: Adverse event.

Fc-mediated effects: Immunological effector functions mediated by the Fc part of an antibody (e.g. complement activation, phagocytosis, antibody-dependent cell killing, etc).

I.M.: Intramuscular injection.

I.V.: Intravenous injection.

mAb: Monoclonal antibody.

PD (pharmacodynamics): Kinetics of SARS-CoV-2 concentration in nasal swabs from sotrovimab-treated patients.

PK (pharmacokinetics): Kinetics of sotrovimab concentration in sera from treated patients.

RT-PCR (reverse transcription - polymerase chain reaction): Method used for quantitation of SARS-CoV-2 RNA in nasopharyngeal swabs of patients.

SAE: Serious adverse event.

SARS-CoV-2 (human acute severe respiratory syndrome coronavirus 2): Causative agent of COVID19.

SmPC: Summary of product characteristics.

VIR-7831: Sotrovimab.

3. Overall conclusion and impact on the benefit/risk balance

For this variation application, the MAH provided data for sotrovimab use in the paediatric population, based on final results from the COMET-PACE study.

The study was terminated prematurely 14.06.2023, due to the emergence of omicron BA.2, the first SARS-CoV-2 variant against which sotrovimab exhibited worsened in vitro neutralization potency, and the provided data is thus very limited [8 paediatric patients; two participants (6 to <12 years) received 250 mg i.v. sotrovimab, and the remaining 6 participants (5 in 12 to <18 years group, 1 in 6 to <12 years group) received 500 mg i.v. sotrovimab; 29 day follow-up].

The virology and ADA data for the 8 paediatric patients raises no concerns.

The PK modelling data provided by the MAH demonstrated that the pharmacokinetics of sotrovimab in adolescents is comparable to adults.

The safety data from 8 patients did not show any new signals.

Thus, with the caveat that the treated paediatric patient population was very limited, the COMET-PACE data raises no concerns.

The MAH proposed to remove the missing information safety concern "Use in children ≥12 to <18 years old" from the sotrovimab RMP, as it is considered sufficiently characterised, and proposed to update the RMP following COMET-PACE study closure accordingly. The PRAC agrees that "Use in children ≥12 to <18 years old" can be deleted as missing information safety concern based on safety data in adolescents coming from clinical studies [7 participants with the approved posology] and post marketing reports including literature [>100 cases] which do not show a difference in sotrovimab safety profile in adolescents compared to the safety profile in adults. In addition, as indicated above, the pharmacokinetic properties of sotrovimab in adolescents are comparable to those in adults.

The MAH also proposed to remove evaluation of spontaneous reports via the targeted follow-up questionnaire for lack of efficacy including information on variant lineage (a routine pharmacovigilance activity) addressing "treatment failure due to emerging variants" [not listed as RMP safety concern] from the RMP (Part III and Annex 4) based on the limited data received via follow-up questionnaire since no new information has been received to what is being acquired from ongoing in vitro testing and literature review.

In December 2022, EMA's Emergency Task Force cautioned that monoclonal antibodies currently authorised for COVID-19 [such as sotrovimab] are unlikely to be effective against emerging strains of SARS-CoV-2. Thus, considering the current knowledge on SARS-CoV-2 sub variant neutralisation by sotrovimab, the decreased exposure to sotrovimab, as described in the last sotrovimab PSURs and, that the MAH will continue to evaluate sotrovimab effectiveness through non-clinical data and literature reports, the added value of retrieving information through the follow-up questionnaire for lack of efficacy becomes questionable. Therefore, this change is acceptable.

Finally, following the MAH's decision to terminate study COMET-PACE, the resulting administrative updates [removing COMET-PACE from RMP Part III] are acceptable.

The proposed changes in RMP version 1.1 are considered acceptable.

The benefit-risk balance of Xevudy remains positive.

4. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

To update sections 4.2, 4.8 and 5.2 of the SmPC in order to update information on paediatric population based on final results from study COMET-PACE (215226), a category 3 study in the RMP; this is an open-label, non-comparator, multicentre study to describe the pharmacokinetics (PK), pharmacodynamics (PD; viral load) and safety following a single intravenous or intramuscular dose of sotrovimab in paediatric participants with mild to moderate COVID-19 at high risk of disease progression. The RMP version 1.1 has also been updated.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and to the Risk Management Plan are recommended.

Annex: CHMP and PRAC assessment comments on the type II variation

5. Introduction

Sotrovimab (VIR-7831, GSK4182136) is a human IgG1 kappa (IgG1κ) SARS-CoV-2 neutralizing monoclonal antibody (mAb) derived from the parental human mAb S309, which was selected from memory B cells of an individual who survived SARS CoV-1 infection in 2003 based on the mAb's ability to cross-neutralize SARS-CoV-2.

I.e., sotrovimab binds to a highly conserved spike protein epitope which is conserved between SARS-CoV-1 and -2.

The epitope has minimal overlap with the binding site of the ACE2 receptor on the receptor-binding part of the spike protein (RBD), and the parental S309 mAb does not compete with ACE2 for binding to the receptor-binding part of the spike protein (assayed on immobilized ACE2 by biolayer inferometry, using S309 in full-length and Fab formats).

Nevertheless, S309 as well as sotrovimab neutralize SARS-CoV-2 in vitro.

The Fc domain of sotrovimab includes an LS modification that extends antibody half-life and may also be expected to enhance distribution to the respiratory mucosa. The LS modification is not expected to impair wild-type Fc-mediated effector functions, i.e., sotrovimab is expected to exhibit the normal, full range of Fc-mediated effector functions known to be exerted by human IgG1.

The Fc-mediated functions have been shown to contribute to efficacy in preclinical animal models.

Since approx. April 2022 i.e. for more than a year (present time June 2023), omicron BA.2 and so-called BA.2-descendant lineages have been driving the COVID-19 pandemic. Further, the antigenic evolution of the spike protein on the BA.2-descendant lineages has markedly eroded the in vitro neutralization activity of all the currently approved monoclonal antibodies.

It is not yet known how worsened in vitro neutralising activity translates to reduced clinical efficacy, and this is indeed expected to differ between mAbs, depending for example on whether Fc-mediated immunological effector functions contribute to the antiviral efficacy (ref 1-7).

Nevertheless, through December 2022 - January 2023, the loss of in vitro activity against omicron BA.2-decendant lineages had reached such proportions that EMA recommended against the use of currently approved mAbs, with the WHO providing even stronger recommendations against the use of currently approved mAbs (ref 8 and 9).

6. Submitted data:

For this variation application, the MAH submitted the following data:

- Report for COMET-PACE paediatric clinical study (TMF-16076269, 09.10.2023).
- Clinical pharmacology modelling report: Population pharmacokinetic analyses to support regulatory submission of sotrovimab (VIR7831) in adolescent participants for the treatment of COVID-19.
- Alliance Pharma method validation report, V2109035.01, 21.01.2022: Validation of the electrochemiluminescence-based assay for detection of neutralizing anti-VIR-7831 antibodies in human serum.
- Alliance Pharma method validation report, V2201157.01, 27.07.2022: Validation of the electrochemiluminescence immunoassay for the quantitation of VIR-7831 in human serum.

- Resolian study report, A2202022.01, 16.08.2023: Detection of neutralizing anti-VIR-7831 antibodies in serum samples from paediatric patients in COMET-PACE.
- Resolian study report, A2202019.01, 29.08.2023: Quantification of VIR-7831 in serum samples from paediatric patients in COMET-PACE.
- Resolian study report, A2202021.01, 25.08.2023: Detection of anti-VIR-7831 antibodies in serum samples from paediatric patients in COMET-PACE.
- Alliance Pharma method validation report, addendum, V2201157.01, 06.12.2022 (addendum to validation report V2201157.01; provides long-term stability data for VIR-7831 in human serum stored at –20°C for up to 160 days, at –80°C for up to 205 days, and the data for a crossvalidation assessment).

7. Clinical pharmacology

7.1. Overview & objectives; COMET-PACE study:

COMET-PACE was an open-label, non-comparator, multicenter study to describe the pharmacokinetics (PK), pharmacodynamics (PD; viral load) and safety following a single intravenous dose of sotrovimab in paediatric participants with mild to moderate COVID-19 at high risk of disease progression.

The study initiated 16.12.2021.

The original co-primary objectives were to evaluate the pharmacokinetics and safety by i.v. or i.m. administration of sotrovimab in participants from birth to <18 years (the i.m. administration arm was not conducted, and infants <6 years of age were not enrolled, as the study was terminated prematurely 14.06.2023, due to the emergence of omicron BA.2, the first SARS-CoV-2 variant against which sotrovimab exhibited worsened in vitro neutralization potency).

The safety endpoints comprised:

- Incidence of adverse events (AEs) through day 29 and week 36
- Incidence of serious adverse events (SAEs) through day 29 and week 36
- Incidence of adverse events of special interest (AESI) through way 29 and week 36

The secondary objectives were to evaluate disease progression and pharmacodynamics (viral load in nasopharyngeal swabs, by RT-PCR) in the treated participants.

- COVID-19 disease progression was monitored for 36 weeks (by phone call on days when a home visit or clinic visit was not scheduled).
- Sotrovimab efficacy was not assessed in the study.

Recruitment to the COMET-PACE study was paused prior to full recruitment on 28.03.2028, due to a decrease in in-vitro neutralisation of sotrovimab against omicron BA.2, and the study was ultimately terminated on 14.06.2023.

All study participants were infected with omicron BA.1 and omicron BA.1.1, against which sotrovimab retains potency.

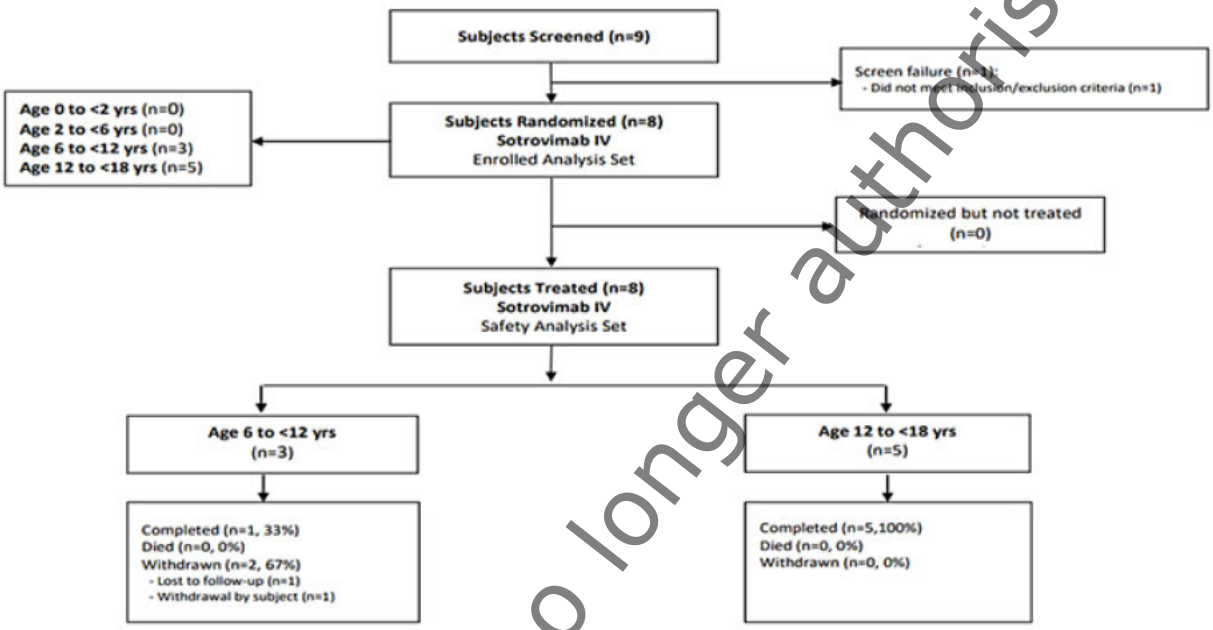
7.2. Participant disposition in COMET-PACE:

Five participants were enrolled in the 12 to <18 years age band and 3 participants were enrolled in the 6 to <12 years age band.

The participant disposition is detailed in the figure below.

Figure 1: Disposition of participants in the COMET-PACE study.

A



B

	Sotrovimab IV (6 to <12 yrs) (N=3)	Sotrovimab IV (12 to <18 yrs) (N=5)	Sotrovimab IV Total (N=8)
Participant status			
Completed[a]	1(33%)	5(100%)	6(75%)
Withdrawn	2 (67%)	0	2 (25%)
Died	0	0	0
Primary reason[b]/sub-reason[c] for study withdrawal			
Lost to follow-up	1 (33%)	0	1 (13%)
Other	1 (33%)	0	1 (13%)
Withdrawal by participant	1 (33%)	0	1 (13%)
Other	1 (33%)	0	1 (13%)

Figure text:
A: Graphical depiction of participant disposition, COMET-PACE.

B: Tabular depiction of participant disposition, COMET-PACE (safety population).

a A participant is considered to have completed the study if he/she has completed the week 36 visit.
b Participants may have only 1 primary reason.
c Percentages for sub-reasons may sum to more or less than 100%. Participants may have more than 1 sub-reason underneath a single primary reason. Participants are not required to indicate sub-reasons.

The figure is collated from figure 2 and table 4 in the COMET-PACE study report (TMF-16076269, 09.10.2023).

7.3. Demographics, COMET-PACE:

The majority of the participants were female (5/8, 63%), white in origin, not hispanic or latino in ethnicity, and had a median age of 13.5 years.

The demographics are detailed in the Table 1 below.

Table 1: Demographics in COMET-PACE.

	Sotrovimab IV (6 to <12 yrs) (N=3)	Sotrovimab IV (12 to <18 yrs) (N=5)	Sotrovimab IV Total (N=8)
Sex			
n	3	5	8
Female	1(33%)	4 (80%)	5 (63%)
Male	2(67%)	1 (20%)	3 (38%)
Age (years)[a]			
n	3	5	8
Mean	9.7	14.2	12.5
SD	0.58	1.10	2.51
Median	10.0	14.0	13.5
Min.	9	13	9
Max.	10	16	16
Ethnicity			
n	3	5	8
Hispanic or Latino	1 (33%)	1 (20%)	2 (25%)
Not Hispanic or Latino	2(67%)	4 (80%)	6 (75%)
Not reported	0	0	0
Unknown	0	0	0
High Level Race			
n	3	5	8
Black or African American	0	1 (20%)	1 (13%)
White	3 (100%)	4 (80%)	7 (88%)
Mixed race	0	0	0
Other	0	0	0
Race detail			
n	3	5	8
Black or African American	0	1 (20%)	1 (13%)
White – White/Caucasian/European Heritage	3 (100%)	4 (80%)	7 (88%)
Mixed Race	0	0	0
Other	0	0	0
Height (cm)			
n	3	5	8
Mean	132.1	164.8	152.5
SD	7.87	7.97	18.47
Median	136.0	166.0	157.5
Min.	123	152	123
Max.	137	173	173
Weight (kg)			
n	3	5	8
Mean	33.00	83.90	64.81
SD	7.908	26.659	33.436
Median	29.10	80.50	59.45
Min.	27.8	55.7	27.8
Max.	42.1	121.0	121.0
BMI (kg/m^2)			
n	3	5	8
Mean	18.87	31.07	26.49
SD	3.676	9.843	9.956
Median	18.38	34.66	21.94
Min.	15.5	20.2	15.5
Max.	22.8	41.9	41.9
BMI Category (kg/m^2)[a]			
N	3	5	8
<95th percentile	2 (67%)	2 (40%)	4 (50%)
>=95th percentile	1 (33%)	3 (60%)	4 (50%)
BMI Category 2 (kg/m^2)[b]			
n	3	5	8
<=25th percentile	1 (33%)	0	1 (13%)
>25th to <=50th percentile	0	1 (20%)	1 (13%)
>50th to <=75th percentile	0	1 (20%)	1 (13%)
>75th to <=95th percentile	1 (33%)	0	1 (13%)
>95th percentile	1 (33%)	3 (60%)	4 (50%)

Table text:

a For participants less than 2 years, full date of birth is collected. For participants 2 years or older, age is imputed from month and year of birth. The calculation uses the last day of the month and calculates age relative to screening date.

b Percentiles based on US Centers for Disease Control and Prevention growth chart for children ≥2 years of age.
Note: Percentages are calculated from the displayed n counts.

The table corresponds to table 7 in the COMET-PACE study report (TMF-16076269, 09.10.2023).

7.4. Sotrovimab dosages used for paediatric patients in COMET-PACE:

The selection of the sotrovimab dosing in COMET-PACE was based on conventional allometric scaling to achieve sotrovimab exposures in paediatric patients that are equivalent to exposures observed in the adult population after a single i.v. 500 mg dose (i.e. the adult exposure that provided protection against hospitalization or death by day 29 in the pivotal COMET-ICE efficacy study, performed in adult unvaccinated participants predominantly infected with the index strain).

Eligible participants were treated with a single i.v. dose of sotrovimab on day 1.

Two participants (6 to <12 years) received 250 mg i.v. sotrovimab and the remaining 6 participants (5 in 12 to <18 years group, 1 in 6 to <12 years group) received 500 mg i.v. sotrovimab.

Intravenous sotrovimab was administered undiluted using a syringe pump for participants under <15 kg, and diluted in 40 mL saline for participants <15 kg.

Because endotoxin specification limits for sotrovimab exceeds allowable levels for infants weighing <1.88 kg, infants <2 kg were excluded from the study.

Dosing was performed within 2 days of screening assessment, and participants were dosed ≤ 7 days from onset of COVID-19 symptoms. Screening could occur on the same day as dosing.

Duration of administration was 30-<35 minutes for 7 participants and 35-<40 minutes for 1 participant, without interruptions.

Additional details for the posology employed in COMET-PACE are given in the Table 2 below.

Table 2: Sotroviman posology employed in COMET-PACE.

Arm Name	Sotrovimab IV
Intervention Label	Sotrovimab
Type	Biologic
Dose Formulation	Solution in single use vial (62.5 mg/mL)
Unit Dose Strength(s)	500 mg/vial (500 mg/8 mL)
Dosage Level(s) by Weight:	0 to <2 years: • 2 to <5 kg: 62.5 mg = 1 mL • 5 to <15 kg: 125 mg = 2 mL • 15 to <40 kg: 250 mg = 4 mL 2 to <6 years: • 5 to <15 kg: 125 mg = 2 mL • 15 to <40 kg: 250 mg = 4 mL
	6 to <12 years: • 15 to <40 kg: 250 mg = 4 mL • ≥40 kg: 500 mg = 8 mL 12 to <18 years: • 15 to <40 kg: 250 mg = 4 mL • ≥40 kg: 500 mg = 8 mL
Route of Administration	IV infusion
Dilution with Saline	• Participants <15 kg: none • Participants ≥15 kg: 40 mL saline
Duration of Infusion	30 minutes
Use	Experimental
IMP and NIMP	IMP
Sourcing	Sotrovimab was provided centrally by the sponsor/designee Saline was provided by the study site.
Packaging and Labeling	Sotrovimab was provided in a single-use vial and labeled as required per country requirement
Current/Former Name(s) or Alias(es)	VIR-7831, GSK4182136

Table text:

IMP: Investigational medicinal product.
NIMP: Non-investigational medicinal product

The table corresponds to table 2 in the COMET-PACE study report (TMF-16076269, 09.10.2023).

7.5. COMET-PACE analysis sets:

In COMET-PACE, 8 participants constituted the enrolled, safety and PK analysis set and 7 participants constituted the virology analysis set.

One participant was excluded from the virology analysis set as it did not have a lab confirmed quantifiable baseline nasopharyngeal swab. All the participants were treated with i.v. sotrovimab.

See details for the COMET-PACE analysis sets in the Table 3 below.

Table 3: Table: COMET-PACE analysis sets.

Population	No treatment (N=1)	Sotrovimab IV (6 to <12 yrs) (N=3)	Sotrovimab IV (12 to <18 yrs) (N=5)	Sotrovimab IV Total (N=8)	Total (N=9)
Screened	1(100%)	3 (100%)	5 (100%)	8 (100%)	9(100%)
Enrolled	0	3 (100%)	5 (100%)	8 (100%)	8(89%)
Safety	0	3 (100%)	5 (100%)	8 (100%)	8(89%)
Pharmacokinetic (PK)	0	3 (100%)	5 (100%)	8 (100%)	8(89%)
PK principal stratum	0	3 (100%)	5 (100%)	8 (100%)	8(89%)
Virology	0	2 (67%)	5 (100%)	7 (88%)	7 (78%)

Table text:

Enrolled: All participants who entered the study and are assigned a randomization ID.

Safety: All participants who are exposed to study treatment.

Pharmacokinetic (PK): All participants who are exposed to study treatment and who had at least 1 non-missing PK assessment (non-quantifiable values were considered as non-missing values).

PK Principal Stratum: All participants in the PK analysis set who would be able to complete the IV dose.

Virology: All participants who are exposed to study treatment and have a quantifiable SARS-CoV-2 viral load measurement at baseline.

No treatment column: Subjects not randomized to study treatment.

The table corresponds to table 6 in the COMET-PACE study report (TMF-16076269, 09.10.2023).

7.6. Results; clinical serology:

The bioanalytical methods used to quantify anti-sotrovimab antibodies (ADAs) and neutralizing anti-sotrovimab antibodies (neutralizing ADAs) were validated.

Treatment-emergent ADAs were reported in 1 participant (20%) in the adolescent age (12 to <18 years) group. No neutralizing ADAs were reported.

7.7. Assessors comments; clinical serology:

ADAs but not neutralizing ADAs have been reported in sotrovimab-treated adults, at low incidence.

This is summarized as follows in the Current SmPC section 5.1: "*Treatment-emergent anti-drug antibodies (ADAs) to a single 500 mg intravenous infusion of sotrovimab were detected in 9% (101/1101) of participants, in controlled clinical studies with follow up durations of 18-36 weeks. No participants with confirmed treatment-emergent ADAs had neutralising antibodies against sotrovimab, and there was no evidence of an association of ADA with any impact on the safety, efficacy, or pharmacokinetics after a single intravenous infusion*".

The finding of ADAs in one sotrovimab-treated adolescent and no neutralizing ADAs in any participant in COME-PACE is thus not surprising.

While the number of participants in COMET-PACE is too low to estimate ADA incidence in paediatric patients, the COMET-PACE data is not concerning.

7.8. Results; clinical virology (sotrovimab PD):

Nasal cavity and nasopharyngeal swabs were collected for quantitation of viral load (concentration of SARS-CoV-2 RNA in nasal swabs by quantitative RT-PCR) and viral variant determination and resistance surveillance (nucleotide sequencing of spike protein gene from viral RNA in the nasal swabs).

On analysis of the virology data, 2 errors were identified. Firstly, the incorrect medium (Amies buffer was used instead of Universal Transport Medium) was used and secondly the volumes in the tubes were lower than specified. This affected all virology samples from the 8 participants in COMET-PACE. The CRO initiated CAPA activities for this quality event/deviation (report PPD, QE-014548). Validation reports for the RT-PCR assay prepared by the CRO concluded that (i) the use of Amies buffer instead of Universal Transport Medium impacts the robustness of the viral load quantitation assay including overall quantitation and ability to call a negative viral load unambiguously, but (ii) technically valid results can be obtained from samples in Amies buffer, and the sensitivity of the assay is comparable to samples in the desired buffer (see details in COMET-PACE study report, section 4.6.2). Based on the abovementioned validation report findings, and because the assay nevertheless yielded quantitative viral load data, and that sequencing of the virological samples was still possible, the MAH considers the results to be interpretable. Also, as all COMET-PACE nasal swab samples were collected in Amies buffer, the virology results are likely to be internally consistent within the study.

Thus, the following findings were made (see also results in the figure and table below):

- All participants exhibited high viral RNA loads before treatment on day 1 (day 1 nasal swabs were collected pre-dosing with sotrovimab).
- Generally, viral loads declined by 3,000-fold to 5,000-fold over time in sotrovimab-treated participants, and all participants had negative viral load results at day 29 (undetectable viral RNA or viral RNA concentration below quantification level, approx. 2 log10 copies/mL).
- All 8 participants were infected with omicron BA.1 (2/8, 25%) or omicron BA.1.1 (6/8, 75%) variants, against which sotrovimab retains in vitro neutralization activity.
- The viral load profiles for 2 participants met the criteria for viral rebound (defined as increase of >1 log10 increase in viral RNA concentration, or viral RNA becomes quantifiable after having been undetectable).
- Both participants were infected with omicron BA.1.1 (against which sotrovimab retains in vitro neutralization activity), and in both participants, viral RNA was undetectable by day 29.
    - One Participant (6 to <12 years old) had an initial viral load of 5.26 log10 copies/mL and experience an initial decline of >2 log10 copies/mL before increasing to 5.85 log10 copies/mL. This increase was followed by a decrease to < lower limit of detection on day 11 that was sustained through day 29.
    - Another Participant (6 to <12 years old) had a detectable but not quantifiable viral load on day 1. On days 3, 5 and 8, viral RNA loads fluctuated between approx. 7.5 and 4.5 log10 copies/mL, and on day 29, viral RNA was no longer detectable.

- Treatment-emergent substitutions were observed in the spike protein, but these affected neither the receptor-binding site nor the sotrovimab epitope.

Figure 2: Levels of SARS-CoV-2 RNA in nasal swabs; sotrovimab-treated participants in COMET-PACE.

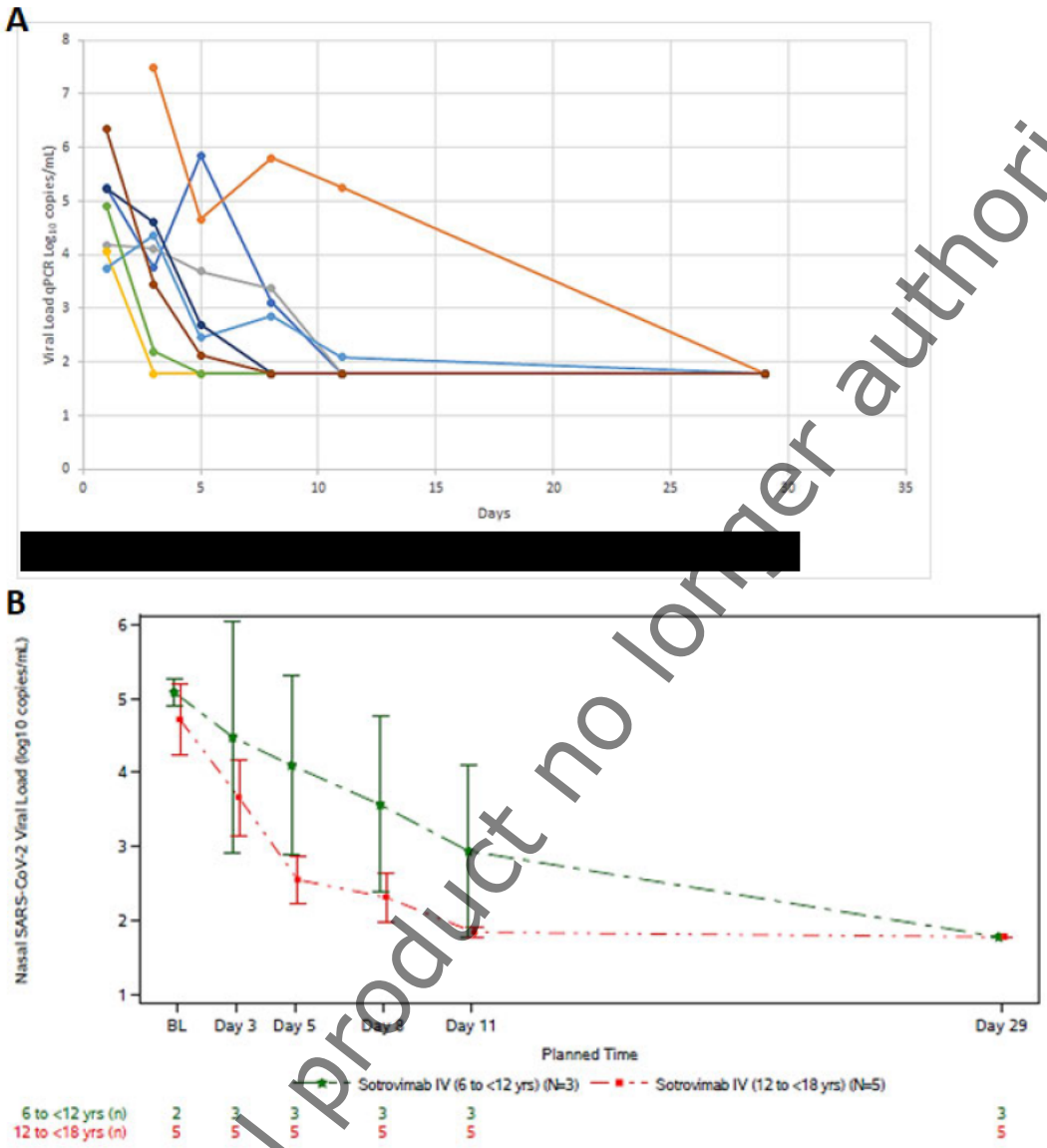


Figure text:

Treatment day 1 (single i.v. dose).

A: Viral RNA loads in nasal swabs of individual participants in COMET-PACE.

B: Average viral RNA loads in nasal swabs of children 6 to <12 years and adolescents 12 to <18 years in COMET-PACE.
Data points, group mean.
Error bars, +/- one standard error.

The figure is collated from figures 3 and 12.4 in the COMET-PACE study report (TMF-16076269, 09.10.2023).

Table 4: Treatment-emergent spike protein mutations determined from SARS-CoV-2 RNA in nasal swabs; sotrovimab-treated participants in COMET-PACE.

Participant Category	Sotrovimab Treatment Groups		
	Sotrovimab IV (6 to <12 yrs) N=3	**Sotrovimab IV (12 to <18 yrs) N=5**	**Sotrovimab IV Total (N=8)**
Participants with Paired Sequence Data, n[a] (%)	2 (67%)	3 (60%)	5 (63%)
Participant with TE Spike protein substitution detected	2 (100%)	1 (33%)	3 (60%)
Participants with a TE RBD substitution	0	0	0
Participants with a TE Sotrovimab Epitope Substitution	0	0	0
Amino Acid Change Per Residue in Spike[b] n (%)[c]			
A27T	1 (50%)	0	1 (20%)
V70I	2 (100%)	0	2 (40%)
D88*	0	1 (33%)	1 (20%)
T167I	0	1 (33%)	1 (20%)
Q218STOP	1 (50%)	0	1 (20%)
V534F	0	1 (33%)	1 (20%)
L945F	0	1 (33%)	1 (20%)
V952I	1 (50%)	0	1 (20%)
T1117I	1 (50%)	0	1 (20%)

Table text:

N: Number of participants in the safety population in COMET PACE.

TE: Treatment-emergent.
An amino acid deletion is represented by "*".
An amino acid substitution resulting in a stop codon is indicated with "STOP".

a. denominator is the number of participants with sequencing data available.

b. n = number of participants with treatment-emergent substitutions in the spike protein.

c. n= number of participants with the amino acid substitution listed.

The table corresponds to table 23 in the COMET-PACE study report (TMF-16076269, 09.10.2023).

7.9. Assessors comments; clinical virology (sotrovimab PD):

The MAH is thanked for the information concerning the errors in the RT-PCR analysis at the CRO. The MAHs conclusion that the clinical virology data is nevertheless interpretable is supported.

The COMET-PACE virology data is obviously too limited to allow conclusions regarding sotrovimab PD in paediatric patients.

Nevertheless, it can be stated that the changes in viral loads in the 8 sotrovimab-treated adolescent patients in COMET-PACE reflect what is seen in adults (relatively rapid decline in viral loads and ultimately clearance in in most patients; treatment-emergent spike amino acid changes relatively common).

This high-level correspondence between sotrovimab PD in adult and paediatric patients is perhaps not surprising, as the MAH considers that the exposure in the COMET-PACE participants were approximately equivalent to exposures considered to be protective in adults, and all participants were infected with omicron BA.1 and BA.1.1, against which sotrovimab retains potency.

As such, the COMET-PACE virology data raises no concerns.

7.10. Methods and Results; pharmacokinetics:

PK-methods: The bioanalytical methods used for COMET-PACE to quantify concentrations of sotrovimab in human serum were selective, accurate, and reproducible. All methods used to analyze PK and immunogenicity samples were validated prior to analysis.

In COMET-PACE study, Blood PK samples were collected post-dose on Day 1, 5, 8, 29, and again at Week 12 (Day 85 ± 7 days). PK parameters for sotrovimab were calculated using standard non-compartmental methods and actual sampling times. PK parameters through Week 12: maximum observed serum concentration (Cmax), concentration at Day 29 (CD29), time to Cmax (Tmax), area under the serum-concentration-time curve extrapolated to infinite time (AUCinf), area under the serum-concentration-time curve to Day 29 (AUC0-D29), terminal elimination half-life (t½), and volume of distribution at steady state (Vss), as data permitted, were reported as primary endpoints. Due to the limited data produced by COMET-PACE due to early study termination, PK data from the 8 enrolled participants were added to a final population PK dataset. The final population PK model was used to generate individual post-hoc parameters for each of those participants. These parameters along with parameters from the non-compartmental analysis were reported in the study results.

PK-results: The discontinued COMET-PACE study had recruited 5 of the intended 6 in the IV adolescent group, all of whom were received 500mg IV, and all of whom completed the study follow-up (Week 36) as defined in the protocol. In addition, 3 of the intended 12 participants in the 6-<12-year age group were enrolled; two of those participants received 250mg IV, and one participant received 500mg IV.

Observed sotrovimab concentrations in COMET-PACE and PK parameters from NCA, table 2 below, revealed similar exposures in the 12 to <18 years age group as compared to results from population PK analysis in adults:

- The Cmax was comparable between the 12-<18 years age group and adults (197.7 and 170.1 µg/mL respectively), and ~2-fold higher in the 6-<12 years age group (342.9 µg/mL).
- The AUC0-D29 was approximately 1.2-fold higher in the 12-<18 years age group (2041.17 versus 1637.1 day*µg/mL) as compared to adults, and approximately 1.9 -fold higher in the 6-<12 years age group (3190.4 versus day*µg/mL).
- Summary values from the 6 to <12 years group are based on one participant's data as the other two participants had missing EOI samples; PK results in the 6-<12 years age group should be interpreted with caution given the small number of participants included in the analysis.

Table 5: Derived Sotrovimab Serum Pharmacokinetic Parameters Through Week 12 Based NCA

Parameter	Treatment	N	n	Mean	95% CI (Lower, Upper)	SD	Median	Min.	Max.	% CV
Cmax (µg/mL)	Sotrovimab IV (6 to <12 yrs)	3	1	342.96			342.96	343.0	343.0	
	Sotrovimab IV (12 to <18 yrs)	5	5	197.72	(133.44,261.99)	51.767	207.63	120.6	263.9	26.18
	Sotrovimab IV Total	8	6	221.92	(142.97,300.87)	75.231	209.07	120.6	343.0	33.90
Ct (µg/mL)	Sotrovimab IV (6 to <12 yrs)	3	3	51.16	(-14.25,116.58)	26.333	58.54	21.9	73.0	51.47
	Sotrovimab IV (12 to <18 yrs)	5	5	19.70	(9.25,30.16)	8.419	21.58	9.3	28.7	42.73
	Sotrovimab IV Total	8	8	31.5	(12.74,50.26)	22.443	24.07	9.3	73.0	71.25
CD29 (µg/mL)	Sotrovimab IV (6 to <12 yrs)	3	3	66.49	(48.26,84.72)	7.338	67.91	58.5	73.0	11.04
	Sotrovimab IV (12 to <18 yrs)	5	5	47	(35.05,58.95)	9.623	50.50	31.2	55.7	20.47
	Sotrovimab IV Total	8	8	54.31	(43.41,65.21)	13.039	54.03	31.2	73.0	24.01
tmax (day)	Sotrovimab IV (6 to <12 yrs)	3	1	0.000			0.000	0.00	0.00	
	Sotrovimab IV (12 to <18 yrs)	5	5	0.007	(-0.004,0.017)	0.008	0.003	0.00	0.02	125.47
	Sotrovimab IV Total	8	6	0.006	(-0.003,0.014)	0.008	0.002	0.00	0.02	143.31
tlast (day)	Sotrovimab IV (6 to <12 yrs)	3	3	46.268	(-32.226,124.763)	31.598	28.071	27.98	82.75	68.29
	Sotrovimab IV (12 to <18 yrs)	5	5	85.351	(76.299,94.404)	7.29	88.903	78.94	97.87	8.54
	Sotrovimab IV Total	8	8	70.695	(48.188,93.203)	26.922	82.396	27.98	97.87	38.08
Vz (L)	Sotrovimab IV (6 to <12 yrs)	3	1	1.42			1.42	1.4	1.4	
	Sotrovimab IV (12 to <18 yrs)	5	5	5.6	(4.07,7.13)	1.232	5.19	4.1	7.4	22.00
	Sotrovimab IV Total	8	6	4.9	(2.77,7.03)	2.032	5.15	1.4	7.4	41.45
CL (mL/day)	Sotrovimab IV (6 to <12 yrs)	3	1	42.62			42.62	42.6	42.6	
	Sotrovimab IV (12 to <18 yrs)	5	5	100.3	(59.50,141.11)	32.863	88.72	73.7	154.8	32.76
	Sotrovimab IV Total	8	6	90.69	(51.17,130.21)	37.662	83.56	42.6	154.8	41.53
Vss (L)	Sotrovimab IV (6 to <12 yrs)	3	1	1.32			1.32	1.3	1.3	
	Sotrovimab IV (12 to <18 yrs)	5	5	5.02	(3.43,6.61)	1.282	4.73	3.3	6.7	25.54
	Sotrovimab IV Total	8	6	4.4	(2.42,6.39)	1.896	4.69	1.3	6.7	43.03
AUC (0-inf) (day* µg/mL)	Sotrovimab IV (6 to <12 yrs)	3	1	5865.29			5865.29	5865.3	5865.3	
	Sotrovimab IV (12 to <18 yrs)	5	5	5349.55	(3585.19,7113.91)	1420.967	5635.5	3230.3	6782.6	26.56
	Sotrovimab IV Total	8	6	5435.51	(4083.55,6787.47)	1288.274	5750.4	3230.3	6782.6	23.70
AUC(0-t) (day* µg/mL)	Sotrovimab IV (6 to <12 yrs)	3	1	3438.29			3438.29	3438.3	3438.3	
	Sotrovimab IV (12 to <18 yrs)	5	5	4080.58	(3054.57,5106.59)	826.321	4373.57	2620.9	4670.8	20.25
	Sotrovimab IV Total	8	6	3973.53	(3150.54,4796.52)	784.22	4367.05	2620.9	4670.8	19.74
AUC (0-29) (day* µg/mL)	Sotrovimab IV (6 to <12 yrs)	3	1	3190.41			3190.41	3190.4	3190.4	
	Sotrovimab IV (12 to <18 yrs)	5	5	2041.17	(1585.72,2496.61)	366.801	2166.23	1409.6	2318.6	17.97
	Sotrovimab IV Total	8	6	2232.71	(1631.90,2833.51)	572.503	2211.59	1409.6	3190.4	25.64
% AUCex (%)	Sotrovimab IV (6 to <12 yrs)	3	1	41.38			41.38	41.4	41.4	
	Sotrovimab IV (12 to <18 yrs)	5	5	22.23	(9.51,34.94)	10.24	22.39	7.7	35.5	46.07
	Sotrovimab IV Total	8	6	25.42	(12.78,38.06)	12.042	24.58	7.7	41.4	47.37
t1/2 (day)	Sotrovimab IV (6 to <12 yrs)	3	3	32.905	(10.192,55.618)	9.143	34.578	23.04	41.1	27.79
	Sotrovimab IV (12 to <18 yrs)	5	5	40.783	(25.988,55.579)	11.916	40.526	27.07	58.14	29.22
	Sotrovimab IV	8	8	37.829	(28.608,47.050)	11.029	37.552	23.04	58.14	29.16

A comprehensive POP-PK model was previously developed to describe sotrovimab pharmacokinetics in adult and adolescent participants with COVID-19 and in healthy volunteers after IM and IV administration. The POP-PK model was used to generate individual post-hoc parameters for the 8 participants who completed COMET-PACE, see table 3 and 4 below.

- The geometric mean bodyweight-adjusted CL was 0.05 L/day in the 3 participants in the 6 to <12 years age group and 0.10 L/day in the 5 participants in the 12 to <18 years age group, as compared to 0.10 L/day in adults.
- The mean AU0-29 in the 6 to<12 years age and 12 to<18 years age band was 2664.0 and 1924.3 µg*day/mL, respectively.

Table 6: Summary Statistics of PK and Exposure Parameters by Age Group Based on Population PK

Exposures	Statistics	12-<18 years	6-<12 years	Total
	n	5	3	8
AUC_{0-inf} (µg* day/mL)	Mean (SD)	5091.0 (1241.1)	6040.1 (477.7)	5421.1 (1130.3)
	Geometric Mean (Geometric %CV)	4928.8 (24.4)	6023.0 (7.91)	5284.8 (20.9)
	Median	5379.1	5742.0	5716.9
	5th, 95th	3182, 6444	5716, 6726	3182, 6726
AUC_{0-D29} (µg* day/mL)	Mean (SD)	1956.8 (363.2)	2711 (571.5)	2292.2 (588.7)
	Geometric Mean (Geometric %CV)	1924.3 (18.6)	2664.0 (21.1)	2223.6 (25.7)
	Median	2089.6	2820.8	2105.6
	5th, 95th	1466, 2181	2088, 3182	1597, 3182
C_{max} (µg/mL)	Mean (SD)	198.6 (42.9)	248.8 (69.5)	216.1 (58.1)
	Geometric Mean (Geometric %CV)	193.3 (21.6)	239.8 (27.9)	208.4 (26.9)
	Median	209.4	239.3	213.4
	5th, 95th	122, 249	170, 339	122, 339
C_{29} (µg/mL)	Mean (SD)	48.0 (9.9)	68.0 (10.4)	56.9 (14.2)
	Geometric Mean (Geometric %CV)	47.0 (20.7)	67.4 (15.3)	55.1 (24.9)
	Median	51.8	69.9	54.9
	5th, 95th	34, 54	57, 77	38, 77

Table 7: Summary Statistics of Derived PK Parameters by Age Group Based on Population PK

Exposures	Statistics	12-<18 years	6-<12 years	Total
	n	5	3	8
CL (L/day)	Mean (SD)	0.10 (0.03)	0.05 (0.01)	0.09 (0.04)
	Geometric Mean (Geometric %CV)	0.10 (28.5)	0.05 (27.6)	0.08 (41.0)
	Median	0.09	0.04	0.08
	5th, 95th	0.07, 0.15	0.04, 0.07	0.04, 0.16
Steady-State Volume of Distribution (L)	Mean (SD)	6.22 (1.5)	2.8 (0.48)	5.02 (2.1)
	Geometric Mean (Geometric %CV)	6.07 (23.8)	2.7 (17.4)	4.59 (41.1)
	Median	5.78	2.87	5.7
	5th, 95th	4.6, 8.9	2.2, 3.3	2.2, 9.0
t½ (days)	Mean (SD)	44.8 (9.9)	37.9 (6.1)	42.4 (9.3)
	Geometric Mean (Geometric %CV)	43.6 (22.0)	37.5 (16.1)	41.4 (21.9)
	Median	44.2	35.7	43.3
	5th, 95th	27, 57	32, 46	29, 57

To comparatively assess sotrovimab exposures between adolescents and adults, data from the five adolescents from COMET-PACE were added to the previously developed POP-PK dataset. Individual post-hoc parameters were generated to compare exposures in adolescents versus exposures in adults. The primary analysis defined adolescents as participants <18 years, while a secondary analysis

included participants ≤18 years; in both analyses, adults were defined as age > 18 years. Mean parameter values from each of these populations were compared against the same parameter values in adults, see table 5, table 6 and figure below.

- The geometric mean CL of sotrovimab in adolescent participants after a 500 mg IV dose was 0.10 L/day in the primary analysis and 0.09 L/day in the secondary analysis, with a comparable value in adult participants of 0.10 L/day.
- In the primary analysis, sotrovimab exposures were comparable between adolescent and adult participants who received a 500 mg IV dose, with a geometric mean AUC0-inf of 5138.9 and 5024.4 µg*day/mL and a geometric mean AUC0-D29 of 1866.4 and 1571.1 µg*day/mL, respectively.
- In the secondary analysis, sotrovimab exposures remained comparable between adolescent and adult participants, with a geometric mean AUC0-inf of 5519.6 and 5024.4 µg*day/mL and a geometric mean AUC0-D29 of 1583.9 and 1571.1 µg*day/mL, respectively.

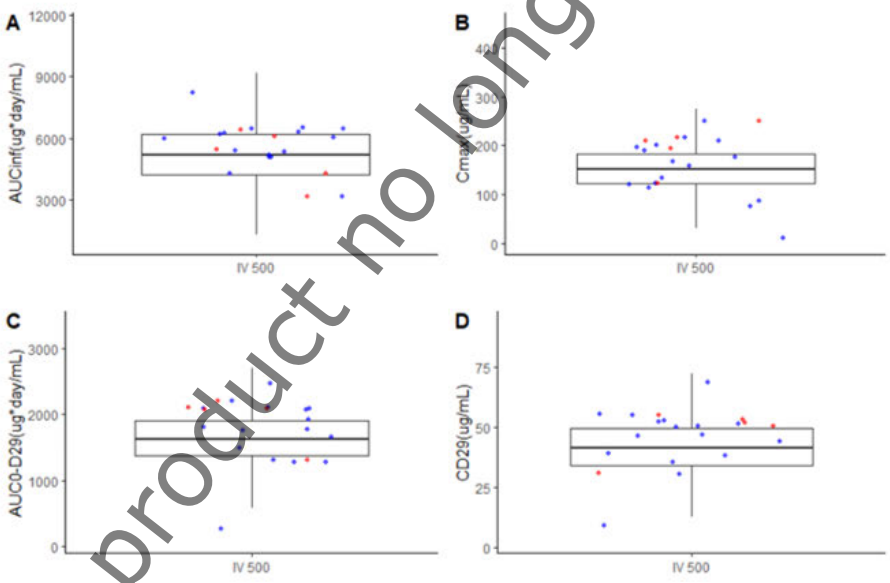
Table 8: Summary Statistics of Pharmacokinetic and Exposure Parameters by Age: Primary and Secondary PPK Analysis

Exposures	Statistics	Primary Population (12 to <18 years)	Secondary Population (12 to ≤18 years)	Adult (>18 years)
	Dose: 500 mg IV			
	n	**7**	**16**	**1179**
AUC0-inf (µg* day/mL)	Mean (SD)	5298.6 (1228.7)	5635.5 (1095.5)	5279.1 (1569.7)
	Geometric Mean (Geometric %CV)	5138.9 (23.2)	5519.6 (19.4)	5024.4 (29.7)
	Median	5674.4	5969.7	5206.7
	5th, 95th	3182, 6521	3182, 6521	2820, 8106
AUC0-D29 (µg* day/mL)	Mean (SD)	1892.3 (319.7)	1723.7 (524.5)	1639.2 (428.1)
	Geometric Mean (Geometric %CV)	1866.4 (16.9)	1583.9 (30.4)	1571.1 (26.1)
	Median	2076.5	1790.2	1619.7
	5th, 95th	1414.5, 2171.4	1025, 2266	988, 2344
Cmax (µg/mL)	Mean (SD)	186.5 (47.8)	168.8 (49.5)	156.8 (58.4)
	Geometric Mean (Geometric %CV)	180.0 (25.6)	155.6 (29.3)	145.1 (37.3)
	Median	202.4	176.2	152.4
	5th, 95th	120, 249	76, 249	75, 253
C29 (µg/mL)	Mean (SD)	48.1 (8.2)	45.2 (13.3)	41.9 (12.3)
	Geometric Mean (Geometric %CV)	47.4 (17.0)	42.2 (29.3)	39.8 (29.4)
	Median	50.4	48.2	41.3
	5th, 95th	35, 54	25, 59	22, 63

Table 9: Table 6. Summary Statistics of Derived Pharmacokinetic Parameters: Primary and Secondary PPK Analysis

Exposures	Statistics	Primary Population (12-<18 years)	Secondary Population (12-≤18 years)	Adult (> 18 years)
	Dose: 500 mg IV			
	n	7	16	1179
CL (L/day)	Mean (SD)	0.10 (0.03)	0.09 (0.02)	0.105 (0.05)
	Geometric Mean (Geometric %CV)	0.10 (1391)	0.09 (7831)	0.09 (5947)
	Median	0.09	0.08	0.09
	5th, 95th	0.08, 0.16	0.08, 0.15	0.06, 0.17
Steady-State Volume of Distribution (L)	Mean (SD)	6.38 (1.4)	7.93 (7.3)	8.6 (6.3)
	Geometric Mean (Geometric %CV)	6.24 (21.9)	7.01 (91.5)	8.01 (73.1)
	Median	5.93	6.98	7.89
	5th, 95th	4.6, 8.9	4.6, 10.2	5.2, 12.9
t½ (days)	Mean (SD)	48.1 (11.7)	62.9 (53.5)	60.6 (39.1)
	Geometric Mean (Geometric %CV)	46.6 (24.3)	55.9 (85.1)	58.7 (64.5)
	Median	47.8	52.9	59.4
	5th, 95th	29, 65	28.6, 85.9	43.8, 74.8

Figure 3: Boxplot of Adult Exposures with Overlaid Adolescent Exposures



Boxes and whiskers represent a summary of adult data from all sotrovimab clinical studies included in the PPK model (adult defined as >18 years). The bottom and top of the box indicate the first quartile (25th percentile) and third quartile (75th percentile) of adult data, respectively. The line in the middle of the box represents the median, and the bottom and top whiskers represent the minimum and maximum of the adult data. Blue dots represent exposures from participants ≤18 years in COMET-PEAK, COMET-ICE, BLAZE-4, and COMET-TAIL; red dots represent exposures from adolescent participants in COMET-PACE.

8.11. Assessor comments; Pharmacokinetics:

In the discontinued paediatric study COMET-PACE, the pharmacokinetics of IV administered sotrovimab were evaluated in 5 adolescent (12 to 18 years) and in three children (6 to 12 years). Sotrovimab was quantified using a validated bioanalytical method and the PK-parameters were determined using NCA. In the cohort of children, NCA analysis was possible only for one child. The previously generated population PK model for sotrovimab was applied to calculate individual post. hoc. PK-parameters for each of the paediatric subjects. The paediatric mean PK-parameters were compared to adult POP-PK model estimates. An additional POP-PK analysis was performed including a few additional data from

adolescents exposed to sotrovimab in other clinical studies of sotrovimab. Overall, the applied PK methodology for the paediatric PK-extrapolation is found to be adequate.

The key exposure parameters of sotrovimab, AUC0-D29 and Cmax, were comparable between adolescents and adults: AUC0-D29 (2041.17 versus 1637.1 day*µg/mL) and Cmax (197.7 versus 170.1 µg/mL). The performed POP-PK analysis provides similar results. In the cohort of children (6 to 12 years) a higher exposure was found. The MAH concludes that the PK-data in children (6 to 12 years) is too limited to establish the pharmacokinetics of sotrovimab in this population. This conclusion is supported. The SmPC, section 5.2, has been adequately updated with the obtained PK-results in adolescents.

In conclusion, it has been demonstrated by the MAH that the pharmacokinetics of sotrovimab in adolescents is comparable to adults.

8. Clinical Safety aspects

8.1. Methods – analysis of data submitted

In addition to safety data from Study VIR-7831-5005 (215226, COMET-PACE) which was the primary paediatric study intended to provide paediatric sotrovimab data in order to present the totality of current paediatric data from participants who received weight-based 500 mg IV sotrovimab, the following safety data are also summarized here:

- Two adolescent participants from the COMET-TAIL study.

- Accumulated post marketing data as of 19 August 2023.

COMET-PACE has been described earlier in this report, please refer to the pharmacology section.

COMET-TAIL was a Phase 3 randomized, multi-center, open-label, non-inferiority study of IM versus IV administration of sotrovimab, in participants aged 12 years and above at high risk of disease progression. The study randomized 1:1:1 to receive a single dose 500 mg IV infusion of sotrovimab or a single IM injection of sotrovimab at 1 of 2 dose levels (250 mg or 500 mg).

8.2. Results

A total of 2289 participants in Vir/GSK sponsored clinical studies have received sotrovimab administered by IV infusion (N=1314) or IM injection (N=975).

There were 11 participants in the COMET-PACE and COMET-TAIL studies who were <18 years of age who received sotrovimab. Ten participants received weight-based sotrovimab 500 mg IV and 1 participant received sotrovimab 250 mg IM.

In COMET-PACE 8 enrolled participants received study intervention, i.e., IV infusion of weight-based 500 mg dosing. Five participants were enrolled in the 12 to <18 years age band and 3 participants were enrolled in the 6 to <12 years age band. Two participants (6 to <12 years) received 250 mg IV sotrovimab and the remaining 6 participants (5 in the 12 to <18 year group, 1 in the 6 to <12 year group) received 500 mg IV sotrovimab.

In COMET-TAIL (GSK Study 217114/VIR-7831-5008), 3 adolescents (12 to <18 years of age) received sotrovimab. Two participants received sotrovimab 500 mg IV. One participant received sotrovimab 250 mg IM.

Overall, the AEs reported from the post marketing use of sotrovimab are consistent with those observed in clinical studies. Following the grant of the regulatory approvals for sotrovimab, spontaneous post-marketing reports of anaphylaxis have been received. Based on the review of these post-marketing reports, the Reference Safety Information for sotrovimab was updated to include anaphylaxis in the Adverse Reactions section. Post-marketing reports received for adolescents 12 to <18 years of age as well as for children <12 years of age (off-label use) by 19 August 2023 have not identified any new safety issues in these age groups.

A total of 8 enrolled participants in the **COMET PACE study** received study intervention, i.e., IV infusion of weight based 500 mg dosing. Five participants were enrolled in the 12 to <18 years age band and 3 participants were enrolled in the 6 to <12 years age band.

Two participants (6 to <12 years) who were < 40 kg received 250 mg IV sotrovimab and the remaining 6 participants (5 in the 12 to <18 year group, 1 in the 6 to <12 year group) received 500 mg IV sotrovimab (all were at least 40 kg). The duration of administration was 30-<35 minutes for 7 participants and 35-<40 minutes for 1 participant, without interruptions.

The majority of the participants were female (5[63%] of 8), White (7 [88%]), non- Hispanic or Latino (6 [75%]), and had a median age of 13.5 years (range: 9 to 16 years).

The majority of participants in both the age bands had at least 1 predefined risk factor associated with COVID-19 progression. The most frequently reported risk factors for disease progression were obesity (4[50%] of 8 participants) and diabetes (3[38%] of 8 participants). The majority of participants had a symptom duration of ≤3 days (5[63%] of 8 participants) at enrolment.

Of the 8 enrolled participants, 5 (63%) experienced at least 1 AE. None of the events were reported in more than 1 participant each and none occurred with a frequency greater than once each. None of the AEs were serious, fatal, or considered related to study intervention by the investigator, and none led to withdrawal from the study. All the AEs were of Grade 1 or Grade 2 severity. Of the 4 participants who reported AEs after dosing with sotrovimab, (the preferred terms of the AEs (generalised as deemed necessary to prevent the identification of study participants)) were:

- 6 to <12year age group: worsening of background medical condition, infective complication of immunosuppression, aspartate aminotransferase increase, alanine aminotransferase increase and blood creatinine increase (1 participant);

- 12 to <18 years age group: contusion (1 participant), gastroenteritis viral (1 participant), congenital heart disease with associated complication (1 participant).

In the **COMET TAIL study**, there were 2 adolescent participants enrolled who received sotrovimab 500 mg IV dose and 1 who received 250 mg IM dose; all 3 were followed through week 24 post infusion. None of the adolescent participants experienced any AE or SAE.

Events related to expected progression, signs, or symptoms of COVID-19 were reported as DRE. One participant who received a 500 mg IV dose reported a disease related event: vomiting of Grade 2 in severity, that started on the day of dosing and resolved in 9 days. There were no laboratory values outside of the normal range or clinically significant changes post baseline observed. The safety profile of sotrovimab in these adolescent participants was consistent with the safety profile of the overall population enrolled in the study. There were no new adverse reactions identified from this study.

A summary of **safety data from post-marketing** sources is presented in the Periodic Benefit Risk Evaluation Reports (PBRER)/European Union (EU) Periodic Safety Update Reports (EU-PSUR) provided

to regulatory agencies on a regular basis. The most recent PBRER/EU-PSUR has a cut-off date of 19 August 2023 with a submission date by 27 October 2023.

8.3. Assessors comment

No new safety issues were identified among the 8 paediatric participants enrolled (5 participants 12 to <18 years and 3 participants in the 6 to <12 years) in the COMET-PACE study. No SAEs, deaths or hypersensitivity reactions were reported. In the COMET-TAIL study, there were 2 adolescent participants receiving a sotrovimab 500 mg IV dose and one receiving a 250 mg IM dose, none of them had any AE. It can be concluded that the safety profile of sotrovimab in these the few adolescent participants was consistent with the known safety profile of the drug.

Thus, the proposed revision of the statement in section 4.2 of the SmPC *"The safety and efficacy of Xevudy in children under 12 years old or weighing less than 40 kg have not yet been established. Currently available data are described in sections 4.8 and 5.2 but no recommendation on posology can be made."* is supported.

Discussion

In the discontinued paediatric study COMET-PACE, sotrovimab was evaluated in 5 adolescent (12 to 18 years) and in three children (6 to 12 years), which Is obviously a very limited sample size.

Sotrovimab was quantified using a validated bioanalytical method and the PK-parameters were determined using NCA. In the cohort of children, NCA analysis was possible only for one child. The previously generated population PK model for sotrovimab was applied to calculate individual post. hoc. PK-parameters for each of the paediatric subjects. The paediatric mean PK-parameters were compared to adult POP-PK model estimates. An additional POP-PK analysis was performed including a few additional data from adolescents exposed to sotrovimab in other clinical studies of sotrovimab. Overall, the applied PK methodology for the paediatric PK-extrapolation is found to be adequate.

The key exposure parameters of sotrovimab, AUC0-D29 and Cmax, were comparable between adolescents and adults, the performed POP-PK analysis provides similar results. In the cohort of children (6 to 12 years) a higher exposure was found. The MAH concludes that the PK-data in children (6 to 12 years) is too limited to establish the pharmacokinetics of sotrovimab in this population. This conclusion is supported. It was requested that the SmPC, section 5.2, is updated with the obtained PK-results in adolescents (SmPC).

In conclusion, it has been demonstrated by the MAH that the pharmacokinetics of sotrovimab in adolescents is comparable to adults.

ADAs but not neutralizing ADAs have been reported in sotrovimab-treated adults, at low incidence and reflected in the SmPC. The finding of ADAs in one sotrovimab-treated adolescent and no neutralizing ADAs in any participant in COME-PACE is thus not surprising. While the number of participants in COMET-PACE is too low to estimate ADA incidence in paediatric patients, the COMET-PACE data is not concerning.

There appeared to be some errors in the RT-PCR analysis at the CRO, the MAHs conclusion that the clinical virology data is nevertheless interpretable is supported. The COMET-PACE virology data is obviously too limited to allow conclusions regarding sotrovimab PD in paediatric patients. Nevertheless, it can be stated that the changes in viral loads in the 8 sotrovimab-treated adolescent patients in COMET-PACE reflect what is seen in adults (relatively rapid decline in viral loads and ultimately clearance in in most patients; treatment-emergent spike aminoacid changes relatively

common).

This high-level correspondence between sotrovimab PD in adult and paediatric patients is perhaps not surprising, as the MAH considers that the exposure in the COMET-PACE participants were approximately equivalent to exposures considered to be protective in adults, and all participants were infected with omicron BA.1 and BA.1.1, against which sotrovimab retains potency. Overall, the virology data raises no concerns.

In the study no AEs reported were serious, fatal, or considered related to study intervention by the investigator, and none led to withdrawal from the study. The safety data from 8 patients did not show any new signals, the safety profile was in line with the known one for adults and the proposed changes to the SmPC reflect this adequately.

9. PRAC advice

Not applicable.

10. Risk management plan

The MAH submitted an updated RMP (Version 1.1; data lock point: 19 August 2023, date of final sign off: 06 November 2023) with this application. The MAH provided the following rationale for submitting an updated RMP:

- remove Use in children ≥12 to <18 years old as missing information (supporting data provided in Part II Module SVII.2)
- remove COMET PACE study as an interventional PASS – study terminated early (see Part II Module SVII.2)
- discontinue use of sotrovimab specific Targeted Follow up Questionnaire (TFuQ) to collect additional information for reports of potential lack of efficacy including information on virus lineage; this proposal is supported by review of information collected and summarized in each 6-monthly PBRER/EU PSUR for sotrovimab since implementation of TFuQ in December 2021; based on the limited data received via TFuQ no new information has been received to what is being acquired from ongoing in vitro testing and literature review

The (main) proposed RMP changes were the following:

Summary of significant changes in this RMP:		
PART	**MODULE**	**Changes made in EU-RMP version 1.1**
II	SI	Relevant epidemiology information updated to reflect current information for the target population
II	SIII	Updated clinical exposures
II	SV	Updated with estimated post authorization exposures
II	SVII1.1, 1.2 and 3.2	Updated to remove Use in children ≥12 to <18 years old as missing information
II	SVII.2	Updated to provide supporting data for removal of Use in children ≥12 to <18 years old as missing information
II	SVIII	Updated to remove Use in children ≥12 to <18 years old as missing information
III	III.1.1	Updated to remove use of TFuQ to collect additional information for reports of potential lack of efficacy including information on virus lineage
III	III.2 and III.3	Updated to remove COMET PACE study
V	V.1 and V.3	Updated to remove Use in children ≥12 to <18 years old as safety concern
VI	II.A, II.B and II.C	Updated to align with changes in the RMP

There are no other RMP versions under evaluation.

10.1. Safety Specification

Epidemiology of the indications and target population

The MAH updated this section with current epidemiology data on the indications and target population.

Non-clinical part of the safety specification

The MAH updated sub section *viral resistance* in line with the information included in the currently approved sotrovimab product information.

Clinical trial exposure

The MAH updated this section with current clinical trial exposure.

Populations not studied in clinical trials

The MAH proposed that the exclusion criterion "Children <18 years old" should no longer be included as missing information and provided an updated brief rationale. The MAH also included updated exposure data from clinical trials for other special population.

Post-authorisation experience

The MAH updated this section with current post-authorisation exposure data.

PRAC Rapporteur assessment comment:

All MAH-proposed changes to the above RMP modules are acceptable: the MAH proposes administrative updates to the number of exposed participants in clinical studies, updated epidemiology information on the approved indication [COVID-19], and non-clinical information in line with approved product information.

The proposed updates regarding "Children <18 years old" are also acceptable, please refer to the following assessment comment on Part II, Module SVII – Missing information.

Missing information

"Use in children ≥12 to <18 years old" previously classified as missing information is removed from the list of safety concerns. The MAH provided the following rationale:

The MAH considers use in children ≥12 to <18 years old (adolescents) to be sufficiently characterized based on the available safety data from clinical studies (8 adolescent participants), post marketing data and/or literature (over 100 adolescent patients) and that there is no supposition based on available data that the safety profile in adolescents is likely to differ from the one in adults. Therefore, missing information: use in children ≥12 to <18 years old is proposed to be removed as safety concern from the RMP. Summary of the supporting available data from clinical studies, literature and/or post marketing reports received in MAH's safety database is provided below.

As stated above, based on the accumulated safety data from clinical studies and post marketing, the safety profile in adolescent is considered similar to the one identified in the adults with no new safety issues identified. Therefore, following termination of COMET-PACE study, no additional PV activities are proposed, and the study is also proposed to be removed as an interventional PASS. Considering that the use in children ≥12 to <18 years old (adolescents) is sufficiently characterized, the relatively low usage of sotrovimab including in pediatric population, as well as the level of burden on healthcare systems and patients, a new observational study is not considered needed or a viable option to collect further information on this patient population.

Clinical trial data

A total of 11 participants <18 years old were enrolled in sotrovimab clinical studies. Of these 11 participants, 3 participants (age 12 to <18 years) were enrolled in COMET-TAIL (2 received sotrovimab 500mg IV, and one 250mg IM), and 8 participants were enrolled in COMET-PACE study. Of the 8 participants in COMET-PACE study, 5 participants were enrolled in the 12 to <18 years age band and 3 participants were enrolled in the 6 to <12 years age band. Two participants (6 to <12 years) received 250 mg IV sotrovimab and remaining 6 participants (5 in 12 to <18-year group, 1 in 6 to <12 year group) received 500 mg IV sotrovimab.

None of the 3 adolescents participants enrolled in COMET-TAIL study reported adverse events. One participant who received 500mg IV dose reported disease related event: vomiting of Grade 2 in severity, which started on the day of dosing and resolved in 9 days. There were no laboratory values outside of normal range or clinically significant changes post baseline observed.

Of the 8 participants enrolled in COMET-PACE, 5 (63%) experienced any AE. None of the AEs were considered related to study intervention by the investigator and none led to withdrawal from the study. All the AEs were non serious and of Grade 1 or Grade 2 severity. There were no SAEs or deaths

reported. Of the 4 participants who reported AEs after dosing, the preferred terms of AEs (generalised as deemed necessary to prevent the reidentification of study participants) were:

- 6 to <12-year age group: worsening of background medical condition and infective complication of immunosuppression, aspartate aminotransferase increase, alanine aminotransferase increases and blood creatinine increase (all in 1 participant) with complex medical history and cytopenias, hypokalemia, neutropenia, hypo-gammaglobulinemia, thrombocytopenia, thrombotic microangiopathy, hypertension, immunocompromised state, seizure disorder, and obesity)
- 12 to <18 years age group: contusion (1 participant), gastroenteritis viral (1 participant), congenital heart disease with complications (1 participant)

No other significant AEs were reported including adverse events of special interest such as IRR within 24 hours post dose, HSR at any time post dose, events suggestive of antibody dependent enhancement (ADE) or immunogenicity related adverse events. There were no reports of MIS-C in this study.

Grade shifts in laboratory parameters, including increases to Grade 3 and 4, were noted for post-baseline versus baseline values in hematology and clinical chemistry parameters and reflected complex medical history or participants' comorbidities.

No evidence of treatment affected changes in vital signs were observed. There were no baseline or post baseline changes in ECG considered clinically significant by the investigator.

PRAC Rapporteur assessment comment:

The MAH enrolled 11 participants <18 years old in clinical studies, including 8 participants ≥12 to <18 years old. Of these 8 participants, 7 participants received 500 mg sotrovimab IV [the approved posology].

The presented data from clinical studies do not suggest new safety concerns for patients ≥12 to <18 years old: the investigator assessed all reported adverse events as unrelated to sotrovimab, and all adverse events (PTs) were non-serious and occurred only once. The CHMP assessment report within this procedure also states that the safety profile of sotrovimab in the few adolescent participants was consistent with the known safety profile of the drug [in adults], based on data from adolescent participants in studies COMET-PACE and COMET-TAIL.

Post marketing data

Cumulatively, by 19 August 2023, 57 post marketing reports have been received in the MAH's safety database for use of sotrovimab in children (<18 years old). Of these, 21 cases were from literature, 35 were spontaneous cases and the remaining one was a post-marketing surveillance case.

Of these 57 reports, 45 cases had age provided and the remaining 12 cases indicate that report is for a child but age is not specified. For these 12 cases, 11 cases did not have any adverse events reported (the PTs include off label use and product prescribing issue). The remaining case was for a child who received sotrovimab off label (hypoxic COVID-19 with symptoms onset more than 5 days). Concurrent comorbidities included acute renal failure, methemoglobinemia and the patient was receiving continuous veno-venous hemofiltration. Concomitant medications included anakinra, dexamethasone, anidulafungin, posaconazole, vancomycin, meropenem and methylthioninium chloride. The patient deteriorated, experienced hypotension requiring inotropic support, and hyperlactacidemia, had to be

admitted to ICU, suffered pulmonary hemorrhage and eventually died. It was unknown if an autopsy was performed.

Of the 45 cases with age provided, 13 cases were for adolescents (12 to <18 years old) and 32 cases were for children <12 years old (range 2 months to 11 years).

For cases received for adolescent patients, majority of the adverse events reported are consistent with known safety profile of sotrovimab and include PTs of drug hypersensitivity, lip oedema, rash, urticaria, pruritus, erythema, hypersensitivity and swelling (one event each). The remaining adverse events reported included PTs of paresthesia, vertigo, vomiting, hyperglycemia and alopecia (one event each).

Of the 32 cases received for children <12 years old, 30 cases did not have any adverse events reported (the PTs include off label use, product use issue, or product prescribing issue). The remaining two cases described non serious event of infusion related reaction and urticaria with outcome resolved and serious event of encephalopathy with significant comorbidities (ruptured spleen and T cell acute leukemia) and the following other medications that were initiated as early as day after sotrovimab infusion: cytarabine, methotrexate, vincristine sulfate, Oncaspar, nelarabine, mitoxantrone hydrochloride and venetoclax.

PRAC Rapporteur assessment comment:

Cumulatively, the MAH retrieved 57 post marketing case reports in children from its safety database. Of these, 13 cases included a confirmed age group of ≥12 to <18 years old.

The presented post marketing case reports do not suggest new safety concerns for patients ≥12 to <18 years old: all reported adverse events (PTs) in adolescents occurred only once, and most events reflect hypersensitivity reactions, which are known to occur with sotrovimab. The reported adverse events for other paediatric age groups or paediatric patients with an unknown age, that may refer to adolescents, mostly concern cases reporting off label use as the only event (41/44 retrieved cases).

In addition, published data on use of sotrovimab in children have been reviewed. There were 13 articles identified which are listed in the Table 18 of the RMP [not replicated in this assessment report]. In summary, these publications describe use of sotrovimab in approximately 200 paediatric patients and of these approximately 90 patients were less than 12 years old. Where dosing of sotrovimab was specified, it was either at approved dose of 500mg or weight adjusted for weight below 40kg. Overall, the data reported provides evidence that sotrovimab treatment was well tolerated in these paediatric patients.

PRAC Rapporteur assessment comment:

The presented literature articles, including 75 – 100 adolescent participants, do not suggest new safety concerns for patients ≥12 to <18 years old: most articles report that no (severe) adverse reactions occurred and, if reported, the adverse events or reactions occurred only once.

In summary, available clinical data, although limited (8 adolescent participants), together with additional supporting post marketing data (over 100 adolescent patients) provides sufficient evidence that treatment of adolescents with 500mg IV dose of sotrovimab is well tolerated and the safety profile appears to be similar to the safety profile established in adults. Therefore, use in children ≥12 to <18 years old is no longer considered to meet the criteria for inclusion as a missing information.

The MAH considers that routine risk minimization measures via sotrovimab labelling (SmPC Section 4.2, 4.8 and 5.2) are sufficient. Routine PV through routine signal detection activities and PSUR assessments of use of sotrovimab in children is also considered sufficient.

Owing to the obligation to fulfil paediatric regulatory requirements, the COMET-PACE study remained on pause since 28 March 2022 due to a decrease in in vitro neutralization of sotrovimab against circulating Omicron BA.2 SARS-CoV-2 variants and awaiting a permissive change in the variant landscape. However, as no significant change in the variant landscape was forthcoming since the study pause, the MAH took the decision to close the study early on 14 June 2023. Since current usage of sotrovimab in general and including the paediatric population is relatively low, an observational study is not considered a viable option to collect further information on this patient population. Moreover, since use in children ≥12 to <18 years old is no longer considered to meet the criteria for inclusion as a missing information no additional PV is proposed.

PRAC Rapporteur assessment comment:

The currently approved sotrovimab RMP includes "Use in children ≥12 to <18 years old" as missing information safety concern. At the time of regulatory approval, only adult patients were included in the sotrovimab clinical program. Although the indication includes patients 12 years old whose weight is at least 40 kg, it was based on adult PK data extrapolation. To address "Use in children ≥12 to <18 years old", the sotrovimab RMP includes study COMET-PACE as a category 3 additional pharmacovigilance activity: *an open-label study to evaluate pharmacokinetics, pharmacodynamics and safety following a single dose of sotrovimab in paediatric patients with mild to moderate COVID-19 at high risk of disease progression*.

Following the MAH's decision to terminate the COMET-PACE study, the MAH proposes to delete "Use in children ≥12 to <18 years old" as missing information from the RMP. The assessor agrees that "Use in children ≥12 to <18 years old" can be deleted as missing information safety concern based on:

1. Safety data in adolescents from clinical studies [7 participants with the approved posology] and post marketing reports including literature [>100 cases] do not show a difference in sotrovimab safety profile in adolescents compared to the safety profile in adults.
2. A possibly different safety profile between adolescents and adults cannot be explained by a difference in pharmacokinetic properties of sotrovimab in these age groups: the CHMP assessment report states that the MAH demonstrated that the pharmacokinetic properties of sotrovimab in adolescents are comparable to those in adults. (At the time of approval, pharmacokinetic properties in adolescents had not been evaluated, as adolescents were excluded from clinical trials.)

Therefore, "Use in children ≥12 to <18 years old" is considered sufficiently characterised.

As a consequence of the above, the MAH also deleted the topic use in children ≥12 to <18 years old from sub section SVII.3 Details of important identified risks, important potential risks, and missing information.

PRAC Rapporteur assessment comment:

This is acceptable, in line with deleting "Use in children ≥12 to <18 years old" as safety concern.

10.2. Summary of the safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy ~~Use in children ≥12 to <18 years old~~

Considering the data in the safety specification, the safety concerns listed above are appropriate.

10.3. Pharmacovigilance plan

Routine pharmacovigilance activities

Treatment failure due to emerging variants

Treatment failure due to emerging variants

Data monitoring, including systematic, and proactive review of the emerging data will be done from all available data sources including but not limited to the following:

- evaluation of new and cumulative non-clinical data (antiviral activity and viral resistance) on new variants found in the sotrovimab epitope
- evaluation of new and cumulative post-baseline epitope variants detected in clinical studies among patients who received sotrovimab, when possible
- ~~evaluation of spontaneous reports via targeted follow up questionnaire for lack of efficacy including information for variant lineage~~
- evaluation of literature reports
- evaluation of studies conducted by public health authorities

Cumulative data from the reviews will be summarized in a dedicated section of the PSUR. If the review of data leads to an impact on the benefit risk profile of sotrovimab appropriate variation (including the data, a benefit-risk discussion and any warranted product information updates) will be submitted to the agency within one month.

PRAC Rapporteur assessment comment:

"Treatment failure due to emerging variants" is not listed as a safety concern in the sotrovimab RMP, however a follow-up questionnaire is in place to address this topic. Monitoring treatment failure due to emerging variants through *evaluation of spontaneous reports via the targeted follow-up questionnaire for lack of efficacy including information for variant lineage*, even if not included as safety concern, is in line with other monoclonal antibodies indicated for COVID-19. In this variation procedure, the MAH proposes to delete the targeted follow-up questionnaire for lack of efficacy reports from Part III and Annex 4 of the RMP. In the rationale for submitting an updated RMP, the MAH explains that "*based on the limited data received via follow-up questionnaire no new information has been received to what is being acquired from ongoing in vitro testing and literature review*".

The assessor agrees that the questionnaire included in Annex 4, can be removed from the RMP. As described in the currently approved product information, SARS-CoV-2 (sub) variants that emerged since Omicron BA.2 show reduced susceptibility to sotrovimab. In December 2022, EMA's Emergency Task Force cautioned that monoclonal antibodies currently authorised for COVID-19 [such as sotrovimab] are unlikely to be effective against emerging strains of SARS-CoV-2. Given sotrovimab's reduced ability to neutralise emerging SARS-CoV-2 sub variants, treatment failure may be considered an expected event and that was also the reason that it was agreed to stop the COMET-PACE study. Considering the current knowledge on SARS-CoV-2 sub variant neutralisation by sotrovimab and that the MAH will continue to evaluate sotrovimab effectiveness through non-clinical data and literature reports, the added value of retrieving information through the follow-up questionnaire for lack of efficacy becomes questionable. Additionally, as the MAH commented, data collected through the targeted follow-up questionnaire has been limited [possibly due to low response rate or lack of information on SARS-CoV-2 sub variants]. The decreased exposure to sotrovimab, as described in the last sotrovimab PSURs, will likely also lead to less (information from) spontaneously reported cases, including cases reporting lack of efficacy.

Additional pharmacovigilance activities

In sections *Additional pharmacovigilance activities* and *Summary table of additional pharmacovigilance activities*, the MAH deleted reference to study COMET-PACE, addressing safety concern "Use in children ≥12 to <18 years old", and proposed a change in the planned date for the COVID-PR [addressing the safety concern "Use in pregnancy"] final study report,:

Milestone	Planned date
Start of data collection	31/12/2021
End of data collection	31/12/2025
Final report of study results	~~31/12/2026~~31/03/ 2027

PRAC Rapporteur assessment comment:

Following the MAH's decision to terminate study COMET-PACE, the resulting administrative updates [removing COMET-PACE from RMP Part III] are acceptable.

The MAH did not justify the change in planned date for the final report of the study COVID-PR. However, the proposed change is acceptable, as the MAH is not the sponsor of this study and the previous date coincided with the date for end of data collection.

10.4. Risk minimisation measures

The MAH updated Part V of the RMP by removing all references to the previously recognised safety concern "Use in children ≥12 to <18 years old".

PRAC Rapporteur assessment comment:

The proposed updates to Part V of the RMP are acceptable, as these result from deleting "Use in children ≥12 to <18 years old" as missing information from the RMP, which was discussed earlier and considered acceptable.

10.5. Elements for a public summary of the RMP

The elements for a public summary of the RMP do not require revision following the conclusion of the procedure.

10.6. Annexes

The annexes have been updated appropriately, in line with the other proposed changes in the RMP.

10.7. Overall conclusion on the RMP

The changes to the RMP are acceptable.

The MAH is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

11. Changes to the Product Information

Sections 4.2, 4.8 and 5.2 of the SmPC are updated with the new information on paediatric population based on final results from study COMET-PACE (215226).

For details, please see attachment 1(SmPC)

12. Request for supplementary information

12.1. Major objections

Clinical aspects

None.

12.2. Other concerns

Clinical aspects

The MAH is requested to update the SmPC. The key PK results from the PK studies in adolescents (COMET-PACE) should be provided as suggested in the EMA guideline, A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS (SmPC): Results of pharmacokinetic studies in the different paediatric age groups should be summarised, with a comparison to adults if available. Furthermore, in the SmPC it should be noted that the paediatric study was discontinued.

13. Assessment of the responses to the request for supplementary information

13.1. Other concerns

Clinical aspects

Question

The MAH is requested to update the SmPC. The key PK results from the PK studies in adolescents (COMET-PACE) should be provided as suggested in the EMA guideline, A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS (SmPC): Results of pharmacokinetic studies in the different paediatric age groups should be summarised, with a comparison to adults if available. Furthermore, in the SmPC it should be noted that the paediatric study was discontinued.

Summary of the MAH's response

The MAH accepts the Rapporteur's requests to update the SmPC to include 1) key PK results from the PK studies in adolescents, and 2) that the paediatric study was discontinued. Of note, commentary comparing the paediatric and adult data was provided in the initial SmPC within this procedure.
The revised product information is attached and has been updated.

Assessment of the MAH's response

The SmPC, section 5.2, has been updated by the MAH as requested. The issue is considered resolved.

Conclusion

☒No need to update overall conclusion and impact on benefit-risk balance

14. References:

(1) Case JB et al, Resilience of S309 and AZD7442 monoclonal antibody treatments against infection by SARS-CoV-2 Omicron lineage strains. Nat Commun. 2022 Jul 2;13(1):3824. doi: 10.1038/s41467-022-31615-7.

(2) Uraki R et al, Characterization and antiviral susceptibility of SARS-CoV-2 Omicron BA.2. Nature. 2022 Jul;607(7917):119-127. doi: 10.1038/s41586-022-04856-1.

(3) Driouich J-S et al, In vivo activity of Sotrovimab against BQ.1.1 Omicron sublineage. bioRxiv preprint doi: https://doi.org/10.1101/2023.01.04.522629; this version posted January 4, 2023

(4) Addetia A et al, Therapeutic and vaccine-induced cross-reactive antibodies with effector function against emerging Omicron variants. bioRxiv preprint doi: https://doi.org/10.1101/2023.01.17.523798; this version posted January 17, 2023

(5) Bruel T et al, Longitudinal analysis of serum neutralization of SARS-CoV-2 Omicron BA.2, BA.4, and BA.5 in patients receiving monoclonal antibodies. Cell Rep Med. 2022 Dec 20;3(12):100850. doi: 10.1016/j.xcrm.2022.100850.

(6) Hérate C et al, Sotrovimab retains activity against SARS-CoV-2 Omicron variant BQ.1.1 in a non-human primate model. bioRxiv preprint doi: https://doi.org/10.1101/2023.02.15.528538; this version posted February 15, 2023.

(7) Bruel T et al, Antiviral activities of sotrovimab against BQ.1.1 and XBB.1.5 in sera of treated patients. medRxiv [Preprint]. 2023 May 30:2023.05.25.23290512. doi: 10.1101/2023.05.25.23290512.

(8) ETF warns that monoclonal antibodies may not be effective against emerging strains of SARS-CoV-2. EMA statement 09.12.2022.

https://www.ema.europa.eu/en/news/etf-warns-monoclonal-antibodies-may-not-be-effective-against-emerging-strains-sars-cov-2#:~:text=Contacts-,ETF%20warns%20that%20monoclonal%20antibodies%20may%20not%20be%20effective,strains%20of%20SARS%2DCoV%2D2&text=EMA's%20Emergency%20Task%20Force%20(ETF,of%20SARS%2DCoV%2D2.

(9) WHO living guideline for COVID-19 therapeutics (v13).

https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2023.1

Assessed 13.01.2023