EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2024
EMA/309000/2024
Human Medicines Division

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

Xevudy

Sotrovimab

Procedure no: EMEA/H/C/005676/P46/010

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	27 May 2024	27 May 2024
☐	CHMP Rapporteur Assessment Report	01 July 2024	01 July 2024
☐	CHMP members comments	15 July 2024	15 July 2024
☐	Updated CHMP Rapporteur Assessment Report	18 Jul 2024	N/A
☒	CHMP adoption of conclusions:	25 July 2024	25 July 2024

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1. Introduction

On 24 April 2024, the MAH submitted a completed paediatric study for Xevudy, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The study includes one patient who was between 12 and 18 years of age.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that XEVUDY General Drug Use Investigation (SARS-CoV-2 Infection) is a stand alone study. It is not part of the agreed sotrovimab PIP (P/0235/2023).

2.2. Information on the pharmaceutical formulation used in the study

In the study "XEVUDY General Drug Use Investigation (SARS-CoV-2 Infection)", the commercial formulation of sotrovimab 500 mg concentrate for solution for infusion was used in accordance with the Special Approval in Emergency in Japan where the study was conducted.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- XEVUDY General Drug Use Investigation (SARS-CoV-2 Infection)

2.3.2. Clinical study

XEVUDY General Drug Use Investigation (SARS-CoV-2 Infection)

Description

The above mentioned was a prospective cohort study that collected information on the occurrence of ADRs and progression to severe SARS-CoV-2 infection among COVID-19 patients at risk of progression to severe SARS-CoV-2 infection, who did not require oxygen therapy at baseline and who received sotrovimab for the first time. The study's primary endpoint was the occurrence of ADRs, which was evaluated among in- and out-patients, and secondary endpoint was the percentage of progressors, and distribution and change of vital signs and clinical symptoms, which was evaluated among in-patients only. The study population consisted of in- and out-patients of all ages with SARS-CoV-2 infection enrolled within 14 days of sotrovimab administration.

Methods

Study participants

Among patients with SARS-CoV-2 infection which is Xevudy's indication, patients who have risk factors for progression to severe SARS-CoV-2 infection and do not require OA for SARS-CoV-2 infection at baseline and receive Xevudy for the first time were included in the study.

Treatments

All of 635 patients included in safety analysis received Xevudy as a single 500-mg intravenous infusion in line with the recommendations in the SmPC. The intravenous flow rate was "100 mL/h (50mL/30 min)" in 253 patients (39.8%) and "200 mL/h (100mL/30min)" in 382 patients (60.2%).

Objective(s)

The objective of this study was to collect and evaluate the following information about safety and clinical outcomes of Xevudy in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who have risk factors for progression to severe SARS-CoV-2 infection and do not require oxygen administration (OA) in realworld clinical practice.

Outcomes/endpoints

Primary endpoint: To understand the occurrence status of adverse drug reactions (ADRs)

Secondary endpoint: To confirm the percentage of progressors, and distribution and change of vital signs and clinical symptoms

Percentage of progressors: Among the patients who can be evaluated for the following items a) to e) from Day 1 to the end of observation period, the following patients are defined as a "progressor", if applicable to any of a) to e). The percentage of progressors is the percentage of patients evaluated as a "progressor" in the clinical outcome analysis population.

a) Patients who receive oxygen at a rate of>5 liters/min as a concomitant therapy for exacerbation of SARS–CoV–2 infection

b) Patients who receive any of the following as a concomitant therapy for exacerbation of SARS–CoV–2 infection

- Non-invasive positive pressure ventilation (NPPV).

- Invasive mechanical ventilation (IMV)

- Extracorporeal membrane oxygenation (ECMO)

c) Patients who require admission to HCU or ICU for exacerbation of SARS–CoV–2 infection in study sites with HCU or ICU

d) Patients who are transferred to another hospital for exacerbation of SARS–CoV–2 infection to receive any of a) to c) mentioned above

e) Patients who die from exacerbation of SARS–CoV–2 infection

Sample size

630 patients enrolled, 1 < 18 years of age

Randomisation and blinding (masking)

Statistical Methods

Results

Participant flow

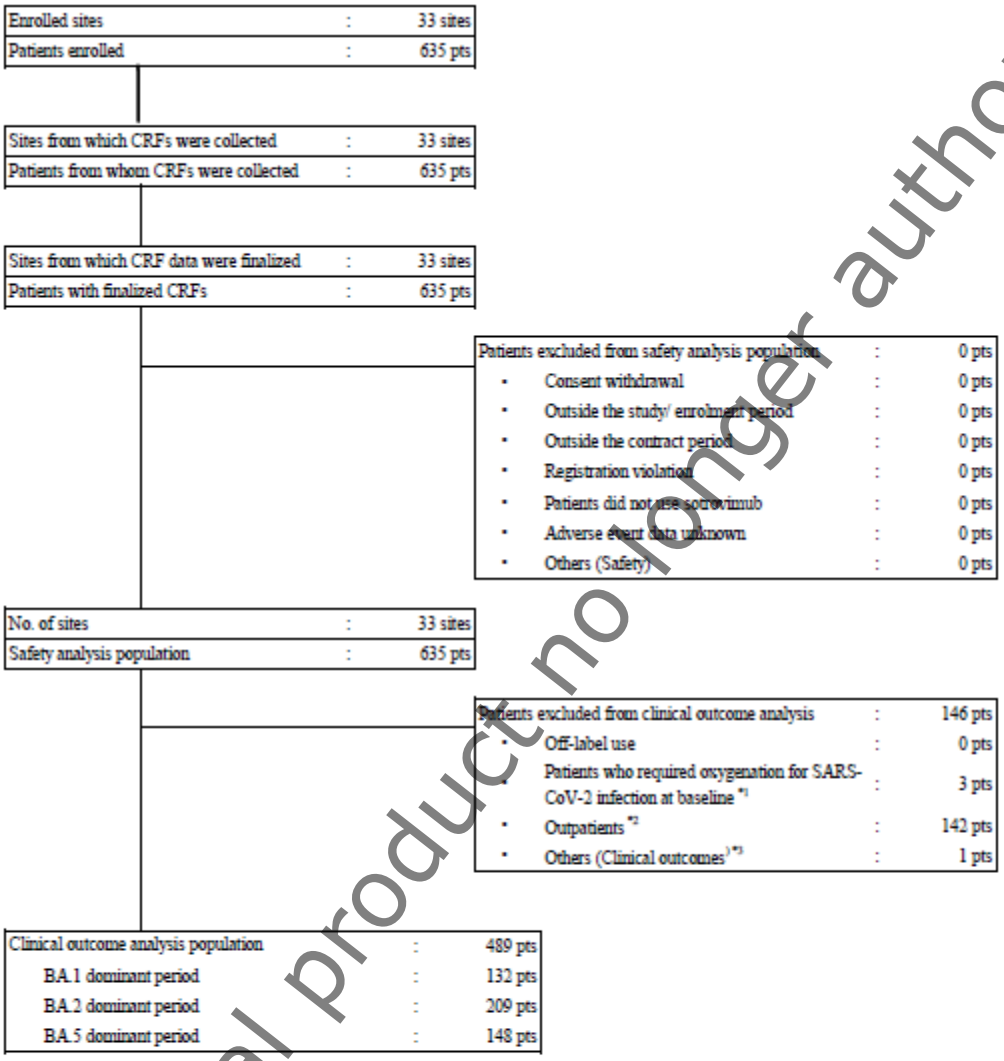

Figure 1 Patient Disposition

*1: These patients were excluded from the clinical outcome analysis because the package insert of the drug states that the drug should be administered to patients who do not require oxygenation.

*2: These patients were excluded from clinical outcome analysis, as no data on clinical outcome evaluation were collected from them.

*3: This patient was temporarily discharged from hospital during the observation period, and we could not collect data on clinical outcome evaluation during the temporary hospital discharge period, therefore, we excluded this patient from clinical outcome analysis. This patient experienced no events which meet the definition of "progressors".

Baseline data

Of the 635 patients included in the safety analysis, 343 patients (54.0%) were male and 292 patients (46.0%), including one pregnant woman (third trimester) and one breast-feeding woman (breast

milk), were female. The mean ± standard deviation (SD) of age was 67.0 ± 18.5 (years), and the mean ± SD of body weight was 61.12±17.15(kg). The hospitalization status at baseline was 493 patients (77.6%) for inpatients and 142 patients (22.4%) for outpatients, and the mean ± SD of the observation period was 7.5 ± 7.3 (days) (inpatients: 9.4 ± 7.2 (days), outpatients: 1.0 ± 0.0 (days)). The types of risk factors for progression to severe SARS-CoV-2 infection at baseline (duplicates included) were, in decreasing order, 55 years of age or older in 479 patients (75.4%), diabetes mellitus requiring medications in 121 patients (19.1%), and chronic renal disorder (eGFR <60 mL/min/1.73m2) in 74 patients (11.7%). "Other" major risk factors included "hypertension" in 96 patients (15.1%), "smoking" in 68 patients (10.7%), "immunosuppression" (due to comorbidities or medications) in 33 patients (5.2%), "malignant tumour" in 35 patients (5.5%), and "dyslipidaemia" in 29 patients (4.6%).

Severity of SARS-CoV-2 infection at baseline was "mild" in 506 patients (79.7%), "moderate I (no respiratory failure)" in 125 patients (19.7%), and "moderate II (with respiratory failure)" in 4 patients (0.6%). The mean ± SD of days from the onset date of SARS-CoV-2 symptoms to the date of Xevudy administration was 2.2 ± 1.7 (days). While 424 patients (66.8%) were "not tested" for SARS-CoV-2 variants, 37 patients (5.8%) were "tested" and the test results in 174 patients (27.4%) were "unknown". In the 37 patients who were tested, the types of SARS-CoV-2 variants were Omicron BA.1 in one patient, BA.2 in 26 patients, and BA.4/5 in 10 patients. Vaccination against SARS-CoV-2 infection was reported for 246 patients (38.7%); the number of vaccine doses was "one dose" in 18 patients (2.8 %), "two doses" in 105 patients (16.5%), "three doses" in 116 patients (18.3%), "four doses" in 6 patients (0.9%), and "five doses" in 1 patient (0.2%). Prior to treatment with Xevudy, 22 patients (3.5%) had used other SARS-CoV-2 medications, inclusive of "antivirals" in 20 patients (3.1%) and "immunosuppressant medications or modulators" in 2 patients (0.3%). Seventy-four patients (11.7%) used concomitantly SARS-CoV-2 medications other than Xevudy, inclusive of "antivirals" in 70 patients (11.0%) and "immunosuppressant medications or modulators" in 16 patients (2.5%).

Efficacy results

In 489 patients included in clinical outcome analysis population, 1.2% (6/489 patients) met the definition of progressors. The type of events defined as progressors was "oxygen at a rate of >5 liters/min" in 1.0% (5/489 patients) and "death due to exacerbation of SARS-CoV-2 infection" in 0.4% (2/489 patients) (duplicates included). All 6 progressors were 70 years of age or older, and 5 of the 6 patients were ranked as moderate I and 1 patient of the 6 patients was ranked as mild in severity at baseline. Four of the 6 patients had 2 or more risk factors and 2 of the 6 patients had one factor for progression to severe SARS-CoV-2 infection at baseline. Furthermore, 5 patients of the 6 patients were not undergoing oxygenation for a disease other than SARS-CoV-2 infection at baseline and one of the 6 patients was undergoing oxygenation (4.5 liters/min) for a disease other than SARS-CoV-2 infection at baseline.

Although it is not possible to compare two studies directly because of the differences in patient characteristics and study methods, etc., the percentage of progressors in this study, 1.2% (6/489 patients), was similar to 1.3% (7/528 patients), the percentage of patients who reported progression to severe or life-threatening respiratory symptoms due to SARS-CoV-2 infection by Day 29 of Xevudy administration as a secondary endpoint for clinical outcomes in the overseas phase II/III clinical trial (COMET–ICE) conducted before approval.

Distribution and change of vital signs and clinical symptoms were assessed in 489 patients and no subgroup analysis by age was performed.

The percentage of non-progressors (patients who did not experience events that met the definition of "progressors" during the observation period) was 98.8% (483/489 patients). Patient outcomes at the end of observation for non-progressors were 6.5% (32/489 patients) for "hospitalized," 62.8% (307/489 patients) for "discharged/transferred as discharge criteria were met," and 29.4% (144/489 patients) for "discharged/transferred for reasons (the shortage of hospital beds, etc.) except for the above." The mean ± SD length of hospitalization was 28.2 ± 4.6, 9.7 ± 4.5, and 4.3 ± 4.7 (days), respectively.

Because the number of progressors was limited to six patients in this study, multivariable analysis was not performed, and the factors affecting the clinical outcomes were investigated in the results of univariate analysis.

The factors which satisfy the criterion "A point estimation of an unadjusted risk ratio is greater than 2 or less than 0.5 and asymptotic 95% CI does not cross 1" were investigated. factors fulfilling the criterion were "body temperature (°C) at baseline" and "clinical symptoms at baseline".

No information regarding clinical outcomes in patients after receiving vaccination against SARSCoV-2 infection was obtained by the approval date of Xevudy; however, in this study, the percentage of progressors was confirmed based on the presence or absence of a history of SARS-CoV-2 vaccination. The results showed that the percentage of progressors in SARS-CoV-2 unvaccinated patients and vaccinated patients were 0.9% (1/114 patients) and 0.5% (1/193 patients) and the point estimate of the unadjusted risk ratio of the percentage of progressors in patients "without" a history of SARS-CoV-2 vaccination to that in patients "with" a history of SARS-CoV-2 vaccination was 1.693 (95% CI: 0.107 - 26.806), which did not satisfy the criterion.

The percentage of progressors in "≤37.5" and ">37.5" were 0.3% (1/315 patients) and 2.9% (5/173 patients) and the percentage of progressors was higher in patients whose baseline body temperature was ">37.5" than in patients whose baseline body temperature was "≤37.5" (point estimate of unadjusted risk ratio, 9.104; 95% CI, 1.072 - 77.302). Of 5 patients whose body temperature (°C) was ">37.5" at baseline and who met the definition of progressors, 4 were patients aged 80 years or older.

The percentage of progressors in the patients without and with clinical symptoms were 4.0% (4/100 patients) and 0.5% (2/388 patients) and the percentage of progressors was low in patients who answered with "yes", compared with in those with "no" (point estimate of unadjusted risk ratio: 0.129, 95% CI: 0.024-0.694). The number of progressors in clinical outcome population was limited to 6 and there is a stratified bias between patients without and with clinical symptoms at baseline in number like 100 and 388 patients, respectively, therefore, it was considered that it might be affected by the bias between these two groups in number.

Safety results

Data on AEs including ADRs and events of special of interest were collected. In this study an event of special interest was "serious hypersensitivity such as anaphylaxis, infusion reactions". Serious AE was defined as any AE that was any of the following:

1) resulted in death

2) was life-threatening

3) required in-patient hospitalization

4) resulted in persistent or significant disability/incapacity

5) was a congenital abnormality/birthdefect;

6) was any other event or reaction judged to be medically important. ADRs were defined using the appropriate lowest level terms from the Japanese version of the MedDRA.

635 patients were enrolled and included in the safety analysis; of them 634 were adults (18 years old and older) and 1 patient was between 12 and 18 years of age. There were no AEs reported in the paediatric patient.

Occurrence of ADRs by age group is presented in *Table 1*. All ADRs occurred in adult patients (18 years old and older).

Table 1. Number of patients with ADRs by age groups

Age group	Number of patients investigated	Number (%) of patients with ADRs
<12	0	0
12≤ - <18	1	0
18≤ - <65	251	7 (2.8%)
65≤	383	3 (0.8%)
Total	635	10 (1.6%)

ADR = adverse drug reaction
Source: Table 1-2 and Table 6 of the XEVUDY General Drug Use-Investigation (SARS-CoV-2 Infection) CSR

In the 635 patients included in safety analysis, 10 patients were reported as having ADRs, and the percentage of patients with ADRs was 1.6% (10/635 patients). The reported ADRs were "pyrexia" in 1.1% (7/635 patients), "COVID-19 pneumonia" in 0.3% (2/635 patients), "dyspnoea", "respiratory disorder", "oropharyngeal pain" and "eczema" in 0.2% each (1/635 patients) in decreasing order, and all of the outcomes were "recovered" or "recovering" except one patient whose outcome was "fatal".

The patient with "respiratory disorder" whose outcome was "fatal" had "pneumonia bacterial" as a comorbidity at baseline, and the severity of SARS-CoV-2 infection at baseline was "moderate I (no respiratory failure)". COVID-19 pneumonia which occurred before Day1 was exacerbated on Day 2 of Xevudy administration and was recovered on Day 7, but "respiratory disorder" occurred with exacerbation of comorbid pneumonia bacterial on Day 10, and the patient died on Day 12. As a factor suspected to be related to "respiratory disorder" other than Xevudy, worsened pneumonia bacterial was reported by the investigator.

In addition, two patients with serious ADRs were reported in 635 patients included in safety analysis. By the type of ADRs, the most frequently reported ones were "COVID-19 pneumonia"*,** 0.3% (2/635 patients), "dyspnoea"**, "respiratory disorder"*, and "oropharyngeal pain"** 0.2% (1/635 patient each) (*, **: 1 patient each).

Although direct comparisons may not be appropriate due to differences in patient characteristics and study methods, 1.6% (10/635 patients), the percentage of patients with ADRs in this study, was similar to 1.5% (8/523 patients) (*Table 3*) reported in the Xevudy arm of the overseas phase II/III clinical trial (COMET–ICE) conducted before approval. Common ADRs reported in this study were events that were assumed to be related to symptoms and progression of the primary disease (infections due to SARS-CoV-2), and no new safety concerns regarding the types and seriousness of ADRs were currently observed.

Table 2 shown the occurrence of ADRs in the study and for comparison the ADRs from the phase II/III clinical trials are displayed in *Table 3* . *Table 4* shows ADRs by age group.

Table 2. occurrence of ADR

Safety analysis population

	Total		Serious	
No. of patients investigated	635			
No. of patients with ADRs	10		2	
Percentage of patients with ADRs (%)	1.6		0.3	
Type of ADRs	No. of patients with ADRs by type (Percentage of patients with ADRs)			
General disorders and administration site conditions	7	(1.1)	0	(0.0)
Pyrexia	7	(1.1)	0	(0.0)
Infections and infestations	2	(0.3)	2	(0.3)
COVID–19 pneumonia	2	(0.3)	2	(0.3)
Respiratory, thoracic and mediastinal disorders	2	(0.3)	2	(0.3)
Dyspnoea	1	(0.2)	1	(0.2)
Respiratory disorder	1	(0.2)	1	(0.2)
Oropharyngeal pain	1	(0.2)	1	(0.2)
Skin and subcutaneous tissue disorders	1	(0.2)	0	(0.0)
Eczema	1	(0.2)	0	(0.0)

MedDRA/J (26.0)

Table 3. Occurrence Status of ADRs/Infections in the overseas phase II/III clinical trial (COMET-ICE) conducted before approval

Name of Investigation/Study: Overseas Phase II/III Clinical Trial (COMET-ICE)

	Status up to the time of approval	
Safety analysis population	523	
No. of patients with ADRs	8	
Percentage of patients with ADRs	1.5%	
Type of ADRs	No. of patients with ADRs by type (Percentage of patients with ADRs)	
Skin and subcutaneous tissue disorders	2	(0.4%)
Rash	1	(0.2%)
Skin reaction	1	(0.2%)
Gastrointestinal disorders	1	(0.2%)
Nausea	1	(0.2%)
General disorders and administration site conditions	2	(0.4%)
Infusion site pain	1	(0.2%)
Pain	1	(0.2%)
Investigations	2	(0.4%)
Blood bicarbonate decreased	1	(0.2%)
C-reactive protein increased	1	(0.2%)
Aspartate aminotransferase increased	1	(0.2%)
Blood alkaline phosphatase increased	1	(0.2%)
Gamma-glutamyltransferase increased	1	(0.2%)
Oxygen saturation decreased	1	(0.2%)
Nervous system disorders	2	(0.4%)
Dysgeusia	1	(0.2%)
Headache	1	(0.2%)
Psychiatric disorders	1	(0.2%)
Insomnia	1	(0.2%)

For the 10 patients having at least one ADR reported in 635 patients included in safety analysis, the time from the start of Xevudy administration to the onset of ADRs was investigated for the type of each ADR. A total of 70% (7/10 patients) were observed on the day of Xevudy administration, but no other notable trends were identified.

Table 4. Occurrence Status of ADRs by Age

Safety analysis population

	Age2[years][1)]									
	<55				55≤				Total	
	Total		Serious		Total		Serious		Total	Serious
No. of patients investigated	160				475				635	
No. of patients with ADRs	7		0		3		2		10	2
Percentage of patients with ADRs(%)	4.4		0.0		0.6		0.4		1.6	0.3
Type of ADRs	No. of patients with ADRs (%)				No. of patients with ADRs (%)				No. of patients with ADRs (%)	
General disorders and administration site conditions	6	(3.8)	0	(0.0)	1	(0.2)	0	(0.0)	7 (1.1)	0 (0.0)
Pyrexia	6	(3.8)	0	(0.0)	1	(0.2)	0	(0.0)	7 (1.1)	0 (0.0)
Infections and infestations	0	(0.0)	0	(0.0)	2	(0.4)	2	(0.4)	2 (0.3)	2 (0.3)
COVID-19 pneumonia	0	(0.0)	0	(0.0)	2	(0.4)	2	(0.4)	2 (0.3)	2 (0.3)
Respiratory, thoracic and mediastinal disorders	0	(0.0)	0	(0.0)	2	(0.4)	2	(0.4)	2 (0.3)	2 (0.3)
Dyspnoea	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)	1 (0.2)	1 (0.2)
Respiratory disorder	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)	1 (0.2)	1 (0.2)
Oropharyngeal pain	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)	1 (0.2)	1 (0.2)
Skin and subcutaneous tissue disorders	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	1 (0.2)	0 (0.0)
Eczema	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	1 (0.2)	0 (0.0)

MedDRA/J (26.0)

1) Age was calculated with imputing date and month with 30th Jun uniformity because only the data about the year of patients' birth were collected in this study from the viewpoint of the protection of personal information.

Univariate analysis was carried out by patient characteristics to investigate the possible factors affecting the safety. Because the number of patients with ADRs was limited to 10 in this study, multivariable analysis was not performed, and the factors affecting ADRs were investigated in the results of univariate analysis.

Regarding the occurrence of ADRs by patient characteristics, factors which satisfy a criterion "A point estimation of an unadjusted risk ratio is greater than 2 or less than 0.5 and asymptotic 95% confidence interval (CI) does not cross 1" were investigated. Factors fulfilling the criterion were "age 2" (<55 years of age/≥55 years of age) and "vaccination against SARS-CoV-2".

The percentage of patients with ADRs aged "<55 years" and "≥55 years" were 4.4% (7/160 patients) and 0.6% (3/475 patients) respectively, and the percentage of patients with ADRs aged "<55 years" was high, compared with that aged "≥55 years" (point estimate of unadjusted risk ratio: 6.927, 95% CI: 1.813-26.470). In the occurrence status of ADRs by factor, the percentage of patients with "pyrexia" was high in patients aged "<55 years" as shown in *Table 4*. In patients aged "<55 years" and those aged "≥55 years", the percentage of patients who were never vaccinated against SARS-CoV-2 was 39.4% (63/160 patients) and 13.5% (64/475 patients) respectively, and the percentage of patients aged "<55 years" who were never vaccinated was high. According to an observation study in Japan, it was reported that odds ratio for pyrexia (fever) in SARS-CoV-2 vaccinated patients (2 times and 3 times) against unvaccinated patients were lower than 1 until 240 days after the last vaccination and this suggest that the risk for pyrexia (fever) is lower in vaccinated patients. Based on the above, the difference in percentage of unvaccinated patients aged "<55 years" between "≥55 years" might affect the occurrence status of pyrexia (fever) in these groups, consequently contributed to the difference of percentage of patients with ADRs among patients aged "<55 years" between "≥55 years".

The percentage of patients with ADRs in unvaccinated patients and vaccinated patients were 5.5% (7/127 patients) and 0.4% (1/246 patients), and the percentage of patients with ADRs was higher in patients who had never been vaccinated against SARS-CoV-2 than in patients who had been vaccinated against SARS-CoV-2 (point estimate of unadjusted risk-ratio, 13.559; 95% CI, 1.687 - 109.003). When the occurrence status of ADRs was investigated by factor, patients with no history of SARS-CoV-2 vaccination reported ADRs (pyrexia [6 patients], COVID-19 pneumonia, and respiratory disorder [1 patient each]) that were presumed to be related to the symptoms and progression of the primary disease (SARS-CoV-2 infection).

2.3.3. Discussion on clinical aspects

The clinical outcome analysis comprised 489 patients, of them 488 were adults (18 years old and older) and 1 patient was between 12 and 18 years of age). Among 489 patients included in the analysis, 6 patients (1.2%) met the definition of progressors; all these events occurred among patients

70 years old and older. The paediatric patient included in the clinical outcome analysis did not experience progression of COVID-19.

Among 635 patients included in the safety analysis, 10 patients were reported as having ADRs (1.6%), of whom 2 patients had serious ADRs (one recovered and one with fatal outcome). None of the ADRs occurred in the paediatric patient. Common ADRs reported in this study were events that were assumed to be related to symptoms and progression of infection due to SARS-CoV-2, and no new safety concerns regarding the types and seriousness of ADRs were observed.

Given that there was only one patient below 18 years of age, this study does not provide sufficient safety or effectiveness data to enable a meaningful appraisal of the benefit-risk ratio for sotrovimab in patients under 18 years of age.

3. Rapporteur's overall conclusion and recommendation

Only one paediatric patient was included in the study, thus no conclusions can be drawn.

☒ **Fulfilled:**