



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 October 2024
EMA/509011/2024
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Xevudy

Sotrovimab

Procedure no: EMEA/H/C/005676/P46/011

Note

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



Status of this report and steps taken for the assessment			
Current step	Description	Planned date	Actual Date
☐	Start of procedure	19 Aug 2024	19 Aug 2024
☐	CHMP Rapporteur Assessment Report	7 Oct 2024	4 Oct 2024
☐	CHMP members comments	9 Oct 2024	9 Oct 2024
☐	Updated CHMP Rapporteur Assessment Report	11 Oct 2024	n/a
☒	CHMP adoption of conclusions:	17 Oct 2024	17 Oct 2024

Medicinal product no longer authorised

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1. Introduction

On 24 April 2024, the MAH submitted a study report 218554 in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The 218554 study report is being submitted to comply with the requirements of Article 46 of the Paediatric Regulation (EC) No 1901/2006. The study is not part of the agreed paediatric investigation plan (PIP) for sotrovimab (EMA-002899-PIP01-20-M02).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that 'The Impact of Early Treatment of COVID-19 with Sotrovimab on Post-Acute COVID-19 Syndrome: An Analysis of National COVID Cohort Collaborative (N3C) Data' is a stand alone study.

Xevudy is currently approved in the EU for the indication treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19.

2.2. Information on the pharmaceutical formulation used in the study

The formulation used in this study is the concentrate for solution for infusion (sterile concentrate) as approved in the US.

Sotrovimab is a sterile, preservative-free, clear, colourless or yellow to brown solution with a pH of approximately 6 and an osmolality of approximately 290 mOsm/kg.

The product is intended for intravenous infusion after dilution.

Assessor's comments

This product formulation is the already approved one for the age group and thus suitable for the use in children.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Study number 218554; The Impact of Early Treatment of COVID-19 with Sotrovimab on Post-Acute COVID-19 Syndrome: An Analysis of National COVID Cohort Collaborative (N3C) Data'.

Clinical study

Study number 218554; The Impact of Early Treatment of COVID-19 with Sotrovimab on Post-Acute COVID-19 Syndrome: An Analysis of National COVID Cohort Collaborative (N3C) Data' is a retrospective cohort study

Description

This was a retrospective cohort study of patients diagnosed with COVID-19 who were at least 12 years old using the N3C database in the US. The study period was from 01 March 2020 to 15 June 2023.

The study elucidates the impact of sotrovimab treatment and the risk of developing post-acute sequelae COVID-19 syndrome (PASC) in high risk patients compared to non-high risk patients.

Methods

Study participants

Cohort 1: high-risk patients with COVID-19 who received treatment with sotrovimab between 26 May 2021 and 05 April 2022 within 10 days of a COVID-19 diagnosis.

Cohort 2 (high-risk, untreated patients):

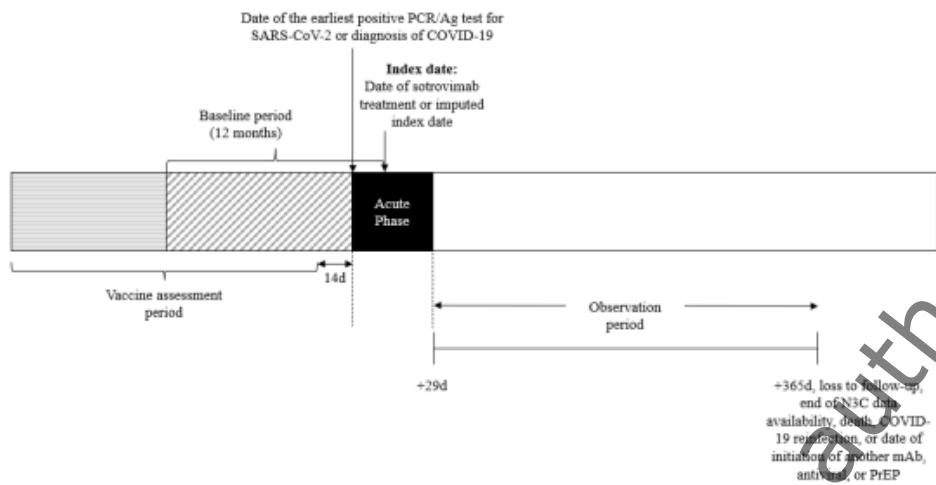
Cohort 2a: high-risk patients with COVID-19 diagnosed between 26 May 2021 and 26 March 2022 who did not receive any treatment for COVID-19 during the acute phase.

Cohort 2b: a random sample of 25% of COVID-19 patients who were high-risk and diagnosed after 01 March 2020 who did not receive any treatment for COVID-19 during the acute phase.

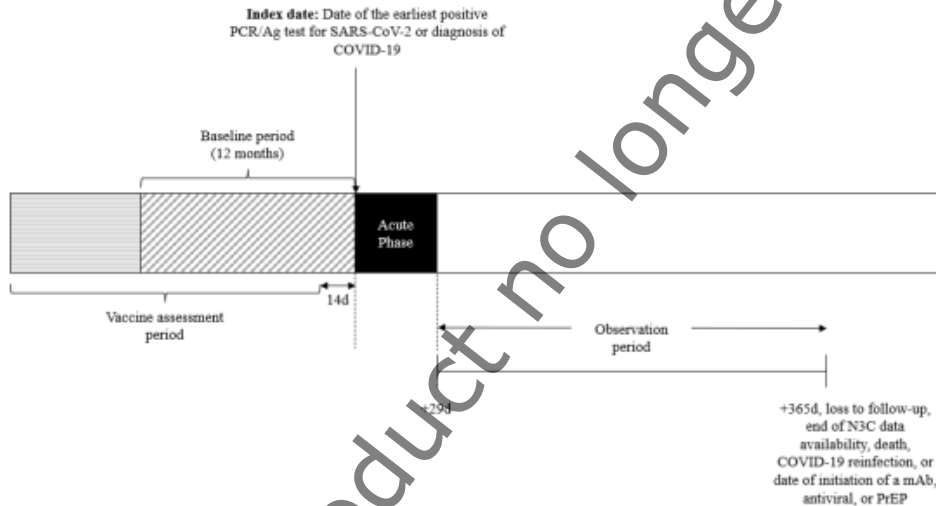
Cohort 3 (non-high-risk, untreated patients): a random sample of 25% of COVID-19 patients who were non-high-risk and did not receive any treatment for COVID-19 during the acute phase.

Figure 1: Study design

Cohort 1 vs. Cohort 2a



Cohort 2b vs. Cohort 3



Criteria for "high-risk" patients where Sotrovimab treatment is indicated:

Table 1: EUA Criteria for Sotrovimab

Variable	Type	Timeframe	Additional information
Age ≥ 65y	Boolean	Index date	Derived from 'age' (see Section 7.4.2)
Obesity or being overweight (Adults with BMI >25 kg/m ² , or if 12 to 17 years of age, have BMI ≥85 th percentile for their age and gender based on CDC growth charts)	Boolean	Baseline period or index date	–
Pregnancy	Boolean	Baseline period or index date	Based on CPT codes for pregnancy-specific procedures (e.g., prenatal visits, ultrasound) [Jones, 2022]
History of CKD (any stage)	Boolean	Baseline period or index date	–
History of diabetes type 1	Boolean	Baseline period or index date	–
History of diabetes type 2	Boolean	Baseline period or index date	–
Immunosuppressive disease (i.e., immunodeficient or immunocompromised)	Boolean	Baseline period or index date	Defined as individuals diagnosed with symptomatic HIV / AIDS, hematologic malignancy, or other immune conditions; individuals diagnosed with solid malignancy, organ transplant, or rheumatologic/inflammatory conditions, all of whom were administered chemotherapy or immune modulators; individuals diagnosed with rheumatologic/inflammatory conditions and administered systemic corticosteroids; or individuals who were administered chemotherapy, immune modulators, or systemic steroids for at least 14 days
Immunosuppressive treatment	Boolean	Baseline period or index date	≥2 drug/exposure events for systemic corticosteroid
			therapy or ≥1 systemic non-corticosteroid immunosuppressants drug exposures
Cardiovascular disease (i.e., congenital heart disease) or hypertension	Boolean	Baseline period or index date	–
Chronic lung disease (i.e., COPD, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)	Boolean	Baseline period or index date	–
Sickle cell disease	Boolean	Baseline period or index date	–
Neurodevelopmental disorders	Boolean	Baseline period or index date	–
A medical-related technological dependence	Boolean	Baseline period or index date	The presence of a procedure occurrence or device exposure event relating to any of the following: respiratory aspirator, gastro- or jejunostomy, mitrofanoff, a nasogastric tube, renal replacement therapy, total parenteral nutrition or ventricular assistance

Abbreviations: BMI: Body mass index; CDC: Center for disease control; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; EUA: Emergency use authorization; ICS: Inhaled corticosteroids.

Treatments

Treatment arm with sotrovimab between 26 May 2021 and 05 April 2022

Objective(s)

Primary Objectives:

Phase 1

Phase 1 primary objective: the objective was to identify and assess multiple definitions of PASC to be used in Phase 2.

Phase 2

Phase 2 primary objective: was to evaluate the risk of PASC in high-risk sotrovimab-treated patients compared to high-risk patients who were not treated with sotrovimab (Cohort 1 vs Cohort 2a).

Phase 2 secondary objectives were:

- 1) to describe baseline demographic and clinical characteristics in all cohorts of interest
- 2) to evaluate the risk of PASC in untreated high-risk patients compared to untreated non-high-risk patients (Cohort 2b vs Cohort 3)
 - To identify baseline predictors of PASC comparing Cohort 2b vs. Cohort 3.

Exploratory Objective:

To conduct analyses in Phase 2 Primary Objective by the following subgroups of interest:

- Adults (age ≥ 18 years).
- Hospitalization and/or intensive care unit (ICU) admission during acute phase.
- Highest risk (i.e., immunocompromised/immunosuppressant treatment, age ≥ 65 years, end stage renal disease, transplant, or late-stage cancer).

Outcomes/endpoints

The study endpoint was PASC.

Based on findings from Phase 1, two definitions of PASC were used in Phase 2 of the study. One definition was selected for the main analysis and the other was used as a sensitivity analysis.

Sample size

Cohort 1 included 9,504 patients (all ages)

Cohort 1 included 53 patients age 12-17 (unweighted sample); 23 were categorized as being in the highest risk subgroup

Cohort 2a included 619,668 patients (all ages)

Cohort 2a included 23,397 patients age 12-17 (unweighted sample); 3149 were categorized as being in the highest risk subgroup

Cohort 2b included 446,425 patients

Cohort 2b included 11,861 patients age 12-17

Cohort 3 included 433,756 patients

Cohort 3 included 47,552 patients age 12-17

Randomisation and blinding (masking)

Not applicable

Statistical Methods

No specific analysis was performed for patients < 18 years.

Results

No specific analysis, describing for example patients' characteristics or clinical outcomes, were performed for patients aged <18 years, as a subgroup analysis of this age group was not included in the original analysis plan.

For the identification of predictors of PASC that were independent of sotrovimab treatment. This analysis showed that, compared to being aged between 18-64 years, being aged <18 years was associated with decreased risk of PASC (HR=0.98, 95% CI [0.96, 0.996], $p = 0.02$).

A similar sensitivity analysis, this time focusing on Cohort 2b and Cohort 3, showed that, compared to being ≥ 18 years, being age <18 years was associated with decreased risk of PASC (HR=0.90, 95% CI (0.88, 0.91), $p = <0.001$). It is important to note that the point estimates for the adolescent groups in these analyses (HR = of 0.98 and 0.90 respectively) are not directly comparable.

Participant flow

Not applicable

Recruitment

The study use patient data from the United States (US) National COVID Cohort Collaborative (N3C) database of patients diagnosed with COVID-19, including high-risk sotrovimab treated patients (Cohort 1), high-risk untreated patients (Cohort 2a [COVID-19 diagnosed between 26 May 2021 and 26 March 2022; not hospitalized between date of COVID-19 diagnosis and index date] and Cohort 2b [a random sample of 25% of patients with COVID-19 diagnosed after 01 March 2020]) and non-high-risk untreated patients (Cohort 3)

Study phase 2:

To conduct analyses in Phase 2 Primary Objective by the following subgroups of interest:

1. Adults (age ≥ 18 years).
2. Hospitalization and/or ICU admission during acute phase.
3. Highest risk (i.e., immunocompromised/immunosuppressant treatment, age ≥ 65 years, end stage renal disease, transplant, or late-stage cancer).

Baseline data

Table 2: Baseline Characteristics among Cohort 1 and Cohort 2a Prior to and After Weighting

	Unweighted sample			ATT weighted sample ¹		
	Cohort 1: High-risk Sotrovimab Cohort N = 9,504	Cohort 2a: High-risk Untreated Cohort N = 619,668	Std Diff (%)	Cohort 1: High-risk Sotrovimab Cohort N = 9,504	Cohort 2a: High-risk Untreated Cohort N = 9,523	Std Diff (%)
Demographic characteristics						
Age at index date (years)						
12 - 17	53 (0.6)	23,397 (3.8)	22.2 *	53 (0.6)	95 (1.0)	5.0
18 - 64	4,938 (52.0)	392,671 (63.4)	23.3 *	4,938 (52.0)	5,045 (53.0)	2.0
≥ 65 years	4,513 (47.5)	203,600 (32.9)	30.2 *	4,513 (47.5)	4,383 (46.0)	2.9
Mean ± SD	60.2 ± 17.3	53.0 ± 19.2	39.2 *	60.2 ± 17.3	60.3 ± 17.2	0.9
Median (IQR)	63.8 (48.0, 73.0)	54.8 (37.7, 68.2)	-	63.8 (48.0, 73.0)	63.0 (49.0, 73.0)	-
Sex, n (%)						
Female	5,648 (59.4)	386,015 (62.3)	5.9	5,648 (59.4)	5,644 (59.3)	0.3
Male	3,855 (40.6)	233,565 (37.7)	5.9	3,855 (40.6)	3,878 (40.7)	0.3
Other/unknown	1 (0.0)	88 (0.0)	0.3	1 (0.0)	1 (0.0)	0.0
Race, n (%)						
White	8,175 (86.0)	464,156 (74.9)	28.3 *	8,175 (86.0)	8,193 (86.0)	0.0
Black or African American	819 (8.6)	92,848 (15.0)	19.8 *	819 (8.6)	819 (8.6)	0.1
Asian or Pacific Islander	165 (1.7)	15,358 (2.5)	5.2	165 (1.7)	165 (1.7)	0.0
Other/unknown ²	345 (3.6)	47,306 (7.6)	17.4 *	345 (3.6)	346 (3.6)	0.0
Ethnicity, n (%)						
Hispanic or Latino	483 (5.1)	52,957 (8.5)	13.8 *	483 (5.1)	483 (5.1)	0.0
Non-Hispanic or Latino	8,826 (92.9)	515,603 (83.2)	30.1 *	8,826 (92.9)	8,843 (92.9)	0.0
Other/unknown	195 (2.1)	51,108 (8.2)	28.3 *	195 (2.1)	197 (2.1)	0.1

Table 3: Baseline Characteristics among Cohort 1 and Cohort 2a to and after ATT Weighting in the Hospitalization

	Unweighted sample			ATT weighted sample ¹		
	Cohort 1: High-risk Sotrovimab Cohort N = 254	Cohort 2a: High-risk Untreated Cohort N = 22,710	Std Diff (%)	Cohort 1: High-risk Sotrovimab Cohort N = 254	Cohort 2a: High-risk Untreated Cohort N = 254	Std Diff (%)
Demographic characteristics						
Age at index date (years)						
12 - 17	1 (0.4)	308 (1.4)	10.3 *	1 (0.4)	2 (1.0)	6.9
18 - 64	170 (66.9)	12,647 (55.7)	23.2 *	170 (66.9)	171 (67.5)	1.2
≥ 65 years	83 (32.7)	9,755 (43.0)	21.3 *	83 (32.7)	80 (31.6)	0.0
Mean ± SD	51.0 ± 20.8	56.7 ± 20.1	27.8 *	51.0 ± 20.8	51.3 ± 20.2	1.5
Median (IQR)	49.0 (31.4, 69.3)	60.7 (38.3, 72.4)	-	49.0 (31.4, 69.3)	52.0 (32.0, 69.0)	-
Sex, n (%)						
Female	187 (73.6)	14,245 (62.7)	23.6 *	187 (73.6)	186 (73.2)	1.0
Male	67 (26.4)	8,463 (37.3)	23.5 *	67 (26.4)	68 (26.8)	1.0
Other/unknown	0 (0.0)	2 (0.0)	1.3	0 (0.0)	0 (0.0)	0.0
Race, n (%)						
White	212 (83.5)	17,052 (75.1)	20.8 *	212 (83.5)	212 (83.5)	0.0
Black or African American	28 (11.0)	3,695 (16.3)	15.3 *	28 (11.0)	28 (11.1)	0.3
Asian or Pacific Islander	7 (2.8)	371 (1.6)	7.7	7 (2.8)	7 (2.6)	0.8
Other/unknown ²	7 (2.8)	1,592 (7.0)	19.8 *	7 (2.8)	7 (2.8)	0.1
Ethnicity, n (%)						
Hispanic or Latino	24 (9.4)	2,224 (9.8)	1.2	24 (9.4)	24 (9.4)	0.3
Non-Hispanic or Latino	224 (88.2)	19,140 (84.3)	11.4 *	224 (88.2)	224 (88.2)	0.1

Table 4: Baseline Characteristics among Cohort 1 and Cohort 2a Prior to and After ATT weighting in the Highest Risk

	Unweighted sample			ATT weighted sample ²		
	Cohort 1: High-risk Sotrovimab Cohort N = 6,846	Cohort 2a: High-risk Untreated Cohort N = 298,648	Std Diff (%)	Cohort 1: High-risk Sotrovimab Cohort N = 6,846	Cohort 2a: High-risk Untreated Cohort N = 6,855	Std Diff (%)
Demographic characteristics						
Age at index date (years)						
12 - 17	23 (0.3)	3,149 (1.1)	8.7	23 (0.3)	33 (0.5)	2.2
18 - 64	2,310 (33.7)	91,899 (30.8)	6.4	2,310 (33.7)	2,291 (33.4)	0.7
≥ 65 years	4,513 (65.9)	203,600 (68.2)	4.8	4,513 (65.9)	4,531 (66.1)	0.4
Mean ± SD	65.7 ± 15.5	64.8 ± 16.5	5.6	65.7 ± 15.5	65.8 ± 15.3	0.7
Median (IQR)	68.9 (58.1, 75.9)	68.6 (57.9, 75.1)	-	68.9 (58.1, 75.9)	69.0 (59.0, 76.0)	-

Number analysed

The study included adolescent patients: 53 (0.6%) in Cohort 1, 23 397 (3.8%) in Cohort 2a, 11 861 (2.7%) in Cohort 2b, and 47 552 (11.0%) in Cohort 3. Cohort 1 and Cohort 2a included 23 and 3149 adolescents respectively who were categorized as being the highest risk subgroup. The number of adolescent patients in Cohort 2b at highest risk was unavailable; Cohort 3 had no high-risk patients, by definition.

Efficacy results

Study phase 1:

Given its high degree of overlap with all other definitions, PASC definition 3 was used as the main PASC definition in Phase 2.

Study phase 2:

Comparing the risk of PASC between Cohort 1 and Cohort 2a (treated patients): compared to being aged between 18-64 years, being aged <18 years was associated with decreased risk of PASC (HR=0.98, 95% CI [0.96, 0.996], p = 0.02).

Comparing Cohort 2b and Cohort 3 (untreated patients): compared to being ≥18 years, being age <18 years was associated with decreased risk of PASC (HR=0.90, 95% CI (0.88, 0.91), p = <0.001).

Characteristics associated with higher risk of PASC included age ≥ 18 years (compared to children < 18 years)

No specific analysis, describing for example patients' characteristics or clinical outcomes, were performed for patients aged <18 years as a subgroup analysis of this age group was not included in the original analysis plan.

Safety results

None.

No data on safety events were collected, as this study used secondary data based on anonymized healthcare records that were insufficient to establish attribution between a potential safety event and an individual patient using sotrovimab.

2.3.2. Discussion on clinical aspects

In this P46, the MAH has submitted data from a retrospective cohort study based on data from the N3C database in the US including patients with COVID-19 during the period 1st March 2020 till 26th March 2022 including children from the age of 12.

The study is based on real world evidence (RWE).

The study phase 1 is a comparison of different definitions of PASC.

The study phase 2 evaluates the risk of PASC in high-risk sotrovimab treated patients compared to high risk, non-sotrovimab treated (cohort 1 vs cohort 2a) as well as the risk of PASC in high-risk non-sotrovimab treated patients compared to non-high risk, non-sotrovimab treated (cohort 2b vs cohort 3).

The total number of children at the age of 12-17 years in the study was (no further age-subgroups were provided):

Cohort 1:	53 (0.6%,)	High risk
Cohort 2.a:	23397 (3.8%)	High risk
Cohort 2.b:	11861 (2.7%)	High risk
Cohort 3:	47552 (11%)	Not high risk patients by definition

Of these

Cohort 1:	23	Highest risk
Cohort 2.a:	3149	Highest risk
Cohort 2.b:		Highest risk data unavailable

Definition highest risk: e.g., immunocompromised/immunosuppressant treatment, age ≥ 65 years, end stage renal disease, transplant, or late-stage cancer)

Of the risk factors listed on the EUA criteria for sotrovimab treatment as well as highest risk factors, children/adolescents cannot be at risk due to age, but also several of the other risk factors are significantly less frequent in children/adolescents compared to individuals ≥ 18 years (e.g. end stage renal disease, late stage cancer, transplant, cardio-vascular disease, type-2 diabetes).

The study suggests that the risk of PASC is lower in children/adolescents, which is clinically in line with data on children/adolescents experiencing less severe disease burden during acute COVID-19 infection.

However, the data from this RWE study does not provide additional meaningful data on the benefit:risk of sotrovimab in paediatric patients and therefore it is acceptable not to include these data in the SmPC.

3. Rapporteur's overall conclusion and recommendation

In conclusion, the real world evidence data provided in this P46 procedure does not change the positive BR of sotrovimab in its approved indication and no SmPC updates are deemed necessary.

☒ **Fulfilled:**

No regulatory action required.