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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/P46/007
Procedure no.: EMA/H/C/005676/P46/008
Procedure no.: EMA/H/C/005676/P46/009

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	25 Dec 2023	25 Dec 2023
☐	CHMP Rapporteur Assessment Report	29 Jan 2024	26 Jan 2024
☐	CHMP members comments	12 Feb 2024	12 Feb 2024
☐	Updated CHMP Rapporteur Assessment Report	15 Feb 2024	19 Feb 2024
☒	CHMP adoption of conclusions:	22 Feb 2024	22 Feb 2024

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1. Introduction

On 5 June 2023, the MAH submitted three completed paediatric studies; Discover 219543, Komodo 219589, N3C 219020, for Xevudy, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study Discover comparative effectiveness study – 219543, Komodo comparative effectiveness study – 219589 and N3C comparative effectiveness study – 219020 are standalone studies.

2.2. Information on the pharmaceutical formulation used in the studies

In the studies described, the commercial formulation of sotrovimab 500 mg concentrate for solution for infusion was used in accordance with the regulatory approvals of the relevant countries.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- study number and title; Discover comparative effectiveness study - 219543
- study number and title; Komodo comparative effectiveness study - 219589
- study number and title; N3C comparative effectiveness study - 219020

2.3.2. Clinical studies

The following studies were included:

• A comparative effectiveness study of COVID-19 patients treated with sotrovimab and untreated controls in England – DISCOVER-NOW database study (Discover comparative effectiveness study - 219543)

• Real-World Effectiveness of Sotrovimab in Early Treatment of Non-Hospitalized Patients with COVID-19 in the United States (N3C comparative effectiveness study - 219020)

• Real-world comparative effectiveness of sotrovimab versus no treatment in preventing acute outcomes associated with COVID-19: An analysis of administrative claims data from Komodo Health (Komodo comparative effectiveness study - 219589)

Clinical study number and title

Discover comparative effectiveness study - 219543

Methods

This retrospective cohort analysis utilized data from the Discover NOW dataset in Northwest London. The study cohort included COVID-19 patients (diagnosed between 01 December 2021 and 31 July 2022) aged ≥12 years who were not hospitalized and met at least one of the NHS's highest-risk criteria [NHS, 2022] for receiving early treatment with sotrovimab, nirmatrelvir/ritonavir, or molnupiravir for COVID-19. The cohort also included patients who were untreated despite being eligible for early treatment based on the NHS's highest-risk criteria at the time of diagnosis. The effectiveness of sotrovimab in preventing COVID-19-related hospitalisation and/or COVID-19-related death within 28 days of treatment versus no treatment was investigated in the overall study population using propensity score methods and for the following subgroups: patients aged< 65 years, ≥65 years, those who had renal disease, or those infected during 3 different periods of circulating variants.

Treatments

The commercial formulation of sotrovimab 500 mg concentrate for solution for infusion was used in accordance with the regulatory approvals of the relevant countries.

Results

A total of 599 patients treated with sotrovimab and 5191 high-risk patients who did not receive any treatment were included in the study. Compared with untreated patients, the risk of COVID-19 hospitalization/death (Hazard Ratio [HR]=0.50, 95% Confidence Interval [CI]=0.24–1.06; P=.07) and the risk of COVID-19 hospitalization (HR=0.43, 95% CI=0.18–1.00; P=.051) were both lower in the sotrovimab-treated group; however, statistical significance was not reached.

Paediatric data

A total of 86 untreated adolescent patients were included in the study; however none received sotrovimab. No analysis of this subgroup of patients was conducted in this study.

2.3.3. Discussion on clinical aspects

The MAH has provided results from the retrospective cohort analysis from the Discover NOW as part of the paediatric obligations. A total of 86 adolescent patients were included in the study, but none of them received sotrovimab, and hence no analysis of the paediatric subgroup was conducted.

Clinical study number and title

N3C comparative effectiveness study - 219020

Methods

This study analysed electronic health records from the National COVID Cohort Collaborative (N3C) in the US [Bell 2023]. Patients aged ≥12 years, diagnosed with COVID-19 between 01 June 2021 and 30 April 2022 and at high risk of COVID-19 progression, were included in the study. Patients who received sotrovimab treatment within 10 days of diagnosis were assigned to the sotrovimab group, while those who did not receive any early mAb treatment, prophylactic mAb or oral antiviral treatment were assigned to the untreated group. The study analysed the effectiveness of sotrovimab compared to untreated patients in terms of all-cause hospitalisation or death within 29 days of follow-up.

Results

The comparative effectiveness analysis evaluated data from 4992 sotrovimab patients and 541325 untreated patients. Among those who received sotrovimab, 3.3% required hospitalization compared to 4.2% of those who were not treated. After inverse probability of treatment weighting (IPTW) adjustment, sotrovimab was associated with a 23% reduction in the likelihood of all-cause hospitalization compared with the untreated cohort (IPTW-adjusted OR=0.77, 95% CI=0.63-0.95). The mortality rate in the sotrovimab group was 0.3%, compared to 0.5% in the untreated group. When hospitalisation and mortality were combined, 3.5% of the sotrovimab group required hospitalisation or died, compared to 4.5% of the untreated group. After IPTW adjustment, sotrovimab was associated with a 25% reduction in the likelihood of combined all-cause hospitalisation and mortality compared with the untreated cohort (IPTW-adjusted OR=0.75, 95% CI=0.61-0.92). The percentages of patients that required all-cause critical care were 0.1% in the sotrovimab-treated group and 0.3% in the untreated group.

Paediatric data

The N3C study included adolescent patients. However, no specific analysis, such as patients' characteristics or clinical outcomes were performed for this specific age group, as a sub-group analysis for adolescents was not included in the original analysis plan. Therefore, no conclusions can be drawn from this study for the adolescent subgroup.

2.3.4. Discussion on clinical aspects

The MAH has provided results from the National COVID Cohort Collaborative (N3C). The study includes adolescent participants, but no data are published specifically on the paediatric population, and it is agreed that no conclusions can be drawn from this population.

Clinical study number and title

Komodo comparative effectiveness study - 219589

Methods

This was a retrospective cohort study that utilised administrative claims data from Komodo Health in the US. Patients aged ≥ 12 years who were diagnosed with COVID-19 in an ambulatory setting between 26 May 2021 and 05 April 2022 were included. Patients treated with sotrovimab as an early treatment were compared with untreated high-risk patients who were eligible to receive a monoclonal antibody or an antiviral treatment but remained untreated.

The objectives were to assess the effectiveness of sotrovimab in preventing all-cause hospitalization, as well as preventing the composite all-cause hospitalization and/or all-cause mortality within 29 days of treatment start (the acute phase).

Exact and propensity score matching methods were employed to construct 1:2 matched cohorts of sotrovimab-treated and untreated patients with similar clinical characteristics. The following variables were used for the exact matching: age (+/- 5 years), diagnosis dates (within 14 days), state of residence. Then, patients were matched on the propensity score (probability of receiving sotrovimab given a set of observed and measured characteristics) that was derived from a logistic regression model based upon the following clinical covariates: age, gender, payor type, US geographic region, Quan-Charlson comorbidity index, individual high risk criteria (obesity, pregnancy, any stage chronic kidney disease, diabetes, immunosuppressive disease, immunosuppressive treatment, cardiovascular

disease / hypertension, chronic lung disease, neurodevelopmental disorders, liver disease), index month, presence of ≥1 hospitalization, ≥1 emergency room admission and ≥1 critical care admission during the baseline period.

Results

A total of 34,160 patients who received sotrovimab and 68,320 propensity score matched untreated patients were included in the study. During the 29-day follow-up period, patients who received sotrovimab had a significantly lower risk of experiencing all-cause hospitalization (Odd Ratio [OR]=0.81, 95% CI=0.76-0.87) or all-cause hospitalization and/or mortality (OR=0.75, 95% CI=0.70-0.80) during the acute phase than the untreated cohort.

Paediatric data

Two ad hoc exploratory analyses for selected age groups, including paediatric patients < 18 years (i.e., 12-54 years and 12-<18) were undertaken. These subgroup analyses were not prespecified in the study protocol and no new propensity scores for matching were derived for these subgroups of patients, hence the propensity score calculated for the overall population was used for these ad hoc exploratory subgroups. The results from these sub-analyses were not optimally adjusted for measured and unmeasured cofounders, but still reported below.

The analysis of data from patients aged 12-54 years (N=16104 for sotrovimab and N=32202 for untreated) indicated that, during the 29-day follow-up period, there was an increased odds of all-cause hospitalization and all-cause hospitalization and/or mortality in the sotrovimab group compared to the untreated group (OR=1.20, 95% CI=1.09-1.33 and OR=1.18, 95% CI=1.07-1.30, respectively).

The sub-analysis that was restricted to patients aged 12-<18 years at the time of diagnosis included 295 patients treated with sotrovimab and 605 untreated patients. The all-cause hospitalization rate during the 29-day follow-up period was higher in the sotrovimab group (4.75%) compared to 1.49% for the untreated group, with a greater odds of hospitalization for the sotrovimab group (OR=4.52, 95% CI=1.52-13.38). No deaths occurred in either group.

The study employed propensity-score matching to achieve balance in the overall measured demographic and clinical characteristics of both groups, however it did not aim to balance these characteristics for the subgroup analyses, as would be required for a definitive comparative analysis. As a result, the adolescent sub-population that received sotrovimab had a greater burden of risk factors for progression to severe COVID-19 disease than untreated patients, such as immunosuppressive disease (25% versus 13% for untreated), diabetes mellitus (11% versus 5% for untreated) and chronic kidney diseases (5% versus 1% for untreated) (Table 1). However, even if the propensity score had been recalculated for the analysis of the paediatric subgroup, it is likely that some residual confounding by indication would remain. Symptomatic and more severely ill patients were more likely to receive sotrovimab than staying untreated, which may have inflated the treatment effect estimates. This is also due to the fact that the demographic and clinical characteristics captured in this study and used to derive the propensity scores were generalisable to the entire patient population, and hence true confounders and risk factors specific to the paediatric population were not captured and could not be controlled for.

The results of the ad hoc exploratory analysis that focused only on patients aged 12-<18 years at the time of diagnosis were not included in the study report. For transparency, the demographics, clinical characteristics, and outcomes of patients aged 12-<18 years at the time of diagnosis are summarized in Table 1.

Table 1 Demographics, Clinical Characteristics and Outcomes of Patients Aged 12≤18 years at the Time of Diagnosis in Komodo Comparative Effectiveness Study

	Sotrovimab cohort (n=295)	Untreated cohort (n=605)	OR [a] (95% CL)
Demographic characteristics			
Age (years), mean (SD)	15.2 (1.5)	15 (1.7)	-
Male, n (%)	152 (51.5)	318 (52.6)	-
High risk as per emergency use authorization criteria, n (%)			
Obesity	13 (4.4)	12 (2)	-
Pregnancy	13 (4.4)	23 (3.8)	-
Chronic kidney disease (any stage)	15 (5.1)	4 (0.7)	-
Chronic kidney disease (stage ≥3)	6 (2)	1 (0.2)	-
Diabetes	32 (10.9)	32 (5.3)	-
Immunosuppressive disease	73 (24.8)	77 (12.7)	-
Immunosuppressive treatment	88 (29.8)	115 (19)	-
Cardiovascular disease (including CHD) or hypertension	63 (21.4)	96 (15.9)	-
Chronic lung disease (COPD or asthma)	86 (29.2)	236 (39)	-
Sickle cell disease	9 (3.1)	3 (0.5)	-
Neurodevelopmental disorders	88 (29.8)	210 (34.7)	-
A medical-related technological dependence	15 (5.1)	5 (0.8)	-
Liver disease	24 (8.1)	16 (2.6)	-
Outcomes, n (%)			
All-cause hospitalization	14 (4.8)	9 (1.5)	4.52 (1.52, 13.38)
All-cause hospitalization/mortality	14 (4.8)	9 (1.5)	4.50 (1.52, 13.31)

CHD: congenital heart disease; COPD: chronic obstructive pulmonary disease OR: Odds Ratio; 95% CL: 95% confidence limits
Odds Ratio (Sotrovimab vs. Untreated) obtained from conditional logistic regression model adjusted for malignancy.

Overview of safety

The 3 observational studies included did not report safety outcomes for patients treated with sotrovimab for the overall cohort or for the subgroup of patients aged < 18 years old.

2.3.5. Discussion on clinical aspects

In accordance with Article 46 of Regulation (EC) 1901/2006, MAH has submitted the final study reports for 3 observational studies all sponsored by the MAH and all including patients aged ≥12 years and < 18 years of age (Discover Study – 219543, Komodo Study – 219589, and N3C Study 219020). The studies are not measures of the agreed Paediatric Investigation Plan for sotrovimab (EMEA-002899-PIP01-20-M02).

The MAH has provided an overview of the three studies. Two of the studies did not address or provide data on the paediatric age group, hence the N3C study did not report paediatric-specific outcomes, and in the Discover study no patient <18 years of age received sotrovimab. However, in the Komodo study an exploratory subgroup analysis of patients aged ≥12 years-old and <18 years-old patients was made and these results are provided by the MAH.

The Komodo study was a retrospective cohort study that evaluated the real-world effectiveness of sotrovimab versus no treatment in reducing the risk of hospitalization and death. The cohorts were matched 1:2 by exact and propensity score matching methods. The variables used were: age (+/- 5 years), date of diagnosis and state of residence. Then, patients were matched on the propensity score based upon the covariates: age, gender, payor type, US geographic region, Quan-Charlson comorbidity index, individual high risk criteria (obesity, pregnancy, any stage chronic kidney disease, diabetes, immunosuppressive disease, immunosuppressive treatment, cardiovascular disease / hypertension, chronic lung disease, neurodevelopmental disorders, liver disease), index month, presence of ≥1 hospitalization, ≥1 emergency room admission and ≥1 critical care admission during the baseline period. In total 34,160 patients who received sotrovimab and 68,320 propensity score matched untreated patients were included in the full cohort study. In the overall cohort risk of experiencing all-cause hospitalization or all-cause hospitalization and/or mortality were lower in sotrovimab treated patients. (OR=0.81, 95% CI=0.76-0.87 and OR=0.75, 95% CI=0.70-0.80, respectively).

As an exploratory study, the cohort of patients above 12 and below the age of 18 was also examined. In total 295 patients were treated with sotrovimab and 605 patients were untreated. The all-cause hospitalization rate was higher in the sotrovimab group (4.75%) compared to the untreated group (1.49%). Odds for hospitalization for the sotrovimab treated was higher than in the untreated cohort. (OR=4.52, 95% CI=1.52-13.38). No deaths occurred in either group.

The MAH finds that the data from the Komodo study are too biased to draw a meaningful conclusion on the benefit:risk of sotrovimab in adolescent patients aged ≥12 years-old. It is agreed with the MAH that a cohort study has significant methodological limitations. Further, the analysis in the adolescent population was exploratory (not part of an a priori analysis plan) and did therefore not have all appropriate adjustment for potential confounders. The MAH also address that the propensity score was calculated for the overall population, and not for this specific population, resulting in an imbalance on a number of comorbidities and risk factors for COVID-19 progression between the two groups of adolescent patients. It is agreed that this imbalance was overall in favour of the untreated patients (not receiving sotrovimab), but not entirely as both Neurodevelopment disorder and Chronic lung disorder existed more often in the untreated population. Overall, it is agreed that confounding by indication is very likely and as the MAH also argues for all retrospective studies even with matching and adjustment, unmeasured confounding could still result in significant bias in the results of the subgroup analysis, and these post-hoc data should not be reflected in the SmPC.

The MAH concludes that no update to the paediatric aspects of the product information is required, which is agreed.

There are no reported safety outcomes, and therefore it is agreed that no updates for section 4.8 are needed.

3. Overall conclusion and recommendation

☒ Fulfilled: