Amsterdam, 22 May 2025
EMADOC-1700519818-1974850
Human Medicines Division

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

Trumenba

Common name: Meningococcal group B vaccine (recombinant, adsorbed)

Procedure no.: EMA/PAM/0000258141

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**
☐	CHMP Rapporteur AR	28 April 2025	25 April 2025
☐	CHMP comments	12 May 2025	12 May 2025
☐	Updated CHMP Rapporteur AR	15 May 2025	N/A
☒	CHMP outcome	22 May 2025	22 May 2025

Table of contents

1. Introduction

On 7 March 2025, the MAH submitted a completed paediatric study for Trumenba, 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 "Effect of Trumenba on Gonococcal infections in adolescents and young adults in the United States: A retrospective cohort study." – Study B1971066 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Trumenba is a bivalent rLP2086 vaccine indicated for active immunisation of individuals 10 years and older to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B. Trumenba was authorised in the EU on 24 May 2017.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- Study B1971066 *"Effect of Trumenba on Gonococcal infections in adolescents and young adults in the United States: A retrospective cohort study."*

2.3.2. Clinical study

Study B1971066 "Effect of Trumenba on Gonococcal infections in adolescents and young adults in the United States: A retrospective cohort study."

Description

Meningococcal vaccines have been hypothesised to confer cross-protection against gonorrhoea due to the biological similarities between *Neisseria meningitidis* and *Neisseria gonorrhoea*. Both pathogens belong to the same genus and share a high degree of genetic and antigenic homology. Studies have indicated some potential effectiveness of Meningococcal B outer membrane vesicle (OMV) vaccines against gonococcal infection. The purpose of this study is to evaluate the effect of Trumenba in the prevention of gonococcal infection among adolescents and young adults 15 to 30 years of age in the US using a health care administrative claims database.

Methods

Study participants

Adolescents and young adults approximately 15 to 30 years of age (calculated from July 1 of their birth year) were identified in an administrative claims database between 01 January 2016 and 31 December 2021.

The study included individuals who received at least one dose of MenACWY vaccine within this period. Subjects were excluded if they were not enrolled in medical and pharmacy benefits on their index date and for at least 15 days after. They were also excluded if they received any doses of Trumenba before MenACWY between 01 January 2016 and 31 December 2021. Additionally, subjects with unknown or missing gender were excluded, as well as those who received at least one dose of 4CMenB within the same period. Finally, subjects who had evidence of gonococcal or chlamydial infection on their index date or within the first 14 days of follow-up were also excluded.

IQVIA PharMetrics Plus is a longitudinal health plan database of adjudicated medical and pharmacy claims, including patient enrollment data for national and sub-national health plans and self-insured employer groups in the United States. Data contributors to the database are largely commercial health plans. It is representative of the commercially insured US national population for patients under 65 years of age.

Treatments

The exposure variables were 1) ≥1 dose of Trumenba and ≥1 dose MenACWY, 2) ≥2 doses of Trumenba and ≥1 dose of MenACWY, and 3) ≥1 dose MenACWY. Vaccine receipt was determined by National Drug Codes and Current Procedural Terminology codes.

Objective(s)

Primary objective:

Examine the effect of at least one dose of Trumenba on gonococcal infection in adolescents and young adults of 15-30 years in the US.

Secondary objectives:

- Examine the effect of at least two doses of Trumenba on gonococcal infection in adolescents and young adults of 15-30 years in the US
- Examine the effect of at least one dose of Trumenba on chlamydial infection in adolescents and young adults of 15-30 years in the US
- Examine the effect of at least two doses of Trumenba on chlamydial infection in adolescents and young adults of 15-30 years in the US

Outcomes/endpoints

The primary outcome of interest was gonococcal infection, and the negative control outcome was chlamydial infection. Only the first episode of gonorrhoea or chlamydia that occurred during the study period was considered for these analyses.

Both the outcome of gonorrhoea infection as well as chlamydia infection were defined on International Classification of Disease, 10th Revision, Clinical Modification (ICD-10-CM) codes. A gonorrhoea only infection, or chlamydia only infection where respectively gonorrhoea or chlamydia infections in which a respectively chlamydia-related or gonorrhoea-related diagnosis code was **not** recorded within 30 days of one another.

The inclusion of chlamydia as a negative control outcome allowed for the evaluation of potential biases within the study. If vaccination with Trumenba demonstrated no impact on chlamydia incidence, this would suggest that the study's findings on gonorrhoea were likely not influenced by unmeasured confounders. Conversely, if Trumenba vaccination appeared to affect chlamydia rates, it would indicate the presence of residual confounding.

Sample size

This was an exploratory study and no hypothesis was generated. All eligible individuals were included in the study.

For sample size estimation, a vaccine effectiveness against gonococcal infection of 20% or more was aimed to be detected with an onset from 14 days after receipt of Trumenba (exposure group) and MenACWY (control group). A Cox regression of the log hazard ratio on a covariate with a standard deviation of 1.50 to achieve 80% power at a 0.05 significance level to detect a regression coefficient equal to -0.2200, a sample of 15,669 would be required. The sample size was adjusted for an anticipated overall event rate of 0.0046. Data from feasibilities suggested that there were more than 500,000 eligible health plan members in the database and illustrated that there was adequate sample size to conduct the analysis.

Randomisation and blinding (masking)

This is a non-interventional study.

Statistical Methods

To evaluate the primary objective, cases were defined as individuals with at least one diagnosis code for gonococcal infection during the follow-up period. Each individual was followed for the outcome from 14 days after their index date until the end of the follow-up period, censoring follow-up at end of health plan enrollment or 31 December 2022 (end of study period), whichever was earlier.

Cox proportional hazard regression models were used to estimate hazard ratios (HRs) by exponentiating the coefficient for receiving at least one dose of Trumenba. The vaccine effectiveness (VE) was estimated as (1–adjusted HR) × 100%. Standard errors for the coefficients were used to estimate p-values and 95% CIs for the HRs. Both crude and adjusted VE with its corresponding 95% CI were calculated. Age, sex, and US Census region were used as the covariates in the model.

Similar statistical methods were applied for secondary objectives, with variations in the vaccine variable and case definitions. Objective 2.1 focused on individuals with at least two Trumenba doses. Objective 2.2 involved cases with at least one chlamydia diagnosis, and Objective 2.3 involved individuals who received at least two doses of Trumenba and had a chlamydia diagnosis.

Results

Participant flow and numbers analysed

There were 5,820,843 individuals enrolled in a health plan covered by Pharmetrics who received at least one dose of MenACWY during January 1, 2016 and December 31, 2021. A subset of 2,705,505 of these individuals were 15 to 30 years of age when the vaccine was administered and were eligible for the study. 968,990 (35.8%) individuals who were not enrolled in both medical and pharmacy benefits on their index date, 19,458 (0.7%) individuals who did not have at least 15 days of medical and pharmacy coverage following their index date, 9,197 (0.3%) individuals who received at least one dose of Trumenba before their first MenACWY dose, 8 (<0.1%) individuals with unknown gender, 399,521 (14.8%) who received Bexsero during the study period, and 953 (<0.1%) individuals who were diagnosed with a gonococcal or chlamydial infection on their index date or during the first 14 days of follow-up were excluded. This resulted in 1,307,378 individuals in the study sample and 214,552 (16.4%) received at least one dose of Trumenba and 92,661 (7.1%) received at least two doses of Trumenba during the study period.

Baseline data

Demographics among adolescents and young adults receiving at least one Trumenba and those who received MenACWY vaccine only are displayed in Table 1. The age and sex patterns for the cohort receiving two doses of Trumenba were consistent.

Table 1. Demographics among adolescents and young adults receiving at least one dose of Trumenba and those who received MenACWY only 2016-2021.

Demographic	≥1 dose of Trumenba and MenACWY (n= 214,552)		MenACWY only (n=1,092,826)		Total (n=1,307,378)	
	N	%	N	%	N	%
Mean (std) age in years at vaccination	16.97 (1.32)		17.18 (1.99)		17.15 (1.90)	
Age group at vaccination, in years						
15 - 17	155,966	72.7	775,793	71.0	931,759	71.3
18 - 19	51,563	24.0	238,461	21.8	290,024	22.2
20 - 24	6,627	3.1	59,408	5.4	66,035	5.1
25 - 30	396	0.2	19,164	1.8	19,560	1.5
Sex						
Male	105,539	49.2	539,613	49.4	645,152	49.4
Female	109,013	50.8	553,213	50.6	662,226	50.7
US Census Region						
Northeast	36,193	16.9	199,905	18.3	236,098	18.1
South	85,947	40.1	390,076	35.7	476,023	36.4
Midwest	68,134	31.8	334,106	30.6	402,240	30.8
West	23,963	11.2	161,031	14.7	184,994	14.2
Unknown	315	0.2	7,708	0.7	8,023	0.6

Efficacy results

Primary analyses

The crude VE for at least one dose of Trumenba against gonorrhoea was 31.7% (95% CI 23.2%, 39.3%) (Module 5.3.5.4 B1971066 Study Report Table 5). After adjustment for patient age, gender, and US Census region, at least one dose of Trumenba provided 24.1% (95% CI 14.6%, 32.6%)

protection against gonorrhoea. However, at least one dose of Trumenba also demonstrated a protective effect against chlamydia, the negative control outcome. In the unadjusted and adjusted models VE estimates for chlamydia were 21.7% (95% CI 16.7%, 26.5%) and 21.4% (95% CI 16.3, 26.2%), respectively. As there is no hypothesised biological mechanism for Trumenba to protect against chlamydia, this indicates there is residual confounding in the adjusted model demonstrating effectiveness of at least one dose of Trumenba against gonorrhoea. Using the results for chlamydia, the calibrated VE for at least one dose of Trumenba against gonorrhoea was 2.7% (calibrated VE = 24.1% - 21.4%).

Secondary analyses

The crude estimates of at least two doses of Trumenba effectiveness against gonorrhoea and chlamydia were 39.2% (95% CI 28.8%, 48.1%) and 31.1% (95% CI 25.0%, 36.7%), respectively (Module 5.3.5.4 B1971066 Study Report Table 5). After covariate adjustment, at least two doses of Trumenba provided 27.9% (95% CI 15.5%, 38.5%) protection against gonorrhoea and 30.1% (95% CI 23.9%, 35.8%) protection against chlamydia. Using the results for chlamydia, the calibrated VE for at least two doses of Trumenba against gonorrhoea is -2.2% (calibrated VE = 27.9% - 30.1%).

The results were consistent when gonorrhoea and chlamydia "coinfections" were excluded, ie, gonorrhoea infections with a chlamydia diagnosis code within 30 days or vice versa. The crude VE for at least one dose of Trumenba against gonorrhoea only and chlamydia only were 32.1% (95% CI 22.4%, 40.7%) and 20.8% (95% CI 15.5%, 25.7%), respectively. After covariate adjustment, the VE for at least one dose of Trumenba provided 23.3% (95% CI 12.2%, 33.0%) protection against gonorrhoea only and 20.8% (95% CI 15.5%, 25.8%) protection against chlamydia only.

The crude VE for at least two doses of Trumenba against gonorrhoea only and chlamydia only were 38.6% (95% CI 26.5%, 48.6%) and 30.1% (95% CI 23.7%, 35.9%), respectively. After covariate adjustment, the VE for at least two doses of Trumenba provided 25.6% (95% CI 11.0%, 37.9%) protection against gonorrhoea only and 29.7% (95% CI 23.3%, 35.6%) protection against chlamydia only.

2.3.3. Discussion on clinical aspects

The MAH has provided a final study report for study B1971066 in accordance to art. 46 of the Paediatric Regulation. The current assessment focusses on the study results with a potential impact on the benefit/risk, SmPC and/or risk management plan (RMP) of Trumenba.

Study B1971066 is an observational study using a longitudinal health care claims database to explore a potential effect of Trumenba on gonorrhoea infections.

The study compares recipients of (at least one dose or two doses of) Trumenba and MenACWY vaccine with those receiving only an MenACWY vaccine. Hypothetically dependent on the method of action of protection, cross-protection from MenACWY could also offer some of protection against gonorrhoea. This would likely underestimate the observed vaccine effectiveness against gonorrhoea and therefore this approach is considered conservative. In principle comparing Trumenba vaccinated individuals to individuals receiving another vaccine will at least diminish some of the healthy vaccinee effect that can be observed in observational studies and is therefore appreciated.

Given the observed results it is likely there is still some residual confounding by comparing the two groups of meningococcal vaccinated individuals. This could partially be due to differences in uptake and recommendations for the different meningococcal vaccines. Advisory Committee on Immunization

Practices (ACIP) recommends routine MenACWY vaccination, whereas for MenB is subject to shared clinical decision-making for individuals 16-23 years of age. (Presa et al. Journal of Adolescent Health 2024, Packnett et al. Human Vaccin Immunother 2023) In total 1,307,378 individuals were included in the study sample (and vaccinated with at least MenACWY) of these 16.4% received at least a dose of Trumenba. The MAH indicates that the data source is representative for commercially insured individuals below the age of 65.

The in-/exclusion criteria seem appropriate as this is the age group eligible for MenB vaccination in the United States, also given the age-specific prevalences of gonorrhoea there is circulation of Neisseria gonorrhoea in this age group.

Outcomes were defined based on ICD-10 codes. ICD-10 codes listed in the Appendix of the Statistical Analysis Plan indeed refer to gonorrhoea and/or chlamydia trachomatis. There might be some misclassification as some cases of sexually transmitted infections including the outcomes of interest might be capture under ICD-10 code A64 (unspecified sexually transmitted disease) as well, although it is unlikely this would differ between the exposure groups and could influence the observed results.

In addition there might be potential misclassification of vaccination status with individuals being vaccinated against meningococcal B (Bexsero or Trumenba) outside the data capture being classified as unvaccinated. As this would potentially dilute the effect of Trumenba on gonococcal infections, the currently obtained effect estimates can be considered conservative and would potentially lead to an underestimation of the vaccine effectiveness (VE).

Vaccine effectiveness both crude and adjusted against gonococcal infections was estimated and calibrated against the negative control outcome of chlamydial infection. As stated by the MAH residual confounding may have been inaccurately assessed since risk factors do not completely overlap. However in absence of data on sexual (risk) behaviour between the exposure group, given the same transmission route and overlap in risk factors between these STIs, inclusion of chlamydia as a negative control is appreciated.

Based on Study B1971066, a retrospective cohort study using administrative claims, the calibrated VE for at least one dose of Trumenba was approximately 2.7%. These results indicate little, if any protection of Trumenba against gonorrhoea. Although the VE in this study might be underestimated given limitations in the study design, findings are in line with those of Abara et al. (Sex Trans Dis 2024) were also no effectiveness was observed against gonorrhoea after Trumenba vaccination in observational study using STI surveillance data in New York and Philadelphia.

Findings of Study B1971066 and those in literature indicating a lack of efficacy for Trumenba against gonorrhoea are not completely unexpected. Potential cross-protection of *Neisseria meningitis* vaccines for *Neisseria gonorrhoea* is considered given the high sequence similarity between these pathogens. However, despite a high percentage of overlap between factor H-binding protein (fHBP) expressed on the surface on meningococcal B with the gonococcal homologue, the gonococcal fHBP is not surface expressed. (Ruiz Garcia et al. NPJ Vaccines 2019).

3. CHMP's overall conclusion and recommendation

The data provided in this art. 46 procedure have not provided additional information on the efficacy or safety of Trumenba, therefore the benefit risk remains unchanged. No changes to the SmPC are proposed, which can be supported.

☒ **Fulfilled:**

No regulatory action required.