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Human Medicines Division

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

Prevenar 13

pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)

Procedure no: EMEA/H/C/001104/P46/071

Note

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

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1. Introduction

On 10 August 2023, the MAH submitted a completed paediatric study B7471012 for Prevenar 13, pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed), 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 B7471012 "*Supplemental Report, Russian Cohort – A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a 20-Valent Pneumococcal Conjugate Vaccine Given as a Series of 2 Infant Doses and 1 Toddler Dose in Healthy Infants*" is part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

13-valent pneumococcal conjugate vaccine (13vPnC) was a sterile liquid suspension formulation containing saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to CRM197. The vaccine was formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B, per 0.5-mL dose. The vaccine contained 295 µg succinate buffer, 0.85% sodium chloride, 100 µg polysorbate 80, and 125 µg aluminium as aluminium phosphate, per 0.5-mL dose. The 13vPnC supply was considered representative of Prevenar 13, as it was manufactured according to the approved Prevenar 13 commercial drug product process using commercially released vaccine drug substances.

The current EU-approved indications for the use of 13vPnC are:
• Active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by Streptococcus pneumoniae in infants, children, and adolescents from 6 weeks to 17 years of age;
• Active immunisation for the prevention of invasive disease and pneumonia caused by Streptococcus pneumoniae in adults ≥18 years of age and the elderly.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study B7471012 "*Supplemental Report, Russian Cohort – A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a 20-Valent Pneumococcal Conjugate Vaccine Given as a Series of 2 Infant Doses and 1 Toddler Dose in Healthy Infants"*.

This assessment concerns only participants receiving the 13vPnC vaccine, in accordance with Article 46 of Regulation (EC) No1901/2006. The results for Study B7471012 primary study population were submitted to the EMA on 20 October 2022 and received a positive CHMP Opinion on 26 January 2023.

2.3.2. Clinical study B7471012

Description

This Phase 3, multicentre, randomised, double-blind study was conducted at investigator sites in Europe and Australia, with additional sites in Russia (Russian cohort). It is part of the Phase 3 paediatric clinical development program to support the use of 20vPnC in the paediatric population. The purpose of the study was to generate data on the safety and immunogenicity of 20vPnC in infants when administered as a series of 2 infant doses and 1 toddler dose and 13vPnC has been used as an active comparator in this study. Data were also generated on key routine paediatric vaccines given concomitantly with 20vPnC or 13vPnC.

Approximately 60 Russian infants born at >36 weeks of gestation and ≥42 to ≤70 days of age at the time of consent by their parents/legal guardians were planned to be enrolled in the study and are referred to as the Russian cohort. Due to an unexpected business disruption event related to global security (unrelated to the COVID-19 pandemic), enrollment was halted at 51 participants on 03 March 2022. There were no other impacts or interruption of study activities due to this event. Participants were randomised in a 1:1 ratio to receive either 20vPnC or 13vPnC (control vaccine) at enrollment and received the initial vaccination at that time. A second dose of vaccine was given 60 to 90 days later, and the third vaccination was given between 335 to 455 days of age (11 to 15 months of age) (Doses 1, 2, and 3 respectively). Participants received the same vaccine (either 20vPnC or 13vPnC) for all 3 doses. It was planned that each participant in the Russian cohort participated in the trial for approximately 10 to 14 months (i.e., from Dose 1 until 1 month after the last study vaccination).

Methods

Study participants

Key inclusion criteria were as follows:

- Male or female infants born at >36 weeks of gestation and 2 months of age (≥42 to ≤70 days) at the time of consent (the day of birth is considered day of life 1).
- Healthy infants determined by clinical assessment, including medical history and clinical judgment, to be eligible for the study.

Key exclusion criteria were as follows:

- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of investigational product or any diphtheria toxoid-containing vaccine.
- Significant neurological disorder or history of seizure including febrile seizure or significant stable or evolving disorders such as cerebral palsy, encephalopathy, hydrocephalus, or other significant disorders. Does not include resolving syndromes due to birth trauma, such as Erb's palsy and/or hypotonic-hyporesponsive episodes.
- Major known congenital malformation or serious chronic disorder.
- Known or suspected immunodeficiency or other conditions associated with immunosuppression, including, but not limited to, immunoglobulin class/subclass deficiencies, DiGeorge syndrome, generalized malignancy, HIV infection, leukaemia, lymphoma, or organ or bone marrow transplant.

Demographic and baseline characteristics of sex, race, ethnicity, and age for the safety population were generally similar in the 20vPnC and 13vPnC groups. There were more female infants enrolled in

the 20vPnC group than the 13vPnC group. Overall, most participants in the Russian cohort were White (98.0%), and non-Hispanic/non-Latino (92.2%), with a median age of 66 days at Dose 1. Demographic characteristics for the Dose 2 and Dose 3 evaluable immunogenicity populations are similar to those for the safety population.

Treatments

Participants received a single dose (0.5 mL) of 20vPnC or 13vPnC intramuscular (IM) into the anterolateral thigh muscle of the left leg at each vaccination visit (Doses 1, 2, and 3 at Visits 1, 2, and 4, respectively). Participants also received 1 dose of DTPa-HBV-IPV/Hib vaccine (Infanrix hexa) in the right leg at Visits 1, 2, and 4. In contrast to the primary study population, participants in the Russian cohort did not receive MMR (measles, mumps, and rubella) and varicella vaccinations as part of the study. Instead, they may have received MMR and varicella as per local requirements/ national immunisation program.

Objectives, estimands and endpoints

The study objectives, estimands, and endpoints related to the Russian cohort are provided in Table 1.

Table 1. Study Objectives, Estimands, and Endpoints – Russian Cohort

Safety Objective	Estimands	Safety Endpoints
To describe the safety profile of 20vPnC	In participants receiving at least 1 dose of investigational product and having safety data reported after any vaccination in each vaccine group: • The percentage of participants reporting prompted local reactions within 7 days after each vaccination • The percentage of participants reporting prompted systemic events within 7 days after each vaccination • The percentage of participants reporting AEs from Dose 1 to 1 month after Dose 2 and from Dose 3 to 1 month after Dose 3 • The percentage of participants reporting SAEs through 1 month after Dose 3 • The percentage of participants reporting NDCMCs through 1 month after Dose 3	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) • AEs • SAEs • NDCMCs
Primary Pneumococcal Immunogenicity Objective	**Estimands**	**Primary Pneumococcal Immunogenicity Endpoints**
To describe the IgG responses induced by 20vPnC in the Russian cohort	In evaluable Russian participants for each of the 20 serotypes in 20vPnC for each vaccine group: • Percentages of participants with predefined IgG concentrations at 1 month after Dose 2 • IgG GMCs at 1 month after Dose 2 • IgG GMCs at 1 month after Dose 3	• Pneumococcal IgG concentrations

Secondary Pneumococcal Immunogenicity Objective	Estimands	Secondary Pneumococcal Immunogenicity Endpoints
To further describe immune responses induced by 20vPnC in the Russian cohort	In evaluable Russian participants for each of the 20 serotypes in 20vPnC for each vaccine group: • Percentages of participants with predefined IgG concentrations at 1 month after Dose 3 • OPA GMTs at 1 month after Dose 2 • OPA GMTs at 1 month after Dose 3	• Pneumococcal IgG concentrations • Pneumococcal OPA titers
Exploratory Pneumococcal Immunogenicity Objective	**Estimands**	**Exploratory Pneumococcal Immunogenicity Endpoints**
To describe additional responses induced by 20vPnC in the Russian cohort	In evaluable Russian participants for each of the 20 serotypes in 20vPnC in each vaccine group: • Percentages of participants with ≥4-fold rise in IgG concentrations from before Dose 3 to 1 month after Dose 3 • GMFRs in IgG concentrations from before Dose 3 to 1 month after Dose 3 • GMFRs in OPA titers from before Dose 3 to 1 month after Dose 3 • Percentage of participants with ≥4-fold rise in OPA titers from before Dose 3 to 1 month after Dose 3 • Percentages of participants with OPA titers ≥ LLOQ at available time points	• Pneumococcal IgG concentrations • Pneumococcal OPA titers

Sample size

Approximately 60 Russian infants were planned to be enrolled. A total of 51 Russian infants were randomised; 47 (92.2%) participants received all 3 doses and completed all visits per protocol. This cohort was referred to as the Russian cohort and was not included in the primary study population. Disposition of all randomised participants was similar in the 20vPnC and 13vPnC groups. The numbers of participants included in the all-available and the evaluable immunogenicity populations in the 2 vaccine groups were similar. Since the difference between the numbers of participants in the evaluable immunogenicity populations and the all-available immunogenicity population was <10%, no analyses were performed for the all-available immunogenicity population per the study Statistical Analysis Plan.

Statistical Methods

The Russian cohort data were summarised separately and descriptively. No formal hypothesis test was planned.

Results

Safety Results

The percentages of participants with prompted local reactions and systemic events were generally similar in the 20vPnC and 13vPnC groups after each dose, with most being mild to moderate in severity. There were no cases of fever above 40°C in either group.

Adverse Event (AE) rates were low in both vaccine groups: 2 participants with AEs from Dose 1 to 1 month after Dose 2 and 1 participant with an AE from Dose 3 to 1 month after Dose 3 in the 20vPnC group; 1 participant with an AE from Dose 1 to 1 month after Dose 2 in the 13vPnC group.

There were no related AEs, Serious Adverse Events (SAEs), or Newly Diagnosed Chronic Medical Condition (NDCMCs) identified in either the 20vPnC or the 13vPnC groups. No safety concerns were identified in the Russian cohort.

Immunogenicity Results

20vPnC and 13vPnC elicited responses to the 13 matched serotypes as assessed by the serotype-specific IgG Geometric Mean Concentrations (GMCs) and percentages of participants with predefined IgG concentrations at 1 month after Dose 2 and Dose 3. The observed IgG GMCs after 20vPnC were higher than those after 13vPnC for all 7 additional serotypes.

Both 20vPnC and 13vPnC elicited OPA responses for the 13 matched serotypes. 20vPnC also elicited functional antibody to the 7 additional vaccine serotypes after Dose 2 and Dose 3 as observed by opsonophagocytic activity (OPA) geometric mean titers (GMTs).

Both IgG and OPA responses increased with 20vPnC and 13vPnC from before to 1 month after Dose 3 and from 1 month after Dose 2 to 1 month after Dose 3 for the majority of the 13 matched serotypes, and increased with 20vPnC for the majority of the 7 additional serotypes, indicating that priming for a memory response was elicited with the infant doses of 20vPnC and 13vPnC.

2.3.3. Discussion on clinical aspects

The MAH concluded that safety and immunogenicity results from this study are consistent with the known profile of 13vPnC as reflected in the EU SmPC and support the continued use of 13vPnC. Therefore, the MAH did not propose changes to the Prevenar 13 product information. The MAH concluded that the submitted study does not change the benefit-risk balance for Prevenar 13 and that the study confirms what is already known about immune responses and safety.

The present study confirmed the safety of Prevenar 13 among Russian infants administered by the IM route. The safety population was small and therefore the chance to detect rare AEs and SAEs is low.

3. CHMP Rapporteur's overall conclusion and recommendation

The overall study design, objectives, endpoints and evaluation methods were appropriate.

The rapporteur agrees on MAH summary on safety and immunogenicity results. Overall, MAH's conclusion is agreed. No new safety concern is raised from this study and the benefit/risk profile of 13vPnC remains unchanged.

☒ Fulfilled:

No regulatory action required.