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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/P46/072

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[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	25 Dec 2023	25 Dec 2023	☐
☐	CHMP Rapporteur Assessment Report	29 Jan 2024	26 Jan 2024	☐
☐	CHMP members comments	12 Febr 2024	12 Febr 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	15 Febr 2024	15 Febr 2024	☐
☒	CHMP adoption of conclusions:	22 Febr 2024	22 Febr 2024	☐

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1. Introduction

On 28 November 2023, the MAH submitted a completed paediatric study B7471027 for Prevenar 13, 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 B7471027, A Phase 3, Randomized, Partially Double-Blind Trial to Evaluate the Safety and Immunogenicity of 20-valent Pneumococcal Conjugate Vaccine in Healthy Toddlers 12 Through 23 Months of Age With 2 Prior Infant Doses of Prevenar 13 is part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

13vPnC is 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 is formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B, per 0.5-mL dose. The vaccine contains 295 µg succinate buffer, 0.85% sodium chloride, 100 µg polysorbate 80, and 125 µg aluminum as aluminum 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: B7471027; *Final Report – A Phase 3, Randomized, Partially Double-Blind Trial to Evaluate the Safety and Immunogenicity of 20-valent Pneumococcal Conjugate Vaccine in Healthy Toddlers 12 Through 23 Months of Age With 2 Prior Infant Doses of Prevenar 13,* in accordance with Article 46 of Regulation (EC) No. 1901/2006.

2.3.2. Clinical study B7471027

Description

This Phase 3, multicenter, randomized, partially double-blind study was conducted at investigator sites in Europe. The purpose of this study is to describe the safety and immunogenicity of 1 or 2 doses of

20vPnC administered to toddlers ≥12 to <24 months of age who have received 2 doses of 13vPnC in infancy (prior to 12 months of age and >56 days prior to vaccination in this study).

Approximately 360 toddlers were planned to be enrolled and randomized in a 1:1:1 ratio to receive either 1 or 2 doses of 20vPnC or 1 dose of 13vPnC (control). Toddlers randomized to receive 1 dose were double-blinded, as 20vPnC and 13vPnC have the same appearance and a single dose was administered at Visit 1 (Day 1) of the study. For participants randomized to receive 2 doses of 20vPnC, the parents/legal guardians and site staff were aware of the randomization assignment for these participants, as the participant needed to return for a second vaccination visit and an additional visit 1 month after Dose 2 these participants received 20vPnC at both Visit 1 and Visit 2 (2 months after Visit 1).

Methods

Study participants

Key inclusion criteria were as follows:

- Healthy male and female toddlers determined by clinical assessment (including medical history and clinical judgment) and at ≥12 to <24 months of age at the time of consent (the day of birth is considered day of life 1).

Key exclusion criteria were as follows:

- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of investigational product or any diphtheria toxoid–containing vaccine.
- Significant neurological disorder or history of seizure (excluding febrile seizure) or significant stable or evolving disorders such as cerebral palsy, encephalopathy, hydrocephalus, or other significant disorders.
- 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, general zed malignancy, HIV infection, leukaemia, lymphoma, or organ or bone marrow transplant.

Demographic and baseline characteristics of sex, race, ethnicity, country, and age for the safety population were generally similar in the 20vPnC and 13vPnC groups. Overall, the majority of the study population was White (98.3%) and non-Hispanic/non-Latino (71.1%), with a median age of 12.0 months at Dose 1. Demographic characteristics for the evaluable immunogenicity population are similar to those for the safety population.

Treatments

Participants received a single dose (0.5 mL) of 20vPnC or 13vPnC intramuscularly into the anterolateral thigh muscle of the left leg or left arm (as appropriate for the age and size of the toddler) at each vaccination visit.

Objective(s)

Study objectives, estimands, and endpoints are provided in in the following table.

Objectives	Endpoints	Estimands
Primary Safety Objective	**Primary Safety Endpoints**	**Primary Safety Estimands**
• To describe the safety profile of 20vPnC	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) • AEs • SAEs	In participants receiving at least 1 dose of study intervention with safety follow-up after the assigned vaccination: • The percentage of participants reporting prompted local reactions within 7 days after the last assigned vaccination in each group • The percentage of participants reporting prompted systemic events within 7 days after the last assigned vaccination in each group • The percentage of participants reporting AEs within 1 month after the last assigned vaccination in each group • The percentage of participants reporting SAEs within 1 month after the last assigned vaccination in each group
Primary Immunogenicity Objective	**Primary Immunogenicity Endpoint**	**Primary Immunogenicity Estimand**
• To describe the immune responses to the additional 7 serotypes after 1 or 2 doses of 20vPnC	Pneumococcal serotype-specific IgG concentration	In participants complying with the key protocol criteria (evaluable participants) in each group: • Percentages of participants with predefined serotype-specific IgG concentrations for the 7 additional serotypes 1 month after the last assigned vaccination
Secondary Immunogenicity Objective	**Secondary Immunogenicity Endpoints**	**Secondary Immunogenicity Estimands**
• To further describe the immune response of 20vPnC after 1 or 2 doses	• Pneumococcal serotype-specific IgG concentration • Pneumococcal serotype-specific OPA titers	In evaluable participants in each group: • IgG GMCs for the vaccine serotypes 1 month after the last assigned vaccination • Percentages of participants with predefined IgG concentrations for the 13 matched serotypes 1 month after the last assigned vaccination • OPA GMTs for the vaccine serotypes 1 month after the last assigned vaccination
Exploratory Immunogenicity Objective	**Exploratory Immunogenicity Endpoints**	**Exploratory Immunogenicity Estimands**
Objectives	**Endpoints**	**Estimands**
• To describe additional immune response of 20vPnC after 1 or 2 doses	• Pneumococcal serotype-specific IgG concentration • Pneumococcal serotype-specific OPA titers	In evaluable participants in each group: • IgG GMFRs from before to 1 month after the last assigned vaccination for the vaccine serotypes • Percentages of participants with OPA titers ≥ LLOQ for the vaccine serotypes before and 1 month after the last assigned vaccination • OPA GMFRs from before to 1 month after the last assigned vaccination for the vaccine serotypes

Sample size

Approximately 360 toddlers were planned to be enrolled and randomized. The number of participants randomized and who received Dose 1 was 356 and 116 (95.9%) participants who were randomized to the 2-dose 20vPnC group received Dose 2. The numbers of participants included in the all-available and the evaluable immunogenicity populations were generally similar in the 3 vaccine groups with 327 in the all-available immunogenicity population, and 318 in the evaluable population. There were 356 participants included in the safety population.

Statistical Methods

The primary safety objectives were evaluated by descriptive summary statistics for local reactions, systemic events and AEs (including SAEs). AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA). A 3-tier approach was used to summarize AEs.

The primary pneumococcal immunogenicity objectives were evaluated by descriptive summary statistics for each of the 7 additional serotypes in 20vPnC. Other secondary and exploratory immunogenicity objectives were evaluated by descriptive summary statistics.

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

Results

Safety results

- The percentages of participants with local reactions were similar in the 2-dose 20vPnC, 1-dose 20vPnC, and 13vPnC control groups. Pain at injection site was the most frequently reported local reaction in the 2-dose 20vPnC group while redness was the most frequently reported local reaction in the 1-dose 20vPnC and 13vPnC (control) groups. Most local reactions were mild or moderate in severity with a median duration of 1 to 3 days.
- The percentages of participants with systemic events were similar in the 2-dose 20vPnC, 1-dose 20vPnC and 13vPnC (control) groups. Irritability was the most frequently reported systemic event in all groups. Most systemic events were mild or moderate in severity with a median duration of 1 to 2 days.
- The percentage of participants with AEs from last vaccination to 1 month after last vaccination were similar in the 2-dose (22.4%), 1-dose 20vPnC (24.6%), and 13vPnC (25.6%) control groups. All AEs were assessed as not related to study intervention by the investigators.
- The percentage of participants with SAEs from last vaccination to 1 month after vaccination were low and similar in the 2-dose 20vPnC, 1-dose 20vPnC, and 13vPnC (control) groups. Most SAEs reported were consistent with medical events that may occur in this population, and all SAEs were assessed by the investigator as not related to study intervention.

The CHMP agrees on MAH summary on safety and for 13vPnC. Overall, no new safety concerns detected in participants receiving IM 13vPnC.

Immunogenicity Results

- In the 2-dose 20vPnC group, ≥91.2% of participants had an IgG concentration greater than or equal to the predefined serotype-specific IgG concentrations for each of the 7 additional serotypes. In the 1-dose 20vPnC group, ≥75.9% of participants had an IgG concentration greater than or equal to the predefined serotype-specific IgG concentrations for each of the 7 additional serotypes, except for serotype 12F (54.6%).
- The percentages of participants with predefined serotype-specific IgG concentrations for the 13 matched serotypes 1 month after 1 or 2 doses of 20vPnC were similar to those after 13vPnC.
- The observed IgG GMCs 1 month after last vaccination for the 7 additional serotypes were higher in the 2-dose 20vPnC group than the 1-dose 20vPnC group.

- The observed IgG GMCs 1 month after last vaccination for the 13 matched serotypes were lower in the 2-dose and 1-dose 20vPnC groups than in the 13vPnC group.

  The CHMP agrees on MAH summary on immunogenicity results.

2.3.3. Discussion on clinical aspects

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

No new safety concern is raised from this study and the benefit/risk profile of 13vPnC remains unchanged.

3. Rapporteur's CHMP overall conclusion and recommendation

☒ **Fulfilled:**

The results of this study indicate no new safety concern. The P46 procedure is considered fulfilled.

No regulatory action required.