EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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/P46/064

Note

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

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1. Introduction

On April 13, 2021, the MAH submitted a completed paediatric study 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 C3571002- A Phase 2, Randomized, Open-Label Trial to Evaluate the Safety and Immunogenicity of a Multivalent Pneumococcal Conjugate Vaccine Given With, or Separately From, 13-Valent Pneumococcal Conjugate Vaccine in Healthy Infants is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Commercially available formulation.

1 dose (0.5 mL) contains Streptococcus pneumoniaesaccharides conjugated to CRM197:

Serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F ..... 2.2 µg

Serotype 6B .....4.4 µg

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- C3571002- A Phase 2, Randomized, Open-Label Trial to Evaluate the Safety and Immunogenicity of a Multivalent Pneumococcal Conjugate Vaccine Given With, or Separately From, 13-Valent Pneumococcal Conjugate Vaccine in Healthy Infants

2.3.2. Clinical study

C3571002- A Phase 2, Randomized, Open-Label Trial to Evaluate the Safety and Immunogenicity of a Multivalent Pneumococcal Conjugate Vaccine Given With, or Separately From, 13-Valent Pneumococcal Conjugate Vaccine in Healthy Infants

Description

Methods

Objectives

Primary

Describe the safety profile of complementary 7-valentpneumococcal conjugate vaccine (c7vPnC) in healthy infants

Secondary

Describe the immunogenicity of c7vPnC in healthy infants

Exploratory

Further describe the immunogenicity of c7vPnC in healthy infants

Describe the immunogenicity of Prevnar 13 administered with or without c7vPnC in healthy infants

Describe the immunogenicity of c7vPnC in toddlers following a 4-dose series of Prevnar 13

Describe the immune responses to concomitantly administered diphtheria and pertussis vaccine antigens

Assessment comment: This report will focus on objectives related to Prevenar 13.

Study design

Phase 2, multicenter, randomized, active-controlled, open-label study with a 3 arm parallel design, conducted at investigator sites in the United States.

Study population /Sample size

Key inclusion criteria are as follows:

1. Evidence of a personally signed and dated informed consent document (ICD) indicating that the participant's legally acceptable representative (LAR) has been informed of all pertinent aspects of the study.

2. Male or female infant born at >36 weeks of gestation and 2 months (≥42 to ≤98days) of age at the time of consent (the day of birth is considered day of life 1).

3. Healthy infant determined by medical history, physical examination, and clinical judgment.

Key exclusion criteria are as follows:

1. Previous vaccination with licensed or investigational pneumococcal vaccine.

2. Contraindication to immunization with diphtheria, tetanus, pertussis, or 13-valent pneumococcal conjugate vaccines, according to each vaccine's product information.

3. History of microbiologically proven invasive disease caused byS pneumoniae.

4. 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.

5. Other acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

6. Participants who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or planned receipt through the last study visit. If systemic corticosteroids had been administered short term (<14 days) for treatment of an acute illness, participants should not have been enrolled into the study until corticosteroid therapy had been discontinued for at least 28 days before investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) corticosteroids are permitted.

7. Participants with known or suspected immunodeficiency or other conditions associated with immunosuppression, including, but not limited to, immunoglobulin class/subclass deficiencies, DiGeorge syndrome, generalized malignancy, human immunodeficiency virus infection, leukemia, lymphoma, or organ or bone marrow transplant.

Sample size

The study was not designed for hypothesis testing, and therefore no formal sample size calculation was made. The study included 565 subjects in total.

Treatments

Five hundred sixty-five infants ≥42 to ≤98 days old were randomized (1:1:1) to receive a vaccine series with:

- c7vPnC coadministered with Prevenar 13 (Group 1 - c7vPnC Coadministered group);
- c7vPnC given 1 month after Prevenar 13 (Group 2 -c7vPnC Separated group); or
- Prevenar 13 alone as the active control group (Group 3 – Prevenar 13 Control group, with Supplemental Dose of c7vPnC). A single dose of c7vPnC was administered after the Prevenar 13 series was completed in this group.

In all groups, Prevenar 13 was administered at 2, 4, 6, and 12 months of age. c7vPnC was administered at 2, 4, 6, and 12 months of age in the c7vPnC Coadministered group; at 3, 5, 7, and 13 months of age in the c7vPnC Separated group; and at 13 months of age in the Prevenar13 Control group.

Assessment comment: The vaccination schedule is in agreement with the approved dosage.

Outcomes/endpoints

Safety

- Proportions of participants reporting prompted local reactions (redness, swelling, and pain at the injection site) within 7 days of each dose
- Proportions of participants reporting prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) within 7 days of each dose
- Proportions of participants reporting adverse events (AEs) from Dose 1 to 1 month following Dose 3 and from Dose 4/Supplemental Dose to 1 month following Dose 4/Supplemental Dose
- Proportions of participants reporting serious adverse events (SAEs) and newly diagnosed chronic medical condition (NDCMCs) from Dose 1 to 6 months following Dose4/Supplemental Dose

Immunogenicity

- Pneumococcal serotype-specific immunoglobulin G (IgG) concentrations 1 month after Dose 3
- Pneumococcal serotype-specific IgG concentrations 1 month after Dose 4
- Pneumococcal serotype-specific IgG concentrations before Dose4
- Pneumococcal serotype-specific opsonophagocytic activity (OPA) titers at various study time points

- Pneumococcal serotype-specific IgG concentrations of the serotypes in Prevnar 13 at various study time points
- To describe the immunogenicity of c7vPnC in toddlers following a 4-dose seriesof Prevnar 13
- Pneumococcal serotype-specific IgG concentrations 1 month after the Supplemental Dose
- To describe the immune responses to concomitantly administered diphtheria and pertussis vaccine antigens
- Diphtheria toxoid and pertussis antibody levels 1 month after Dose 3

Statistical Methods

Descriptive statistics were used to summarize demographic characteristics, immunogenicity endpoints, and reactogenicity. AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) and were summarized by vaccine group.

Results

Recruitment/ Number analysed

A total of 565 participants were randomized. These were 512 participants from 39 sites, and 53 participants from the 2 sites terminated early due to serious quality issues. The disposition of the 512 subjects included in the study are summarised below. The subjects from the 2 excluded sites are accounted for in the CSR.

Table 5. Disposition of All Subjects – Dose 1 to 1 Month After Dose 3

	Vaccine Group (as Randomized)			
	Group 1 - c7vPnC Coadministered n[a] (%)	Group 2 - c7vPnC Separated n[a] (%)	Group 3 - Prevnar 13 Control n[a] (%)	Total n[a] (%)
Randomized[b]	174 (100.0)	170 (100.0)	168 (100.0)	512 (100.0)
Not vaccinated[c]	3 (1.7)	23 (13.5)	2 (1.2)	28 (5.5)
Vaccinated				
Dose 1	171 (98.3)	147 (86.5)	166 (98.8)	484 (94.5)
Dose 2	159 (91.4)	135 (79.4)	153 (91.1)	447 (87.3)
Dose 3	151 (86.8)	127 (74.7)	146 (86.9)	424 (82.8)
Completed 1-month visit after Dose 3	137 (78.7)	115 (67.6)	124 (73.8)	376 (73.4)
Withdrawn before 1-month visit after Dose 3	27 (15.5)	28 (16.5)	34 (20.2)	89 (17.4)
Reason for withdrawal				
Withdrawal by parent/guardian	17 (9.8)	15 (8.8)	21 (12.5)	53 (10.4)
Lost to follow-up	4 (2.3)	4 (2.4)	5 (3.0)	13 (2.5)
No longer meets eligibility criteria	3 (1.7)	4 (2.4)	6 (3.6)	13 (2.5)
Study terminated by sponsor[d]	3 (1.7)	3 (1.8)	1 (0.6)	7 (1.4)
Other	0	1 (0.6)	1 (0.6)	2 (0.4)
Adverse event	0	1 (0.6)	0	1 (0.2)

Note: Group 1 = c7vPnC coadministered with Prevnar 13, Group 2 = c7vPnC given 1 month after Prevnar 13, and Group 3 = Prevnar 13 alone as the active control group with a supplemental dose of c7vPnC.

Note: Doses 1, 2 and 3 are the doses of c7vPnC administered in Groups 1 and 2, or the doses of Prevnar 13 administered in Group 3.

a. n = Number of subjects in the specified category.

b. The values in this row are the denominators for the percentage calculations for the vaccine groups.

c. For Group 2, "not vaccinated" includes subjects who received their first dose of Prevnar 13 but did not receive Dose 1 of c7vPnC.

d. Vaccinations and blood draws were terminated; however, safety follow-up procedures were continued per protocol.

Baseline data

The study population consisted of racially diverse, male and female participants aged 43 to 126 days, with mean ages of 65.9, 95.1, and 64.9 days at Dose 1 for the c7vPnC Coadministered, c7vPnC Separated, and Prevnar 13 groups, respectively. The mean age of the c7vPnC Separated group at Dose 1 was approximately 1 month older than the c7vPnC Coadministered and Prevnar 13 Control groups, which was consistent with the vaccination schedule. The demographic characteristics for sex, race, and ethnicity among the 3 vaccine groups were similar. The percentages of participants of Hispanic/Latino ethnicity (47.6% to 52.0%) from the 3 vaccine groups were consistently higher than the general United States infant population.

Efficacy results

Considering that this procedure concerns Prevenar13, the antibody responses to the 13 serotypes in Prevenar 13 are presented, and the responses to the experimental 7-valent vaccine are only briefly summarised in this report.

Pneumococcal Immune Response for Prevnar 13 Serotypes

One month after the third dose of Prevnar 13, there were relatively high (≥90%) proportions of participants with the prespecified serotype-specific IgG concentrations for the Prevnar 13 serotypes in all 3 vaccine groups. The percentages of participants with the prespecified IgG concentrations ranged from 93.8% (serotype 3) to 99.2% (serotype 19F) in the c7vPnC Coadministered group, 97.9% (serotypes 3, 9V, and 14) to 100.0% (serotypes 1, 4, 5, 6A, 6B, 7F, 18C, 19A, and 23F) in the c7vPnC

Separated group, and 90.8% (serotype 3) to 100.0% (serotypes 6A, 7F, and 19F) in the Prevnar 13 Control group (Table 24).

Table 24. Subjects Achieving a Prespecified Level of Pneumococcal IgG Antibody Concentrations for Prevnar 13 Serotypes – 1 Month After 3rd Dose of Prevnar 13 – Dose 3 Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)											
		Group 1 - c7vPnC Coadministered				Group 2 - c7vPnC Separated				Group 3 - Prevnar 13 Control			
Serotype	Comparison Level	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
1	≥0.35 µg/mL	128	124	96.9	(92.2, 99.1)	94	94	100.0	(96.2, 100.0)	109	108	99.1	(95.0, 100.0)
3	≥0.35 µg/mL	128	120	93.8	(88.1, 97.3)	94	92	97.9	(92.5, 99.7)	109	99	90.8	(83.8, 95.5)
4	≥0.35 µg/mL	128	124	96.9	(92.2, 99.1)	94	94	100.0	(96.2, 100.0)	109	106	97.2	(92.2, 99.4)
5	≥0.23 µg/mL	128	124	96.9	(92.2, 99.1)	94	94	100.0	(96.2, 100.0)	109	106	97.2	(92.2, 99.4)
6A	≥0.35 µg/mL	128	125	97.7	(93.3, 99.5)	94	94	100.0	(96.2, 100.0)	109	109	100.0	(96.7, 100.0)
6B	≥0.10 µg/mL	128	124	96.9	(92.2, 99.1)	94	94	100.0	(96.2, 100.0)	109	107	98.2	(93.5, 99.8)
7F	≥0.35 µg/mL	128	126	98.4	(94.5, 99.8)	94	94	100.0	(96.2, 100.0)	109	109	100.0	(96.7, 100.0)
9V	≥0.35 µg/mL	128	124	96.9	(92.2, 99.1)	94	92	97.9	(92.5, 99.7)	109	106	97.2	(92.2, 99.4)
14	≥0.35 µg/mL	128	123	96.1	(91.1, 98.7)	94	92	97.9	(92.5, 99.7)	109	106	97.2	(92.2, 99.4)
18C	≥0.35 µg/mL	128	126	98.4	(94.5, 99.8)	94	94	100.0	(96.2, 100.0)	109	108	99.1	(95.0, 100.0)
19A	≥0.12 µg/mL	128	126	98.4	(94.5, 99.8)	94	94	100.0	(96.2, 100.0)	109	108	99.1	(95.0, 100.0)
19F	≥0.35 µg/mL	128	127	99.2	(95.7, 100.0)	94	93	98.9	(94.2, 100.0)	109	109	100.0	(96.7, 100.0)
23F	≥0.35 µg/mL	128	122	95.3	(90.1, 98.3)	94	94	100.0	(96.2, 100.0)	109	105	96.3	(90.9, 99.0)

Abbreviations: IgG = immunoglobulin G; SAP = statistical analysis plan.

Note: Group 1 = c7vPnC coadministered with Prevnar 13, Group 2 = c7vPnC given 1 month after Prevnar 13, and Group 3 = Prevnar 13 alone as the active control group with a supplemental dose of c7vPnC.

a. N = number of subjects with a valid and determinate concentration for the specified serotype. These values are the denominators for the percentage calculations.

b. n = Number of subjects with an antibody concentration ≥ specified comparison level (per the SAP) for the given serotype.

c. Exact 2-sided CI based on the Clopper and Pearson method

One month after the fourth dose of Prevnar 13, strong immune responses to the Prevenar 13 serotypes were observed. IgG GMCs ranged from 1.61 µg/mL (serotype 3) to 22.25 µg/mL (serotype 6A) in the c7vPnC Coadministered group, 1.63 µg/mL (serotype 3) to 28.36 µg/mL (serotype 23F) in the c7vPnC Separated group, and 1.82 µg/mL (serotype 3) to 23.42 µg/mL (serotype 6A) in the Prevenar 13 Control group.

Pneumococcal Immune Response for c7vPnC Serotypes

One month after Dose 3 of c7vPnC, there were high proportions (≥89%) of participants with the prespecified IgG concentrations (≥0.35 μg/mL) for all of the c7vPnC serotypes in both c7vPnC groups. The percentages of participants with prespecified IgG concentrations ranged from 89.8% (serotype 10A) to 98.4% (serotype 8) in the c7vPnC Coadministered group and from 98.1% (serotypes 10A and 12F) to 100.0% (serotypes 8, 15B, and 22F) in the c7vPnC Separated group. As expected, the IgG concentrations in the Prevnar 13 Control group were low (≤6.4%).

One month after Dose 4, the IgG GMCs ranged from 3.15 µg/mL (serotype 12F) to 25.68 µg/mL (serotype 22F) in the c7vPnC Coadministered group and 2.57 µg/mL (serotype 12F) to 29.92 µg/mL (serotype 22F) in the c7vPnC Separated group. As expected, the GMCs in the Prevnar 13 Control group were low (Table 16). In contrast to 1 month after Dose 3, the IgG GMCs were slightly higher for most serotypes in the c7vPnC Coadministered group than in the c7vPnC Separated group.

Immune Response to Concomitant Vaccines

Antibody concentrations to the diphtheria and pertussis vaccine antigens were determined on sera collected 1 month after Dose 3 from a randomly selected subset of participants in the c7vPnC Coadministered and the Prevnar 13 Control groups.

Overall, ≥92.2% and ≥95.2% of the tested participants in the c7vPnC Coadministered and Prevnar 13 Control groups, respectively, achieved the prespecified antibody concentrations for diphtheria and pertussis.

Safety results

vPnC was well tolerated, and there were acceptable rates of local reactions and systemic events after vaccination with c7vPnC in the c7vPnC Coadministered and c7vPnC Separated groups. Most were mild or moderate in severity and resolved within 1 to 3 days.

There appeared to be a milder tolerability profile in the c7vPnC Separated group. This may in part be explained by the fact that Doses 1 to 4 in the c7vPnC Coadministered and Prevnar 13 Control groups were administered with permitted nonstudy vaccines, while the c7vPnC Separated group received permitted nonstudy vaccines with the intervening Prevnar 13 doses and not Doses 1 to 4.

Proportions of participants reporting any AE were low and similar in the c7vPnC Coadministered, c7vPnC Separated, and Prevnar 13 Control groups. Upper respiratory tract infection, otitis media, and bronchiolitis were the most frequently reported AEs.

One participant reported 1 AE that was considered related to vaccination in the SOC of skin and subcutaneous disorders. Few severe AEs were reported. No immediate AEs were reported.

None of the SAEs or NDCMCs reported during the study were considered related to vaccination. One participant was withdrawn from the study for safety-related reasons and there were no deaths during the study.

2.3.3. Discussion on clinical aspects

The purpose of this study was to study the experimental 7-valent pneumococcal conjugate vaccine, given either separated from Prenvenar 13 or co-administered. The results from this study regarding the immune responses and safety of Prevenar 13 are considered to be in agreement with previously reported results. An evaluation of the 7-valent experimental vaccine is not considered to be in the scope of this procedure.

3. Overall conclusion and recommendation

As discussed above, the submitted study does not change the benefit-risk balance for Prevenar 13, and no further regulatory action is needed. The study confirms what is already known about immune responses and safety of Prevenar 13.

☒ Fulfilled:

No regulatory action required.