15 August 2014
EMA/189944/2015
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No1901/2006, as amended

Prevenar 13

pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)

Procedure No: EMEA/H/C/001104

P46 056

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

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1. Introduction

On July 21, 2013, 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.

Scientific discussion

Information on the development program

The MAH stated that "B1851037: Final 1- and 2-Year Report: A Phase 4, Open-label Trial Describing the Safety, Tolerability, and Immunogenicity of the 13-valent Pneumococcal Conjugate Vaccine in Preterm Compared to Term Infants is a standalone study" is a stand-alone study. The primary part of the study was submitted to the EMA in December 2012 to fulfil the post-marketing commitment (FUM 014) and add information to the SmPC and package leaflet on the use of Prevenar 13 in infants born prematurely (EMEA/H/C/1104/II/76).

Information on the pharmaceutical formulation used in the study

The formulation used in this study was the same as the commercially available.

Clinical aspects

Introduction

The MAH submitted a final report for:

- Protocol B1851037 Final 1- and 2-Year Report: A Phase 4, Open-label Trial Describing the Safety, Tolerability, and Immunogenicity of the 13-valent Pneumococcal Conjugate Vaccine in Preterm Compared to Term Infants;

Clinical study

Protocol B1851037: Final 1- and 2-Year Report: A Phase 4, Open-label Trial Describing the Safety, Tolerability, and Immunogenicity of the 13-valent Pneumococcal Conjugate Vaccine in Preterm Compared to Term Infants;

Description

Methods

Objectives

Primary Objectives:

- To describe the pneumococcal immune response induced by pneumococcal 13-valent pneumococcal conjugate vaccine (13vPnC) when measured 1 month after the infant series in preterm infants compared to term infants (≥37 weeks of gestation)

- To evaluate the safety profile of 13vPnC administered at 2, 3, 4, and 12 months of age to preterm and term infants, as measured by the incidence rates of local reactions, systemic events, and adverse events (AEs)

Secondary Objective: The secondary objective of this study was to describe the pneumococcal immune response induced by 13vPnC when measured 1 month after the toddler dose in preterm infants compared to term infants (≥37 weeks of gestation).

Exploratory Objectives:

- To describe the pneumococcal immune response induced by 13vPnC when measured 1 month after the infant series in the following preterm infant subgroups:
    - Born at more than or equal to 32 weeks and less than 37 weeks of gestation (32≤ gestational age [GA] <37)
    - Born at more than or equal to 29 weeks and less than 32 weeks of gestation (29≤ GA <32)
    - Born at less than 29 weeks of gestation (GA <29)
- To describe the pneumococcal immune response induced by 13vPnC when measured before and 1 month after the toddler dose in the following preterm infant subgroups:
    - Born at more than or equal to 32 weeks and less than 37 weeks of gestation (32≤ GA <37)
    - Born at more than or equal to 29 weeks and less than 32 weeks of gestation (29≤ GA <32)
    - Born at less than 29 weeks of gestation (GA <29)

Study design

This was a multicenter, Phase 4, open-label, 2-arm, parallel-group study to assess the safety, tolerability, and immunogenicity of 13vPnC in preterm infants compared to term infants (≥37 weeks of gestation) receiving 13vPnC at 2, 3, 4, and 12 months of age. This was a post-authorization safety study carried out in response to a request from the European Medicines Agency.

Study population /Sample size

Inclusion Criteria:

Group 1: Preterm Infant

1. Male or female infant born at <37 weeks of gestation (GA as determined by the investigator).
2. Chronological age ≥42 to ≤98 days (approximately 2 months) at the time of enrolment.
3. Otherwise healthy preterm infant as determined by medical history, physical examination, and judgment of the investigator.
4. Parent/legal guardian was able to complete all relevant study procedures during study participation.

5. Available for the entire study period and whose parent/legal guardian could be reached by telephone.

Group 2: Term Infant

As for preterm infants but:

1. Male or female infant born at ≥37 weeks of gestation (GA as determined by the investigator).
2. Chronological age ≥42 to ≤98 days (approximately 2 months) at the time of enrolment.

Exclusion Criteria: Subjects were ineligible to participate in this study if they met any of the following exclusion criteria:

Previous vaccination with licensed or investigational pneumococcal vaccine, Haemophilus influenzae type b (Hib) conjugate vaccine, meningococcal C conjugate vaccine, or diphtheria, tetanus, pertussis, or poliovirus vaccines

A previous anaphylactic reaction or allergy to any vaccine or vaccine-related component

Contraindication to vaccination with any routine pediatric vaccines

Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate intramuscular injection

History of culture-proven invasive disease caused by Streptococcus pneumonia

Known or suspected immune deficiency or immune suppression

Major known congenital malformation or serious chronic disorder

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 disorder

Receipt of any other investigational vaccines, drugs, or medical devices from 28 days before inclusion and the first study vaccination until the end of the study. (Note: participation in purely observational studies was acceptable.)

Infant who was a direct descendant (e.g., child or grandchild) of the study personnel

Major illness or conditions that, in the investigator's judgment, substantially increased the risk associated with the subject's participation in, and completion of, the study, or could have precluded the evaluation of the subject's response

Treatments

No vaccinations were given during the study period covered by this report.

Outcomes/endpoints

Immunogenicity Evaluations: Blood samples were obtained, according to the subject's weight, at 1 month after the third dose of the infant series (Visit 4, at approximately 5 months of age), just before the toddler dose (Visit 5, at approximately 12 months of age), 1 month after the toddler dose (Visit 6, at approximately 13 months of age), the 1-year follow-up (Visit 7, at approximately 24 months of age), and the 2-year follow-up (Visit 8, at approximately 36 months of age). A total volume of up to

approximately 5 mL to 25 mL of blood (depending on the subject's weight) was collected during the study.

Serotype-specific immunoglobulin G (IgG) concentrations to the 13 pneumococcal serotypes in 13vPnC were determined by enzyme-linked immunosorbent assay in all subjects for each blood sample and expressed as micrograms per milliliter (μg/mL).

Assays of serum OPA elicited by the 13 pneumococcal serotypes were performed for all subjects where sufficient sera was available, and the results were reported as OPA titers.

Safety Evaluations: AEs were collected and recorded on the case report form based on ancillary information on the electronic diary, clinical evaluation during a study visit, and verbal questioning of the parent or legal guardian about the child's health since the last visit. AEs were collected from the signing of the informed consent to Visit 4 and from Visit 5 to Visit 6, and for 24 hours after Visits 7 and 8. All serious adverse events (SAEs) were recorded from the signing of the informed consent to Visit 6 and for 24 hours after Visits 7 and 8, and were to be reported at any time an investigator became aware. When a subject withdrew from the study due to an SAE, the SAE was reported in accordance with the reporting requirements. For SAEs, the active reporting period to Pfizer or its designated representative began at the time that the subject's parent(s) or legal guardian(s) provided informed consent, which was obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including Visit 6 but no less than 28 calendar days after the last administration of the investigational product. If an investigator was made aware of any SAE occurring any time after the active reporting period, it was to be promptly reported. Local reactions and systemic events were not applicable to the study period covered by this report.

Statistical Methods

Immunogenicity analyses were performed for 2 populations, the evaluable and all-available immunogenicity populations. The primary immunogenicity population was the evaluable immunogenicity population.

The primary endpoint for each of the pneumococcal serotypes was the proportion of subjects achieving a serotype-specific IgG concentration $\geq$0.35 μg/mL measured 1 month after the infant series. Within each group, geometric mean concentrations (GMCs) of the pneumococcal IgG antibody were calculated for each visit at which blood was drawn.

Additionally, the geometric mean fold rises (GMFRs) in antibody concentration (post-vaccination/pre-vaccination) were summarized by geometric means and confidence interval (CI), and also computed using the logarithmically transformed assay results at appropriate time points, for all groups. Only subjects with both pre- and post-vaccination results were included in the derivation of GMFRs.

Comparisons between Groups 1 and 2 were constructed using geometric mean ratios and 95% CI following the infant series, prior to the toddler dose, after the toddler dose, and at each persistence time point as data permitted. The OPA data were similarly analysed.

Subgroup data in Group 1 was descriptively summarized by subgroup, but no formal comparisons between subgroups were constructed.

The safety populations included all subjects who received at least 1 dose of 13vPnC, and who had a safety observation during the follow-up period.

Immunogenicity:

For each of the pneumococcal serotypes, the proportion of the subjects achieving IgG concentration ≥ 0.35 μg/mL measured 1 month after the infant series was calculated along with an exact, 2-sided 95% CI. The difference in the proportion between the 2 groups was computed along with exact, unconditional, 2-sided 95% CI, with the standardized test statistics and gamma=0.000001. In addition, the ratio of the GMCs of the 2 groups with 2-sided 95% CI was calculated for each serotype.

For the assay results 1 month after the toddler dose, immunogenicity analyses were performed similarly. In addition, the serotype-specific fold rise in antibody concentration from the pre-toddler dose to 1 month after the toddler dose was derived for each subject and summarized using GMFR along with 2-sided 95% CI. The 2 groups were compared by computing the ratio of the GMFR along with 2-sided 95% CI.

For the 3 subgroups in Group 1 (32≤ GA <37 weeks, 29≤ GA <32 weeks, and GA <29 weeks), the above descriptive statistics were summarized by subgroup following the infant series and the toddler dose.

Serum OPA was described by geometric mean titer (GMT) along with 2-sided 95% CI for each serotype. The OPA results following the infant series and the toddler dose and at 1 and 2 years following the toddler dose were analysed in the same manner as IgG concentration.

Proportions of the subjects achieving OPA titers ≥ lower limit of quantitation (LLOQ) were derived. Proportions were compared between groups in a manner similar to what was done for the IgG proportions.

Reverse cumulative distribution curves (RCDCs) are presented graphically by group for each serotype-specific pneumococcal IgG antibody concentration and for OPA titers. The RCDCs for each group plot pre- and post-vaccination IgGs on the same graph where appropriate, distinguishable by symbol and/or line style choice. Separate plots were generated for the subgroups in Group 1.

Safety:

The safety endpoints were AEs, local reactions, and systemic events including fever, and use of antipyretic medications to treat and prevent symptoms. AEs were categorized according to the Medical Dictionary for Regulatory Activities and were summarized by vaccine group for each pneumococcal conjugate vaccination separately. All summaries showed, by vaccine group, the number, and the percentage of subjects experiencing at least 1 event and the number of events. SAEs were summarized for the infant series and toddler dose, rather than for each vaccination separately.

Comparisons between Groups 1 and 2 were constructed using Fisher's exact test for proportions and 95% CIs. Proportions were also derived for the subgroup data from Group 1, but no formal comparison between subgroups was constructed.

Results

Recruitment/ Number analysed

Subject Disposition and Demography: Of the 200 subjects enrolled in the study, 176 subjects (88.0%) completed the 1-year follow-up after the toddler dose visit and 161 subjects (80.5%) completed the 2-year follow-up after the toddler dose visit. Twenty (20) subjects (10.0%) were withdrawn from the study before the 1-year follow-up:

16 subjects (8.0%) were no longer willing to participate in the study (7 subjects in Group 1 and 9 subjects in Group 2) and 4 subjects (2.0%) in Group 1 were lost to follow-up. An additional 15 subjects (7.5%) were withdrawn from the study before the 2-year follow-up: 11 subjects (5.5%) were no longer willing to participate in the study (5 subjects in Group 1 and 6 subjects in Group 2) and 4 subjects (2.0%) no longer met eligibility criteria (2 subjects in Group 1 and 2 subjects in Group 2).

For the evaluable 1-year follow-up immunogenicity population, subjects in Groups 1 and 2 were similar with respect to race, sex, and age at Dose 1. All subjects were white and there were more male (55.0%) than female (45.0%) subjects enrolled in Group 1, while there were more female (58.8%) than male (41.3%) subjects enrolled in Group 2. The mean age at Dose 1 was 1.8 months for Group 1 and 1.6 months for Group 2. The mean GA was 30.8 weeks for Group 1 and 39.4 weeks for Group 2. The mean birth weight was 1.5 kg for Group 1 and 3.3 kg for Group 2.

For the evaluable 2-year follow-up immunogenicity population, subjects in Groups 1 and 2 were similar with respect to race, sex, and age at Dose 1. Subjects in Groups 1 and 2 were similar with respect to race, sex, and age at Dose 1. The gender distribution, mean age at Dose 1, mean GA, and mean birth weight were all similar to the evaluable 1-year follow-up immunogenicity population for both groups.

Immunogenicity results

Pneumococcal IgG Response

Pneumococcal IgG GMCs for each time point and the ratio of GMCs between groups are presented for the evaluable immunogenicity population in Table 11. The results 1 month after the infant series, before the toddler dose, and 1 month after the toddler dose were presented in the primary-analysis report; they are shown again here to provide a frame of reference for the results at the 1- and 2-year follow-up.

Table 11. Comparison of Pneumococcal IgG GMCs (μg/mL) by Time Point - Evaluable Immunogenicity

Population

Serotype	Sampling Time[a]	Group (as Enrolled)						Comparison (Group 1 to Group 2)	
		Group 1 (Preterm Infant)			Group 2 (Term Infant)				
		n[b]	GMC[c]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])	Ratio[e]	(95% CI[f])
7vPnC									
4	1 month after infant series	99	1.96	(1.67, 2.31)	97	2.46	(2.04, 2.97)	0.80	(0.62, 1.02)
	Before toddler dose	85	0.31	(0.26, 0.37)	85	0.41	(0.34, 0.49)	0.76	(0.60, 0.97)
	1 month after toddler dose	86	2.57	(2.18, 3.03)	87	3.97	(3.32, 4.74)	0.65	(0.51, 0.82)
	1 year after toddler dose	80	0.30	(0.25, 0.36)	79	0.37	(0.31, 0.44)	0.81	(0.63, 1.04)
	2 years after toddler dose	70	0.19	(0.16, 0.23)	71	0.24	(0.20, 0.29)	0.80	(0.61, 1.03)
6B	1 month after infant series	99	0.73	(0.55, 0.97)	97	1.30	(1.00, 1.67)	0.56	(0.38, 0.82)
	Before toddler dose	82	0.48	(0.39, 0.58)	85	0.94	(0.79, 1.11)	0.51	(0.39, 0.66)
	1 month after toddler dose	86	4.42	(3.64, 5.37)	87	7.27	(6.09, 8.68)	0.61	(0.47, 0.79)
	1 year after toddler dose	80	1.26	(1.02, 1.57)	80	2.01	(1.69, 2.39)	0.63	(0.48, 0.83)
	2 years after toddler dose	70	1.44	(1.13, 1.85)	70	2.70	(2.10, 3.48)	0.53	(0.38, 0.76)
9V	1 month after infant series	99	1.26	(1.08, 1.47)	97	1.70	(1.45, 2.00)	0.74	(0.59, 0.93)
	Before toddler dose	85	0.39	(0.33, 0.46)	85	0.62	(0.53, 0.72)	0.64	(0.51, 0.80)
	1 month after toddler dose	86	2.30	(1.99, 2.66)	87	3.06	(2.62, 3.56)	0.75	(0.61, 0.93)
	1 year after toddler dose	80	0.61	(0.48, 0.78)	80	0.98	(0.82, 1.19)	0.62	(0.46, 0.84)
	2 years after toddler dose	71	0.74	(0.58, 0.94)	70	0.99	(0.80, 1.23)	0.74	(0.54, 1.03)
14	1 month after infant series	99	7.48	(6.23, 8.99)	97	6.08	(4.82, 7.67)	1.23	(0.92, 1.65)
	Before toddler dose	85	2.02	(1.68, 2.43)	85	2.36	(1.94, 2.87)	0.86	(0.66, 1.12)
	1 month after toddler dose	86	9.24	(7.66, 11.14)	87	11.02	(9.44, 12.86)	0.84	(0.66, 1.07)
	1 year after toddler dose	79	1.43	(1.15, 1.78)	80	1.73	(1.40, 2.14)	0.83	(0.61, 1.12)
	2 years after toddler dose	70	1.06	(0.78, 1.43)	71	1.37	(1.03, 1.82)	0.77	(0.51, 1.17)
18C	1 month after infant series	99	1.93	(1.66, 2.24)	97	1.93	(1.62, 2.29)	1.00	(0.80, 1.25)
	Before toddler dose	85	0.32	(0.28, 0.37)	85	0.30	(0.26, 0.36)	1.06	(0.85, 1.32)
	1 month after toddler dose	86	2.37	(2.02, 2.79)	87	2.81	(2.32, 3.40)	0.84	(0.66, 1.08)
	1 year after toddler dose	80	0.33	(0.27, 0.41)	79	0.66	(0.54, 0.81)	0.50	(0.37, 0.67)
	2 years after toddler dose	69	0.32	(0.24, 0.42)	71	0.57	(0.47, 0.69)	0.56	(0.40, 0.78)
19F	1 month after infant series	99	2.21	(1.89, 2.58)	97	3.05	(2.62, 3.55)	0.72	(0.58, 0.90)

	Before toddler dose	85	0.68	(0.57, 0.80)	85	0.93	(0.79, 1.10)	0.73	(0.58, 0.92)
	1 month after toddler dose	86	7.38	(6.23, 8.76)	87	11.67	(9.47, 14.36)	0.63	(0.48, 0.83)
	1 year after toddler dose	80	0.96	(0.80, 1.15)	79	1.78	(1.40, 2.26)	0.54	(0.40, 0.72)
	2 years after toddler dose	71	1.10	(0.83, 1.46)	70	2.43	(1.71, 3.44)	0.45	(0.29, 0.71)
23F	1 month after infant series	99	0.86	(0.69, 1.07)	97	1.36	(1.10, 1.68)	0.64	(0.47, 0.86)
	Before toddler dose	81	0.24	(0.18, 0.31)	83	0.40	(0.33, 0.48)	0.60	(0.43, 0.83)
	1 month after toddler dose	86	2.45	(2.01, 2.98)	87	4.03	(3.36, 4.85)	0.61	(0.46, 0.79)
	1 year after toddler dose	79	0.59	(0.47, 0.74)	80	1.24	(1.01, 1.52)	0.47	(0.35, 0.64)
	2 years after toddler dose	71	1.03	(0.77, 1.38)	71	1.83	(1.42, 2.37)	0.56	(0.38, 0.83)
Additional 1	1 month after infant series	99	1.26	(1.06, 1.48)	97	1.79	(1.50, 2.13)	0.70	(0.55, 0.89)
	Before toddler dose	85	0.39	(0.34, 0.46)	85	0.41	(0.35, 0.48)	0.96	(0.77, 1.20)
	1 month after toddler dose	86	3.32	(2.83, 3.89)	87	4.09	(3.42, 4.89)	0.81	(0.64, 1.03)
	1 year after toddler dose	78	0.40	(0.35, 0.46)	80	0.53	(0.45, 0.62)	0.76	(0.61, 0.94)
	2 years after toddler dose	70	0.32	(0.26, 0.38)	69	0.39	(0.32, 0.47)	0.82	(0.63, 1.07)
3	1 month after infant series	99	0.83	(0.70, 0.98)	97	0.86	(0.75, 1.00)	0.96	(0.77, 1.19)
	Before toddler dose	84	0.07	(0.05, 0.09)	84	0.11	(0.09, 0.14)	0.60	(0.41, 0.87)
	1 month after toddler dose	85	0.52	(0.44, 0.62)	87	0.57	(0.49, 0.65)	0.92	(0.73, 1.15)
	1 year after toddler dose	78	0.13	(0.10, 0.17)	78	0.22	(0.16, 0.30)	0.59	(0.39, 0.90)
	2 years after toddler dose	65	0.17	(0.12, 0.25)	63	0.27	(0.18, 0.40)	0.66	(0.39, 1.11)
5	1 month after infant series	99	0.56	(0.44, 0.70)	97	1.03	(0.87, 1.22)	0.54	(0.40, 0.72)
	Before toddler dose	82	0.74	(0.64, 0.87)	85	1.06	(0.90, 1.26)	0.70	(0.56, 0.88)
	1 month after toddler dose	86	2.63	(2.28, 3.02)	87	3.72	(3.19, 4.33)	0.71	(0.58, 0.87)
	1 year after toddler dose	79	1.10	(0.91, 1.32)	78	1.63	(1.35, 1.97)	0.67	(0.52, 0.87)
	2 years after toddler dose	69	1.34	(1.07, 1.68)	69	1.97	(1.60, 2.41)	0.68	(0.50, 0.92)
6A	1 month after infant series	98	1.22	(0.98, 1.53)	97	2.01	(1.65, 2.46)	0.61	(0.45, 0.82)
	Before toddler dose	85	0.54	(0.45, 0.65)	85	1.01	(0.82, 1.24)	0.54	(0.41, 0.70)
	1 month after toddler dose	86	5.64	(4.86, 6.54)	87	7.84	(6.59, 9.33)	0.72	(0.57, 0.90)
	1 year after toddler dose	80	1.08	(0.89, 1.32)	79	1.59	(1.34, 1.90)	0.68	(0.52, 0.88)
	2 years after toddler dose	71	1.41	(1.09, 1.82)	71	2.10	(1.64, 2.70)	0.67	(0.47, 0.95)
7F	1 month after infant series	99	2.14	(1.81, 2.53)	97	3.02	(2.63, 3.48)	0.71	(0.57, 0.88)
	Before toddler dose	85	0.72	(0.63, 0.82)	85	0.84	(0.73, 0.96)	0.86	(0.71, 1.03)
	1 month after toddler dose	86	4.25	(3.75, 4.82)	87	5.13	(4.48, 5.87)	0.83	(0.69, 1.00)
	1 year after toddler dose	79	0.68	(0.59, 0.80)	80	0.83	(0.72, 0.96)	0.82	(0.67, 1.02)
	2 years after toddler dose	71	0.60	(0.50, 0.71)	70	0.67	(0.57, 0.80)	0.89	(0.70, 1.13)
19A	1 month after infant series	99	2.85	(2.44, 3.33)	97	3.35	(2.85, 3.94)	0.85	(0.68, 1.07)
	Before toddler dose	85	0.86	(0.72, 1.03)	85	1.57	(1.27, 1.92)	0.55	(0.42, 0.72)
	1 month after toddler dose	86	5.57	(4.66, 6.65)	87	8.84	(7.45, 10.48)	0.63	(0.49, 0.81)
	1 year after toddler dose	80	1.61	(1.22, 2.12)	80	3.16	(2.53, 3.95)	0.51	(0.36, 0.72)
	2 years after toddler dose	71	2.33	(1.76, 3.10)	71	4.36	(3.40, 5.61)	0.53	(0.37, 0.78)

Preterm Infant Subgroups (Groups 1A, 1B, and 1C)

Pneumococcal IgG GMCs for each time point were presented for the preterm infant subgroups of the evaluable immunogenicity population. In summary, at the 1- and 2-year follow-up, for all serotypes, there were no discernible patterns in GMCs across the preterm infant subgroups based on GA. For all serotypes, there was a pattern of decline of GMCs from 1 month after the toddler dose to the 1-year follow-up. For the majority of serotypes, GMCs remained higher than or similar to those before the toddler dose.

CHMP's comment: The three groups were children born 32 ≤GA <37 wks, 29 ≤GA <32 and GA ≤29 wks. As in the primary report for this study (infant and boster dose) it is noted that the first subgroup generally had numerically higher IgG GMC compared to the other groups, but the differences were not statistically differences (overlapping 95% CI).

Pneumococcal IgG Concentrations ≥0.35 µg/mL

The proportion of subjects in the evaluable immunogenicity population with a residual pneumococcal IgG concentration ≥0.35 µ g/mL at the 1-year follow-up was numerically lower for subjects in Group 1 compared to Group 2 for all serotypes and statistically significantly lower (upper limit of 95% CI for the

difference <0) for 6 of 13 serotypes (3, 4, 9V, 18C, 19A, and 23F). At the 2-year follow-up, the proportion of subjects in the evaluable immunogenicity population with IgG concentrations ≥0.35 µg/mL was numerically lower for subjects in Group 1 compared to Group 2 for all serotypes and statistically significantly lower (upper limit of 95% CI for the difference <0) for 3 serotypes (18C, 19A, and 23F).

Pneumococcal OPA Geometric Mean Titers

Group 1 (Preterm Infant) versus Group 2 (Term Infant)

A comparison of the Group 1 and Group 2 pneumococcal OPA GMTs at each time point, along with ratios, is presented for the evaluable immunogenicity population in Table 13. For all serotypes, GMTs at the 1- and 2-year follow-up were generally numerically higher than or similar to those before the toddler dose and numerically lower than those 1 month after the toddler dose. At the 1-year follow-up, Group 1 had significantly lower GMTs compared to Group 2 for serotypes 6A, 18C, 19A, and 23F (the upper limit of the 95% CI ratios of the GMTs were <1.0). At the 2-year follow-up, Group 1 had significantly lower GMTs compared to Group 2 for serotypes 5 and 19A (the upper limit of the 95% CI ratios of the GMTs were <1.0).

Table 13. Comparison of Pneumococcal OPA GMTs by Time Point - Evaluable Immunogenicity Population

		Group (as Enrolled)							
		Group 1 (Preterm Infant)			Group 2 (Term Infant)			Comparison (Group 1 to Group 2)	
Serotype	Sampling Time[a]	n[b]	GMT[c]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])	Ratio[e]	(95% CI[f])
7vPnC									
4	1 month after infant series	58	1231	(986.5, 1537.3)	62	923	(746.9, 1139.7)	1.3	(0.99, 1.81)
	Before toddler dose	56	10	(6.0, 15.3)	59	13	(7.9, 21.9)	0.7	(0.37, 1.44)
	1 month after toddler dose	67	1154	(879.2, 1514.5)	61	1757	(1329.1, 2322.4)	0.7	(0.45, 0.97)
	1 year after toddler dose	66	24	(12.9, 45.5)	59	29	(15.2, 54.5)	0.8	(0.35, 2.05)
	2 years after toddler dose	46	15	(7.0, 32.9)	54	17	(9.0, 32.6)	0.9	(0.33, 2.37)
6B	1 month after infant series	51	835	(478.6, 1455.2)	61	732	(494.0, 1086.0)	1.1	(0.59, 2.20)
	Before toddler dose	59	12	(6.8, 20.1)	62	15	(8.5, 25.6)	0.8	(0.37, 1.71)
	1 month after toddler dose	64	1229	(877.2, 1722.1)	61	1406	(1003.4, 1970.3)	0.9	(0.54, 1.40)
	1 year after toddler dose	65	38	(19.0, 74.9)	59	36	(19.2, 68.8)	1.0	(0.41, 2.63)
	2 years after toddler dose	56	29	(13.7, 59.9)	48	27	(12.4, 58.2)	1.1	(0.37, 3.07)
9V	1 month after infant series	54	151	(70.8, 321.1)	60	211	(108.2, 413.4)	0.7	(0.26, 1.93)
	Before toddler dose	52	11	(6.2, 20.9)	63	7	(4.9, 11.1)	1.5	(0.76, 3.12)
	1 month after toddler dose	60	1871	(1217.8, 2873.6)	58	2542	(1711.6, 3775.2)	0.7	(0.41, 1.31)
	1 year after toddler dose	61	141	(67.5, 293.1)	63	244	(126.3, 469.7)	0.6	(0.22, 1.53)
	2 years after toddler dose	50	132	(57.5, 301.5)	55	75	(34.7, 163.7)	1.7	(0.57, 5.36)
14	1 month after infant series	55	1298	(968.3, 1740.3)	66	1033	(735.7, 1451.0)	1.3	(0.80, 1.98)
	Before toddler dose	60	242	(148.5, 394.0)	55	389	(260.4, 582.2)	0.6	(0.33, 1.17)
	1 month after toddler dose	62	1294	(969.0, 1728.4)	62	1651	(1300.1, 2097.1)	0.8	(0.54, 1.14)
	1 year after toddler dose	59	276	(169.0, 449.4)	54	372	(236.1, 586.5)	0.7	(0.38, 1.44)
	2 years after toddler dose	49	262	(142.0, 482.8)	45	296	(161.6, 543.8)	0.9	(0.38, 2.07)
18C	1 month after infant series	56	2931	(2341.2, 3669.3)	63	2057	(1594.0, 2655.1)	1.4	(1.01, 2.00)
	Before toddler dose	54	32	(16.1, 61.7)	58	51	(26.8, 98.3)	0.6	(0.24, 1.55)
	1 month after toddler dose	62	2464	(1696.0, 3579.4)	63	4510	(3399.7, 5981.7)	0.5	(0.34, 0.87)
	1 year after toddler dose	62	33	(16.4, 67.4)	60	121	(56.9, 258.1)	0.3	(0.10, 0.76)
	2 years after toddler dose	56	14	(7.1, 25.9)	56	29	(14.3, 57.9)	0.5	(0.18, 1.21)
19F	1 month after infant series	55	417	(330.7, 525.8)	58	335	(237.2, 472.3)	1.2	(0.82, 1.89)
	Before toddler dose	57	6	(4.1, 7.4)	60	4	(3.8, 4.7)	1.3	(0.97, 1.77)

	1 month after toddler dose	61	376	(229.1, 617.1)	62	640	(431.5, 948.3)	0.6	(0.31, 1.10)
	1 year after toddler dose	67	11	(6.2, 17.7)	57	18	(9.6, 35.4)	0.6	(0.25, 1.30)
	2 years after toddler dose	60	13	(7.4, 22.5)	58	20	(10.1, 39.9)	0.6	(0.27, 1.53)
23F	1 month after infant series	55	733	(539.3, 997.3)	60	582	(413.7, 817.8)	1.3	(0.80, 1.99)
	Before toddler dose	59	11	(6.9, 19.0)	62	16	(9.6, 26.6)	0.7	(0.35, 1.46)
	1 month after toddler dose	65	1048	(738.6, 1488.0)	63	1657	(1217.7, 2255.0)	0.6	(0.40, 1.01)
	1 year after toddler dose	67	45	(23.7, 86.6)	62	168	(92.4, 303.9)	0.3	(0.11, 0.65)
	2 years after toddler dose	58	60	(29.7, 122.2)	59	135	(71.2, 255.3)	0.4	(0.17, 1.15)
Additional									
1	1 month after infant series	88	10	(8.0, 13.4)	87	13	(10.0, 16.8)	0.8	(0.56, 1.15)
	Before toddler dose	76	6	(4.5, 6.8)	80	4	(3.9, 4.8)	1.3	(1.00, 1.60)
	1 month after toddler dose	80	59	(43.7, 78.6)	83	107	(83.0, 137.0)	0.5	(0.38, 0.81)
	1 year after toddler dose	76	5	(4.2, 6.3)	74	5	(4.3, 5.8)	1.0	(0.81, 1.32)
	2 years after toddler dose	70	5	(4.1, 5.4)	68	4	(3.9, 4.6)	1.1	(0.96, 1.31)
3	1 month after infant series	83	61	(51.2, 73.2)	86	57	(46.3, 69.5)	1.1	(0.83, 1.41)
	Before toddler dose	73	8	(6.2, 10.0)	77	8	(6.6, 10.4)	1.0	(0.68, 1.33)
	1 month after toddler dose	78	114	(97.1, 132.7)	79	121	(103.4, 140.4)	0.9	(0.76, 1.17)
	1 year after toddler dose	76	11	(8.6, 15.4)	70	13	(9.2, 18.7)	0.9	(0.56, 1.37)
	2 years after toddler dose	69	11	(8.1, 15.2)	66	16	(10.7, 24.2)	0.7	(0.41, 1.14)
5	1 month after infant series	83	37	(25.9, 53.9)	85	64	(47.2, 86.9)	0.6	(0.36, 0.94)
	Before toddler dose	74	5	(4.2, 6.0)	79	5	(4.2, 5.6)	1.0	(0.82, 1.31)
	1 month after toddler dose	80	166	(127.9, 216.3)	83	260	(203.9, 331.9)	0.6	(0.45, 0.91)
	1 year after toddler dose	72	8	(5.6, 10.4)	70	10	(7.0, 13.3)	0.8	(0.51, 1.23)
	2 years after toddler dose	68	5	(4.1, 5.6)	69	7	(5.4, 9.4)	0.7	(0.49, 0.92)
6A	1 month after infant series	88	1566	(1312.3, 1869.0)	88	1287	(980.1, 1691.1)	1.2	(0.88, 1.68)
	Before toddler dose	69	45	(25.2, 81.1)	76	91	(56.6, 146.3)	0.5	(0.24, 1.04)
	1 month after toddler dose	78	1978	(1571.5, 2489.7)	74	3154	(2606.0, 3816.0)	0.6	(0.47, 0.85)
	1 year after toddler dose	70	98	(53.0, 183.0)	70	255	(152.9, 424.8)	0.4	(0.17, 0.86)
	2 years after toddler dose	68	42	(21.5, 81.1)	62	102	(53.7, 193.4)	0.4	(0.16, 1.03)
7F	1 month after infant series	93	1605	(1277.9, 2014.7)	86	1539	(1297.4, 1826.3)	1.0	(0.78, 1.39)
	Before toddler dose	75	228	(137.6, 377.1)	79	188	(109.3, 323.1)	1.2	(0.58, 2.53)
	1 month after toddler dose	81	2915	(2453.4, 3462.7)	82	3154	(2746.2, 3622.4)	0.9	(0.74, 1.15)
	1 year after toddler dose	71	599	(411.0, 873.3)	71	533	(348.3, 814.1)	1.1	(0.64, 1.97)
	2 years after toddler dose	64	170	(87.7, 330.9)	65	269	(155.6, 463.7)	0.6	(0.27, 1.48)
19A	1 month after infant series	92	283	(232.4, 344.1)	86	244	(204.1, 290.6)	1.2	(0.89, 1.51)
	Before toddler dose	77	9	(6.3, 12.0)	79	10	(7.1, 14.8)	0.8	(0.52, 1.37)
	1 month after toddler dose	81	558	(456.3, 682.6)	82	825	(692.4, 983.8)	0.7	(0.52, 0.88)
	1 year after toddler dose	74	28	(17.2, 43.9)	73	54	(34.2, 85.5)	0.5	(0.27, 0.97)
	2 years after toddler dose	68	22	(13.6, 37.1)	67	50	(30.1, 82.6)	0.5	(0.22, 0.91)

Preterm Infant Subgroups (Groups 1A, 1B, and 1C)

GMTs at each time point were presented for the preterm infant subgroups of the evaluable immunogenicity population (data not shown in this AR). For the 3 preterm infant subgroups, there were no discernible patterns in GMTs across the preterm infant subgroups based on GA at the 1- and 2-year follow-up. GMTs at the 1- and 2-year follow-up were generally numerically higher than or similar to those before the toddler dose and numerically lower than those 1 month after the toddler dose for all serotypes.

CHMP's comment: As for the IgG GMCs it is noted that the first subgroup generally had numerically higher IgG GMC compared to the other groups, but the differences were not statistically differences (overlapping 95% CI).

OPA Titer ≥LLOQ

The proportion of subjects of the evaluable immunogenicity population who had pneumococcal OPA antibody titers ≥LLOQ at the 1-year follow-up was numerically lower for subjects in Group 1 compared to Group 2 for the majority of serotypes and statistically significantly lower (upper limit of 95% CI <0) for serotypes 6A, 18C, 19A, and 23F.

This trend was also observed at the 2-year follow-up, with the addition that OPA antibody titers ≥LLOQ was also statistically significantly lower (upper limit of 95% CI <0) for serotype 5 as well.

There were no discernible patterns in the proportion of subjects who had OPA antibody titres ≥LLOQ among preterm infant subgroups based on GA for the evaluable and all-available immunogenicity populations at the 1-year follow-up and at the 2-year follow-up.

MAH Immunogenicity conclusions

This study assessed the immunogenicity of 13vPnC in preterm infants compared to term infants receiving 13vPnC at 2, 3, 4, and 12 months of age. During the vaccination phase, which was detailed in the primary-analysis report, the immune responses to 13vPnC were lower for preterm infants than for term infants after both the infant series and toddler dose. This report evaluated the persistence of antibody responses at the 1- and 2-year follow-up among former preterm (Group 1) and term (Group 2) infants, in the absence of any additional 13vPnC vaccination. The differences in the immune responses between former preterm and term infants persisted through 2 years after the last vaccination.

At the 1- and 2-year follow-up, in both groups, GMCs for all serotypes were, with few exceptions, numerically higher than or similar to those before the toddler dose; and were numerically lower than those 1 month after the toddler dose. These findings were consistent with decay of antibody from the booster response after the toddler dose.

At both the 1- and 2-year follow-up, the Group 1/Group 2 GMC ratios were <1.0 for all 13 serotypes, and the difference was statistically significant for the majority of serotypes.

There were no discernible patterns in GMCs across the preterm infant subgroups based on GA at the 1- and 2-year follow-up.

At the 1- and 2-year follow-up, the proportion of subjects in the evaluable immunogenicity population with a residual pneumococcal IgG concentration ≥0.35 µg/mL was lower for Group 1 than Group 2 for all serotypes.

Fewer differences in OPA GMTs between groups were apparent than in IgG GMCs. At the 1-year follow-up, Group 1 had significantly lower GMTs compared with Group 2 for serotypes 6A, 18C, 19A, and 23F. At the 2-year follow-up, Group 1 had significantly lower GMTs compared with Group 2 for serotypes 5 and 19A.

For the 3 preterm infant subgroups, there were no discernible patterns in GMTs across the preterm infant subgroups based on GA at the 1- and 2-year follow-up.

At both the 1- and 2-year follow-up, the proportion of subjects who had a pneumococcal OPA antibody titer ≥LLOQ was numerically lower for Group 1 compared to Group 2 for the majority of serotypes. There were no discernible patterns in the proportion of subjects who had OPA antibody titers ≥LLOQ among preterm infant subgroups based on GA.

CHMP's comment: The results of this long-term follow-up are in agreement with the primary phase of the study. It is not surprising that the lower titres seen after the primary and booster dose in pre-term infants compared to full term infants remain lower at one and 2 years after the booster dose. It is somewhat reassuring that the differences were generally smaller when looking at functional immune responses, i.e. OPA responses between the two groups.

Safety results

At the 1-year follow-up, SAEs overall were reported for similar proportions of subjects in Group 1 (13 subjects, 13.1%) and in Group 2 (8 subjects, 8.2%) (p=0.357). Infections and infestations (including pneumonia, bronchitis and respiratory tract infection) were among the most common SAEs, and were reported for significantly more subjects in Group 1 (12 subjects, 12.1%) than in Group 2 (3 subjects, 3.1%) (p=0.029).

At the 2-year follow-up, SAEs were reported for similar proportions of subjects in Group 1 (6 subjects, 6.8%) and in Group 2 (8 subjects, 9.1%). Infections and infestations, the most common SAE by system organ class (SOC), were reported for a similar proportion of subjects in Group 1 (3 subjects, 3.4%) and Group 2 (4 subjects, 4.5%).

None of the AEs reported at the 1- and 2-year follow-up were considered related to the investigational product. No subjects were withdrawn from the study for safety-related reasons and no deaths were reported during the study period covered in this report.

Discussion on clinical aspects

The results of this 2-year follow up of vaccination of preterm infants compared to full-term infants are in agreement with the results of the primary phase of the study, as evaluated in type II variation II76. The pre-term infants have lower IgG GMCs to the majority of serotypes at 1 and 2 years after the booster dose compared to the full-term infants, and to a lesser degree also lower OPA titres. When looking at subgroups of pre-term infants, the group with the highest gestational age (GA) at birth had consistently higher immune responses compared to the two groups with lower GA, but there were no consistent differences between these two latter groups. Thus, it is possible that the immune responses vary according to GA, but the data presented in this study do not provide clear evidence for this. The data support the conclusions drawn in variation II76, i.e. preterm infants generally had lower responses than the full term infants, but the responses were still considered adequate to provide a significant benefit for these children. Thus, the rapporteur does not consider it necessary to update the SPC to include these new data which were very much as expected.

The safety r the MAH should provide the assessment of immune response against HPV antigens from study V59P40 when available.

Results from this follow-up study do not cause any new safety concerns.

Rapporteur’s overall conclusion and recommendation

Overall conclusion

This P46 procedure is considered fulfilled, and no further regulatory action is needed. The results confirm the conclusions of the previously assessed data from the primary phase of the study.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

Additional clarifications requested

Not applicable.