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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/P46/066

Note

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

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1. Introduction

On 17 October 2022, the MAH submitted a completed paediatric study B7471012 for the assessment of Prevenar 13, pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) EU/1/09/590/001-016, EMEA/H/C/1104, in accordance with Article 46 of the 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

This paediatric study B7471012 is part of the Phase 3 clinical development program to support the use of 20-valent pneumococcal conjugate vaccine (20vPnC) in the pediatric population.

2.2. Information on the pharmaceutical formulation used in study B7471012

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 aluminum as aluminum phosphate, per 0.5-mL dose.
The 13vPnC supply was considered representative of Prevnar 13, as it was manufactured according to the approved Prevnar 13 commercial drug product process using commercially released vaccine drug substances.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted results for paediatric study B7471012 (Phase 3 study comparing 20vPnC with 13vPnC) according to Article 46, as 13vPnC has been used as an active comparator in this study.

Study B7471012 is a Phase 3, randomized (1:1), double-blind trial to evaluate the safety and immunogenicity of a 20vPnC given as a series of 2 infant doses and 1 toddler dose in healthy infants. The B7471012 study was part of the Phase 3 clinical development program to support the use of 20vPnC in the pediatric population, by generating key safety and immunogenicity data. The participants in the primary study population were administered either 20vPnC or 13vPnC in a 3-dose vaccination schedule.

This assessment concerns only the 13vPnC vaccine in accordance with Article 46 of Regulation (EC) No1901/2006.

2.3.2. Clinical Study B7471012

Description

The primary study population in study B7471012 was planned to include approximately 1200 infants

from sites in Europe and Australia. The targeted enrolment age of the population for this study, infants born at >36 weeks of gestation and ≥42 to ≤112 days of age, was selected as the routinely recommended vaccination schedule for pneumococcal conjugate vaccines and other vaccines in infants. To expand the study to describe the safety and immunogenicity of 20vPnC in infants from Russia, approximately 60 Russian infants were planned to be enrolled in the study and referred to as the Russian cohort. The Russian cohort was not included in the primary study population due to planned earlier completion of study visits in the primary study population than the Russian cohort and differences in concomitant vaccine schedule and visit windows in the Russian participants.

The safety and immunogenicity results in the Russian cohort will be summarized in a sCSR. The participants in the primary study population were administered either 20vPnC or 13vPnC in a 3-dose vaccination schedule with the first dose at 42 to 112 days of age, the second dose 42 to 63 days later, and the third dose at 11 to 12 months of age (hereafter known as a 2+1 schedule). Data were also generated on select routine pediatric vaccines given concomitantly with 20vPnC or 13vPnC.

Methods

Study participants

This Phase 3, multicenter, randomized, double-blind study was conducted at investigator sites in Europe and Australia, with additional sites in Russia (Russian cohort).

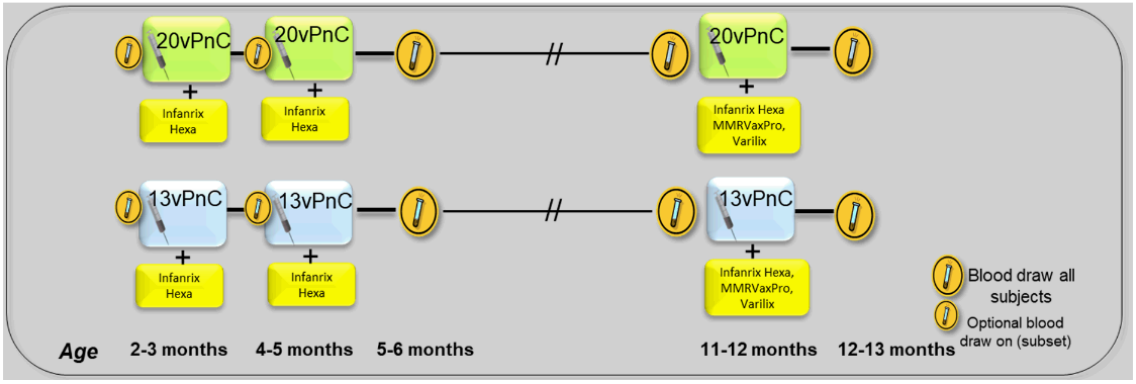
Sample size

Approximately 1200 infants born at >36 weeks of gestation and ≥42 to ≤112 days of age at the time of consent by their parents/legal guardians were planned to be enrolled. Overall, a total of 1207 participants were randomized and 1173 (97.2%) completed all visits per protocol. Disposition of all randomized participants was similar in the 20vPnC and 13vPnC groups. 1204 (99.8%) participants were included in the safety population.

The numbers of participants included in the all-available, evaluable immunogenicity populations for Dose 2, and the evaluable immunogenicity population for Dose 3 in the 2 vaccine groups were similar (1187 [98.3%], 1129 [93.5%], and 1001 [82.9%] of participants, respectively).

Participants were randomized in a 1:1 ratio to receive either 20vPnC or 13vPnC (control vaccine) at enrolment following a 2+1 schedule (Doses 1, 2, and 3). Participants received the same vaccine (either 20vPnC or 13vPnC) for all 3 doses.
Approximately 60 Russian infants were planned to be enrolled in the study and are referred to as the Russian cohort. The Russian cohort is not included in the primary study population. The safety and immunogenicity results in the Russian cohort will be summarized separately in a sCSR.
It was planned that each participant in the primary study population participated in the trial for approximately 11 months (i.e., from Dose 1 until 1 month after the last study vaccination). A brief overview of the study design is presented in Figure 1.

Figure 1. Study Design Overview



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Healthy male and female infants determined by clinical assessment (including medical history and clinical judgment) and born at >36 weeks of gestation and 2 months of age (≥42 to ≤112 days) at the time of consent (the day of birth is considered day of life 1) were included in the study. Exclusion criteria included 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, leukemia, lymphoma, or organ or bone marrow transplant.

Populations Analyzed

The numbers of participants included in the all-available and the evaluable immunogenicity populations in the 2 vaccine groups were similar (Table 4). Since the difference between the numbers of participants in the Dose 2 evaluable immunogenicity population and the all-available immunogenicity population were <10%, no analyses were performed for the all-available immunogenicity population per the study SAP.

Three (0.2%) of the participants did not receive any vaccination and were excluded from the safety population, one of these participants was in the 13vPnC group.

There were 78 (6.5%) participants excluded from the Dose 2 evaluable immunogenicity population and 206 (17.1%) participants excluded from the Dose 3 evaluable immunogenicity populations; there was a generally even distribution excluded from each group at each time point. The numbers are summarized along with the reasons for exclusion in Table 4. The most common reason for exclusion from the Dose 2 evaluable immunogenicity population was not having a blood draw 1 month after Dose 2. Not receiving Dose 3 at 335 to 386 days of age was the most common reason for exclusion from the Dose 3 evaluable immunogenicity population.

Table 4. Analysis Populations

	Vaccine Group (as Randomized)		
	20vPnC n[a] (%)	13vPnC n[a] (%)	Total n[a] (%)
Randomized[b]	603 (100.0)	604 (100.0)	1207 (100.0)
Vaccinated	601 (99.7)	603 (99.8)	1204 (99.8)
Safety population	601 (99.7)	603 (99.8)	1204 (99.8)
Excluded from safety population	2 (0.3)	1 (0.2)	3 (0.2)
Reason for exclusion[c]			
Did not receive any vaccination	2 (0.3)	1 (0.2)	3 (0.2)
All-available immunogenicity population	591 (98.0)	596 (98.7)	1187 (98.3)
Excluded from all-available immunogenicity population	12 (2.0)	8 (1.3)	20 (1.7)
Reason for exclusion[c]			
Did not receive any vaccination	2 (0.3)	1 (0.2)	3 (0.2)
Did not have at least 1 valid immunogenicity result	10 (1.7)	7 (1.2)	17 (1.4)
Dose 2 evaluable immunogenicity population	567 (94.0)	562 (93.0)	1129 (93.5)
Excluded from Dose 2 evaluable immunogenicity population	36 (6.0)	42 (7.0)	78 (6.5)
Reason for exclusion[c]			
Not eligible at randomization/dose[d]	1 (0.2)	1 (0.2)	2 (0.2)
Did not receive first 2 vaccinations as randomized	9 (1.5)	5 (0.8)	14 (1.2)
Did not have blood draw 1 month after Dose 2	25 (4.1)	33 (5.5)	58 (4.8)
No blood drawn within 27 to 56 days after Dose 2	0	3 (0.5)	3 (0.2)
Did not have at least 1 valid immunogenicity result at 1 month after Dose 2	1 (0.2)	0	1 (0.0)
Dose 3 evaluable immunogenicity population	497 (82.4)	504 (83.4)	1001 (82.9)
Excluded from Dose 3 evaluable immunogenicity population	106 (17.6)	100 (16.6)	206 (17.1)
Reason for exclusion[c]			
Not eligible at randomization/dose[d]	1 (0.2)	1 (0.2)	2 (0.2)
Did not receive all 3 vaccinations as randomized	14 (2.3)	9 (1.5)	23 (1.9)
Not 335 to 386 days of age at Dose 3	52 (8.6)	49 (8.1)	101 (8.4)
Did not have blood draw 1 month after Dose 3	29 (4.8)	26 (4.3)	55 (4.6)
No blood drawn within 27 to 56 days after Dose 3	7 (1.2)	14 (2.3)	21 (1.7)
Did not have at least 1 valid immunogenicity result at 1 month after Dose 3	1 (0.2)	1 (0.2)	2 (0.2)
Other major protocol deviation	2 (0.3)	0	2 (0.2)

a. n = Number of participants with the specified characteristic.
b. These values are the denominators for the percentage calculations.
c. Reasons are listed in hierarchical order. Each excluded participant is counted only once under the first applicable reason.
d. Violation of any protocol defined inclusion or exclusion criteria.
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Treatments

Participants received a single dose (0.5 mL) of 13vPnC 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) at Visits 1, 2, and 4. Participants also were to receive MMR (M-M-RVAXPRO) and varicella (Varilrix) vaccines at Visit 4. The MMR and varicella vaccines were intended to be given to all participants. However, some countries and sites did not administer MMR and varicella vaccines as concomitant study vaccines at Dose 3 due to local practices/recommendations. If they were not given at Dose 3 they were to be considered non-study vaccines.

Vaccine administration is presented in Table 6. There was 1 (0.2%) participant in the 13vPnC group who was randomized to study intervention but not vaccinated. MMR and varicella vaccines were to be administered in study, however, the protocol noted that due to local practice/recommendations some sites would not administer the vaccines to their participants at Dose 3. Despite this, approximately 86% of participants received both MMR and varicella vaccines at Dose 3.

Table 6. Vaccine Administration – All Randomized Participants

Vaccine (as Administered)	Vaccine Group (as Randomized) 20vPnC n[a] (%)	13vPnC n[a] (%)	Total n[a] (%)
Randomized[b]	N=603	N=604	N=1207
Not vaccinated[c]	2 (0.3)	1 (0.2)	3 (0.2)
Dose 1[d]	N=601	N=603	N=1204
20vPnC or 13vPnC	601 (100.0)	603 (100.0)	1204 (100.0)
DTPa-HBV-IPV/Hib	601 (100.0)	603 (100.0)	1204 (100.0)
Dose 2[d]	N=593	N=598	N=1191
20vPnC or 13vPnC	593 (100.0)	598 (100.0)	1191 (100.0)
DTPa-HBV-IPV/Hib	593 (100.0)	598 (100.0)	1191 (100.0)
Dose 3[d]	N=588	N=594	N=1182
20vPnC or 13vPnC	588 (100.0)	594 (100.0)	1182 (100.0)
DTPa-HBV-IPV/Hib	587 (99.8)	593 (99.8)	1180 (99.8)
MMR[e]	505 (85.9)	514 (86.5)	1019 (86.2)
Varicella[e]	503 (85.5)	513 (86.4)	1016 (86.0)

a. n = Number of participants with the specified characteristic.
b. This value is the denominator for the percentage calculations for the "not vaccinated" row.
c. Not vaccinated with 20vPnC or 13vPnC.
d. N = number of participants who received the specified dose. This value is the denominator for the percentage calculations for the specified dose.
e. Some sites may not have administered MMR and varicella vaccines to the participants at Dose 3 due to local practice/recommendations, in which case these vaccines were considered nonstudy vaccines.
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Statistical Methods

The primary safety objectives were evaluated by descriptive summary statistics for local reactions, systemic events and AEs (including SAEs) and NDCMCs. AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA). The primary pneumococcal immunogenicity objectives for the 20vPnC were evaluated by hypothesis tests for noninferiority of 20vPnC to 13vPnC based on serotype-specific IgG results 1 month after Dose 2 and 1 month after Dose 3. The primary concomitant immunogenicity objectives were evaluated by hypothesis tests for noninferiority of concomitant vaccines given with 20vPnC to with 13vPnC based on antibody levels induced by the concomitant vaccines 1 month after Dose 3. Other secondary and exploratory immunogenicity objectives were evaluated by descriptive summary statistics.

CHMP rapporteur comments:

Methods for paediatric study B7471012 are noted and are overall relevant for the assessment of Prevenar 13, pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) EU/1/09/590/001-016, EMEA/H/C/1104, in accordance with Article 46 of the Regulation (EC) No1901/2006.

Results

Baseline data

Overall, most of the study population was White (97.8%), and non-Hispanic/non-Latino (96.6%). Demographic characteristics for the Dose 2 and Dose 3 evaluable immunogenicity populations are like those for the safety population.

Efficacy results

MAH summary on Immunogenicity Results

• The serotype-specific IgG GMCs or percentage of participants with predefined IgG concentrations for the 13 matched serotypes in the 20vPnC group were evaluated for NI (a total of 60 comparisons) to the corresponding serotypes in the 13vPnC group, and the 7 additional serotypes in the 20vPnC group were evaluated for NI to the lowest among the vaccine serotypes in the 13vPnC group.

The RCDCs show that the distributions of IgG concentrations and OPA titers for the 13 matched serotypes are generally similar to those in the 13vPnC group. IgG and OPA GMFRs, OPA GMTs, proportion of participants with ≥4-fold rise in IgG concentrations and OPA titers, and percentages of participants with OPA titers ≥ LLOQ show that 20vPnC elicited responses that were generally like the responses to 13vPnC, induced functional antibody responses, and primed for memory responses after 2 infant doses for all vaccine serotypes.

• At 1 month after Dose 3, the percentages of participants with prespecified antibody levels to specific concomitant vaccine antigens (diphtheria toxoid, tetanus toxoid, pertussis antigens [PT, FHA, PRN], HBsAg, poliovirus strains, and Hib) and GMs to specific concomitant vaccine antigens (measles, mumps, rubella, and varicella viruses) when given with 20vPnC were noninferior to those when given with 13vPnC.

CHMP rapporteur comments: The rapporteur agrees on MAH summary on immunogenicity results.

Safety results

Local Reactions

The percentages of participants with local reactions after Doses 1 through 3 in the 13vPnC group were 47.1%, 42.9%, and 57.0%. The most frequently reported local reaction after Dose 1 and Dose 3 was pain at the injection site and the most frequently reported local reaction after Dose 2 was redness. Most local reactions were mild or moderate in severity. There was a trend of increased frequency at Dose 3. There was no strong trend in severity of local reactions across all 3 doses.

CHMP rapporteur comments: No new safety concerns detected in participants receiving 13vPnC.

Systemic Events

The percentages of participants with any systemic events after Doses 1 through 3 were 86.6%, 82.2%, and 81.4% in the 13vPnC group. The most frequent systemic events reported were irritability and drowsiness. Most systemic events were mild or moderate in severity.

The percentages of participants with any fever were 8.5%, 14.0%, and 23.7% in the 13vPnC groups after each dose and fever ≥38.9°C was reported infrequently (≤3.6%). There was a modest increase in frequency of reported fever with each subsequent dose, this trend may have been influenced by the concomitant vaccines that the participants received at the study vaccination visits.

The percentage of participants with use of antipyretic or pain medication were generally similar at Dose 1 and 2 and increased after Dose 3 (22.7%, 26.6%, and 47.4%). The median day of onset for systemic events was Day 1 or Day 2. The median duration of systemic events was 1 to 3 days.

Summary of Adverse Events

From Dose 1 to 1 month after Dose 2, at least 1 AE was reported in 14.4% of participants in the 13vPnC group. As commonly seen in this population, AEs in the SOC of infections and infestations were reported most frequently and included upper respiratory tract infection (2.0%), and nasopharyngitis (2.0%). From Dose 3 to 1 month after Dose 3, at least 1 AE was reported in 16.5% of participants in

the 13vPnC group. As with the AEs from Dose 1 to 1 month after Dose 2, AEs in the SOC of infections and infestations were reported most frequently and included upper respiratory tract infection (4.4%) and nasopharyngitis (1.7%).

CHMP rapporteur comments: No new safety concerns detected in participants receiving 13vPnC.

Related Adverse Events

From Dose 1 to 1 month after Dose 2, related AEs were reported in the SOC of general disorders and administrative site conditions (Table 21). The most frequently reported AEs in the 13vPnC group were vaccination site pain (0.3%), and vaccination site erythema (0.3%). Most related AEs from Dose 1 to 1 month after Dose 2 were mild.

Table 21. Related Adverse Events Reported From Dose 1 to 1 Month After Dose 2, by System Organ Class and Preferred Term – Safety Population

	Vaccine Group (as Administered)					
	20vPnC (N[a]=601)			13vPnC (N[a]=603)		
System Organ Class Preferred Term	n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])
Any event	2	0.3	(0.0, 1.2)	4	0.7	(0.2, 1.7)
General disorders and administration site conditions	2	0.3	(0.0, 1.2)	4	0.7	(0.2, 1.7)
Inflammation	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Injection site pain	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Vaccination site erythema	1	0.2	(0.0, 0.9)	2	0.3	(0.0, 1.2)
Vaccination site pain	1	0.2	(0.0, 0.9)	2	0.3	(0.0, 1.2)

Note: MedDRA (v25.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event", n = number of participants reporting at least 1 occurrence of any specified event.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
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From Dose 3 to 1 month after Dose 3, 1 related AEs were reported in the 13vPnC group who had a mild AE of injection site nodule. (Table 22).

Table 22. Related Adverse Events Reported From Dose 3 to 1 Month After Dose 3, by System Organ Class and Preferred Term – Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered) 20vPnC (N[a]=588) n[b]	%	(95% CI[c])	13vPnC (N[a]=594) n[b]	%	(95% CI[c])
Any event	1	0.2	(0.0, 0.9)	1	0.2	(0.0, 0.9)
General disorders and administration site conditions	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Injection site nodule	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Skin and subcutaneous tissue disorders	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Dermatitis allergic	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)

Note: MedDRA (v25.0) coding dictionary applied.
a. N = number of participants who received Dose 3 in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event", n = number of participants reporting at least 1 occurrence of any specified event.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
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(Database snapshot date : 24AUG2022) Output File: ./B7471012_sec/B7471012_CSR/adae_rel_2_saf

Immediate Adverse Events

Immediate AEs were reported infrequently in the 13vPnC group (for ≤0.7% of participants after each dose). There were no immediate AEs reported after Dose 3 in the 13vPnC group.

Severe Adverse Events

Severe AEs were reported infrequently from Dose 1 to 1 month after Dose 2 (for ≤0.7% of participants) and from Dose 3 to 1 month after Dose 3 (for ≤0.9% of participants) in the 13vPnC group. There was one severe AE of inflammation assessed by the investigator as related to study intervention, further described as a participant that 8 days after Dose 1 was reported with inguinal hernia, assessed as a mild, non-SAE, mild, with the duration of 280 days, together with inflammation, assessed as severe, SAE with the duration of 10 days.

Newly Diagnosed Chronic Medical Conditions (NDCMCs)

The percentages of participants with NDCMCs after Dose 1 were low (≤1.0%) in the 13vPnC group. From Dose 1 to 1 month after Dose 2 of 13vPnC, NDCMCs were reported for ≤0.7% of participants. There were no NDCMCs reported from Dose 3 to 1 month after Dose 3. The majority of NDMCs were new diagnoses of atopic dermatitis.

Deaths

There were no deaths during the study.

Serious Adverse Events

The percentages of participants with SAEs after Dose 1 were 6.6% in the 13vPnC group. SAEs most frequently reported included gastroenteritis (0.8%) and urinary tract infection (0.7%). SAEs were reported in 2.3% participants from Dose 1 to 1 month after Dose 2. From Dose 3 to 1 month after Dose 3 there were 7 (1.2%) participants in the 13vPnC group with SAEs. A total of 2 participants had SAEs of seizure or seizure-like events in the 13vPnC group. None of the SAE in the 13vPnC group was considered by the investigator to be potentially related to study vaccine (see section below; Other Significant Adverse Events).

Table 23. Serious Adverse Events Reported After Dose 1, by System Organ Class and Preferred Term – Safety Population

System Organ Class Preferred Term	Vaccine Group (as Administered) 20vPnC (N[a]=601) n[b]	%	(95% CI[c])	13vPnC (N[a]=603) n[b]	%	(95% CI[c])
Any event	34	5.7	(3.9, 7.8)	40	6.6	(4.8, 8.9)
Blood and lymphatic system disorders	1	0.2	(0.0, 0.9)	3	0.5	(0.1, 1.4)
Lymphadenitis	1	0.2	(0.0, 0.9)	1	0.2	(0.0, 0.9)
Neutropenia	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Thymus enlargement	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Congenital, familial and genetic disorders	2	0.3	(0.0, 1.2)	0	0	(0.0, 0.6)
Aorticopulmonary septal defect	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Bronchogenic cyst	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Gastrointestinal disorders	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Colitis	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
General disorders and administration site conditions	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Inflammation	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Immune system disorders	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Anaphylactic reaction	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Infections and infestations	23	3.8	(2.4, 5.7)	28	4.6	(3.1, 6.6)
Bacterial infection	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Bronchiolitis	2	0.3	(0.0, 1.2)	2	0.3	(0.0, 1.2)
Bronchitis	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
COVID-19	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Erythema infectiosum	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Escherichia urinary tract infection	0	0	(0.0, 0.6)	2	0.3	(0.0, 1.2)
Gastroenteritis	4	0.7	(0.2, 1.7)	5	0.8	(0.3, 1.9)
Gastroenteritis rotavirus	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Gastroenteritis viral	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Gastrointestinal infection	2	0.3	(0.0, 1.2)	2	0.3	(0.0, 1.2)
Gastrointestinal viral infection	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Herpangina	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Laryngitis	1	0.2	(0.0, 0.9)	2	0.3	(0.0, 1.2)
Lower respiratory tract infection viral	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Meningitis	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Meningitis enteroviral	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Oral candidiasis	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Otitis media	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Pneumonia	1	0.2	(0.0, 0.9)	3	0.5	(0.1, 1.4)
Pneumonia respiratory syncytial viral	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Pyelonephritis	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Pyelonephritis acute	1	0.2	(0.0, 0.9)	1	0.2	(0.0, 0.9)
Respiratory syncytial virus bronchiolitis	2	0.3	(0.0, 1.2)	1	0.2	(0.0, 0.9)
Skin infection	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Urinary tract infection	4	0.7	(0.2, 1.7)	4	0.7	(0.2, 1.7)
Viral infection	3	0.5	(0.1, 1.5)	1	0.2	(0.0, 0.9)
Injury, poisoning and procedural complications	2	0.3	(0.0, 1.2)	1	0.2	(0.0, 0.9)
Foreign body aspiration	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Skull fracture	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Thermal burn	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Metabolism and nutrition disorders	2	0.3	(0.0, 1.2)	4	0.7	(0.2, 1.7)
Feeding disorder	0	0	(0.0, 0.6)	3	0.5	(0.1, 1.4)
Poor feeding infant	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)

Type 1 diabetes mellitus	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Underweight	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Benign salivary gland neoplasm	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Nervous system disorders	3	0.5	(0.1, 1.5)	3	0.5	(0.1, 1.4)
Cerebral haemorrhage	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Febrile convulsion	1	0.2	(0.0, 0.9)	1	0.2	(0.0, 0.9)
Hypotonia	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Intracranial pressure increased	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Seizure	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Renal and urinary disorders	2	0.3	(0.0, 1.2)	1	0.2	(0.0, 0.9)
Nephritis	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Tubulointerstitial nephritis	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Vesicoureteric reflux	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Respiratory, thoracic and mediastinal disorders	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Bronchial hyperreactivity	1	0.2	(0.0, 0.9)	0	0	(0.0, 0.6)
Skin and subcutaneous tissue disorders	0	0	(0.0, 0.6)	2	0.3	(0.0, 1.2)
Dermatitis atopic	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)
Urticaria	0	0	(0.0, 0.6)	1	0.2	(0.0, 0.9)

Note: MedDRA (v25.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event. For "any event", n = number of participants reporting at least 1 occurrence of any specified event.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
PFIZER CONFIDENTIAL SDTM Creation: 25AUG2022 (22:32) Source Data: adae Table Generation: 06SEP2022 (05:06)
(Database snapshot date : 24AUG2022) Output File: ./B7471012_sec/B7471012_CSR/adae_s150_ser_d1_1md3_saf

Discontinuations from Study Intervention or Study Due to Adverse Events

No participants in the 13vPnC group were withdrawn from the trial because of AEs.

Other Significant Adverse Events

There were 2 participants (narratives described below) with a seizure or seizure-like event in the 13vPnC group. One participant in the 13vPnC group had a seizure on Day 19 after Dose 1 that resolved after 1 day. Both cases with seizure or seizure-like events were assessed as not related to study intervention.

- A 3-month-old male participant with no relevant medical history, received 3 doses of 13vPnC (Day 1; Dose 1), Day 50; Dose 2, and Day 260; Dose 3). Infanrix hexa (diphtheria, tetanus, acellular pertussis, hepatitis B virus, poliovirus, and Haemophilus influenzae type b vaccine) was also given at the same time as 13vPnC at Doses 1, 2, and 3. Additionally, the participant received MMRVAXPRO and Varilrix with Dose 3. The participant experienced a seizure on Day 19; 18 days after Dose 1. The participant's mother reported that the participant was a bit spastic for a moment and was sounding a "little weird" at night, which lasted for 2 minutes. The participant was taken to the hospital, where he was assessed as normal, with a normal hematological investigation, showing no signs of infection. There was no seizure-like activity noted at the hospital and the participant was observed overnight (symptoms resolved within the day of onset, Day 19). No health problems were observed during the hospital stay and the participant was discharged home on Day 20. On Day 26, the participant was examined by a physiotherapist, and slight muscle tension was noted with no other findings. On Day 28, an electroencephalogram was normal. The final document from the children's neurology unit received on Day 55 confirmed that there was no suspicion of epilepsy or other disease, and no other examinations were recommended. The participant completed the study by the end of

2021. In the opinion of the investigator, there was not a reasonable possibility that the seizure was related to 13vPnC, concomitant vaccinations, or a clinical trial procedure.

- A 11-month-old female participant with no reported medical history, received 3 doses of 13vPnC on Day 1; Dose 1, Day 63; Dose 2 and (Day 333; Dose 3.). Infanrix hexa (diphtheria, tetanus, acellular pertussis, hepatitis B virus, poliovirus, and Haemophilus influenzae type b vaccine) and rotavirus vaccine (live oral 1V) were also given at the same time as 13vPnC at Doses 1 and 2. Infanrix hexa, MMRVAXPRO, and Varilrix were administered with Dose 3. On Day 313; 250 days after Dose 2), the participant was admitted to the hospital with vomiting, diarrhea, and an episode of febrile seizures. The participant was treated with calcium chloride dihydrate/magnesium chloride hexahydrate/potassium chloride/sodium acetate trihydrate/sodium chloride/sodium citrate dihydrate (Optilyte) 250 mL intravenously (IV) (on D131) , probiotic lactose 2 capsules every day and oral electrolytes 2 x 200 mL every day, midazolam 1 mg IV before lumbar puncture (on D314), glucose/potassium chloride/sodium chloride/sodium citrate (Acidolit) orally once daily (from Day 313 to Day 315), and Lactobacillus rhamnosus orally every day (from D313 to D319). It was unknown if an electroencephalogram was performed, and no details on fever were available. Final diagnoses of febrile convulsion and gastrointestinal infection were made, and the febrile convulsion resolved on the same day of onset (Day 313). The participant was discharged home in good condition on (Day 315) and the gastrointestinal infection resolved on (Day 319). The participant completed the study. In the opinion of the investigator, there was not a reasonable possibility that the febrile convulsion was related to 13vPnC or a clinical trial procedure but was related to the viral infection. MAH concurred with the investigator's causality assessment and stated that febrile convulsion was a complication secondary to the gastrointestinal infection, which represented as a coincidental infectious condition

Subgroup Analyses

Subgroup analyses were performed for local reactions, systemic events, and AEs by sex. The percentages of participants who reported local reactions and systemic events within 7 days after each vaccination were generally similar in male and female participants. The percentages of participants who reported AEs from Dose 1 to 1 month after Dose 2 were generally similar in male and female participants. The percentages of participants who reported AEs from Dose 3 to 1 month after Dose 3 were also generally similar in male and female participants.

CHMP rapporteur comments: There were 2 participants with a seizure or seizure-like event in the 13vPnC group. Both cases with seizure or seizure-like events were by the MAH and investigator assessed as not related to study intervention, and these assessments are agreed upon.

Overall, no new safety concerns detected in participants receiving 13vPnC.

CONCLUSIONS

MAH conclusion

Safety and immunogenicity results from this study were concluded by the MAH to be consistent with the known profile of 13vPnC as reflected in the EU SmPC and support the continued use of 13vPnC. No changes are being proposed by the MAH to the Prevenar 13 label in this submission.

CHMP rapporteur comments: MAH conclusion is agreed. No changes are being proposed to the Prevenar 13 label.

2.3.3. Discussion on clinical aspects

Present submitted study (B7471012) confirmed safety of Prevenar 13 among infants born at >36 weeks of gestation and ≥42 to ≤112 days of age at inclusion. The results agree with previously reported studies. The safety population was small (N= 604) and therefore the chance to detect rare AEs and SAEs is low.

The safety results are a in agreement with previously reported studies. No new safety concern is raised from this study. The study confirms what is already known about immune responses and safety of Prevenar 13. The submitted study does not change the benefit-risk balance for Prevenar 13.

3. Overall conclusion and recommendation

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

☒ **Fulfilled:**

No regulatory action required.