Amsterdam, 30 March 2023
EMA/CHMP/107792/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Prevenar 13

pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)

Procedure no. EMEA/H/C/001104/P46/068

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

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1. Introduction

On the 10 January 2023, the MAH submitted a completed paediatric study for Prevenar 13 (13vPnC), 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 A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Infants B7471011 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

20vPnC is a sterile liquid suspension formulation containing saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F 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 5 mM succinate buffer, 150 mM sodium chloride, 0.02% polysorbate 80, and 125 µg aluminium as aluminium phosphate, per 0.5-mL dose.

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 is considered representative of Prevnar 13, as it is manufactured according to the approved Prevnar 13 commercial drug product process using commercially released vaccine drug substances.20vPnC and 13vPnC are both white suspensions and have a matching appearance and were supplied as prefilled syringes.

DTaP combination vaccine is indicated for active immunization against diphtheria, tetanus, pertussis, infection caused by all known subtypes of hepatitis B virus, and poliomyelitis. The vaccine is supplied as a prefilled syringe.

Hib vaccine is indicated for the prevention of invasive disease caused by Hib. The vaccine is supplied in vials.

MMR is a live virus vaccine for vaccination against measles (rubeola), mumps, and rubella (German measles). The vaccine is supplied in vials.

Varicella vaccine is a live virus vaccine for vaccination against varicella. The vaccine is supplied in vials.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- B7471011: A Phase 3, Randomized, Double- Blind Trial to Evaluate the Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Infants.

2.3.2. Clinical study

B7471011: A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Infants.

Description

Methods

Study participants

Approximately 2000 infants ≥42 to ≤98 days of age at the time of consent, by their parents/legal guardians, were enrolled. Infants were eligible if they were naïve to pneumococcal vaccination. 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 ≤98 days) at the time of consent (the day of birth is considered day of life 1) were included in the study.

Study design

This Phase 3, multicenter, randomized, double-blind trial was conducted at investigator sites in the continental United States and the territory of Puerto Rico. The purpose of this study was to describe safety and conduct the noninferiority immunogenicity comparison of 20vPnC to the licensed pneumococcal conjugate vaccine, 13vPnC, in infants receiving a 4-dose series. Data were also generated on responses to key routine pediatric vaccines given concomitantly with 20vPnC, where 13vPnC served as an active comparator.

Treatments

The participants were administered either 20vPnC or 13vPnC at 2, 4, 6, and 12 to 15 months of age. This was consistent with the pneumococcal vaccine recommendations for infants in the United States (including Puerto Rico). 13vPnC served as the comparator to 20vPnC for assessment of safety and immunogenicity. Participants received the same vaccine (20vPnC or 13vPnC) for all 4 doses. It was planned that each participant participated in the trial for approximately 16 to 19 months. Participants received a single dose (0.5 mL) of 20vPnC or 13vPnC intramuscularly into the anterolateral thigh muscle of the left leg at each vaccination visit (Doses 1, 2, 3, and 4 at Visits 1, 2, 3, and 5, respectively). Participants also received a dose of a DTaP-containing vaccine in combination with other antigens (including poliovirus and hepatitis B) (PEDIARIX) and a dose of a Hib vaccine (HIBERIX) at Visits 1, 2, and 3. MMR (M-M-RII) and varicella (VARIVAX). Vaccines were administered concomitantly with 20vPnC or 13vPnC at Visit 5 with Dose 4. All concomitant vaccinations were administered into a limb other than the left leg (the site of 20vPnC or 13vPnC injection).

Objectives, Outcomes, Endpoints

Primary Safety Objective	Estimands	Primary Safety Endpoints
• To describe the safety profile of 20vPnC	In participants receiving at least 1 dose of investigational product and having safety data reported after any vaccination: • The percentage of participants reporting prompted local reactions within 7 days after each vaccination in each group • The percentage of participants reporting prompted systemic events within 7 days after each vaccination in each group • The percentage of participants reporting AEs from Dose 1 to 1 month after Dose 3 in each group • The percentage of participants reporting AEs from Dose 4 to 1 month after Dose 4 in each group • The percentages of participants reporting SAEs up to 6 months after Dose 4 in each group • The percentages of participants reporting NDCMCs up to 6 months after Dose 4 in each group	• Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) • AEs • SAEs • NDCMCs
Primary Pneumococcal Immunogenicity Objectives	**Estimands**	**Primary Pneumococcal Immunogenicity Endpoints**
• To demonstrate that the percentages of participants with predefined serotype-specific IgG concentrations for the 13 serotypes in the 20vPnC group are noninferior to the percentages for the corresponding serotypes in the 13vPnC group at 1 month after Dose 3	In participants in compliance with the key protocol criteria (evaluable participants) at 1 month after Dose 3: • For each of the 13 matched serotypes: difference in the percentages of participants with predefined serotype-specific IgG concentrations between the 20vPnC group and the 13vPnC group	• Pneumococcal serotype-specific IgG concentration
• To demonstrate that the percentages of participants with predefined serotype-specific IgG concentrations for the 7 additional serotypes in the 20vPnC group are noninferior to the lowest percentage among the 13 serotypes in the 13vPnC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 7 additional serotypes in 20vPnC: difference in the percentages of participants with predefined serotype-specific IgG concentrations, between the 20vPnC group and the lowest percentage of participants with predefined serotype-specific IgG concentrations among the 13 serotypes from the 13vPnC group	• Pneumococcal serotype-specific IgG concentration
• To demonstrate that the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC group are noninferior to the GMCs for the corresponding serotypes in the 13vPnC group at 1 month after Dose 4	In evaluable participants at 1 month after Dose 4: • For each of the 13 matched serotypes: GMR of serotype-specific IgG concentrations from the 20vPnC group to the 13vPnC group	• Pneumococcal serotype-specific IgG concentration
• To demonstrate that the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC group are noninferior to the lowest IgG GMC among the 13 serotypes in the 13vPnC group at 1 month after Dose 4	In evaluable participants at 1 month after Dose 4: • For each of the 7 additional serotypes in 20vPnC: GMR of serotype-specific IgG concentration from the 20vPnC group to that from the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group	• Pneumococcal serotype-specific IgG concentration
Primary Concomitant Immunogenicity Objective	**Estimand**	**Primary Concomitant Immunogenicity Endpoints**
• To demonstrate that percentages of participants with prespecified antibody levels to specific concomitant vaccine antigens when given with 20vPnC are noninferior to the corresponding percentages when the antigens are given with 13vPnC at 1 month after Dose 3	In evaluable participants who receive the appropriate concomitant vaccines: • Differences in percentages of participants with prespecified antibody levels to diphtheria toxoid, tetanus toxoid, pertussis antigens (PT, FHA, PRN), HBsAg, poliovirus strains, and Hib between the 20vPnC group and the 13vPnC group at 1 month after Dose 3	• Antibody levels to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN) • Antibody levels to HBsAg • Antibody levels to poliovirus strains (types 1, 2, and 3) • Antibody levels to Hib

Key Secondary Pneumococcal Immunogenicity Objectives	Estimands	Key Secondary Pneumococcal Immunogenicity Endpoints
• To demonstrate that the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC group are noninferior to the GMCs for the corresponding serotypes in the 13vPnC group at 1 month after Dose 3	In participants in compliance with the key protocol criteria (evaluable participants) at 1 month after Dose 3: • For each of the 13 matched serotypes: GMR of serotype-specific IgG concentrations from the 20vPnC group to the 13vPnC group	Pneumococcal serotype-specific IgG concentration
• To demonstrate that the serotype-specific IgG GMC for the 7 additional serotypes in the 20vPnC group are noninferior to the lowest IgG GMC among the 13 serotypes in the 13vPnC group at 1 month after Dose 3	In evaluable participants at 1 month after Dose 3: • For each of the 7 additional serotypes in 20vPnC: GMR of serotype-specific IgG concentration from the 20vPnC group to that from the serotype with the lowest IgG GMC among the 13 serotypes from the 13vPnC group	Pneumococcal serotype-specific IgG concentration
Secondary Pneumococcal Immunogenicity Objective	**Estimands**	**Secondary Pneumococcal Immunogenicity Endpoints**
• To further describe the immunogenicity of 20vPnC	In evaluable participants at 1 month after Dose 3 and 1 month after Dose 4: • Serotype-specific OPA GMTs at 1 month after Dose 3, prior to Dose 4, and 1 month after Dose 4 in each group In evaluable participants at 1 month after Dose 4: • For each of the serotypes in 20vPnC: percentages of participants with the predefined serotype-specific IgG concentration in each group In evaluable participants: • GMFRs in serotype-specific IgG concentrations from 1 month after Dose 3 to before Dose 4, from before Dose 4 to 1 month after Dose 4, and from 1 month after Dose 3 to 1 month after Dose 4 in each group	• Pneumococcal serotype-specific OPA titers • Pneumococcal serotype-specific IgG concentrations
Secondary Concomitant Immunogenicity Objectives	**Estimands**	**Secondary Concomitant Immunogenicity Endpoints**
• To further describe the immune responses induced by specific concomitant vaccine antigens given with 20vPnC or 13vPnC	In evaluable participants who receive the appropriate concomitant vaccines: • Differences in percentages of participants with alternative prespecified antibody levels to Hib between the 20vPnC group and the 13vPnC group at 1 month after Dose 3	• Antibody levels to Hib
• To demonstrate that GMCs to specific concomitant vaccine antigens when given with 20vPnC are noninferior to the corresponding GMCs when the antigens are given with 13vPnC at 1 month after Dose 4	• GMRs of antibody levels to measles, mumps, rubella, and varicella viruses from the 20vPnC group to the 13vPnC group at 1 month after Dose 4	• Antibody levels to measles, mumps, rubella, and varicella viruses

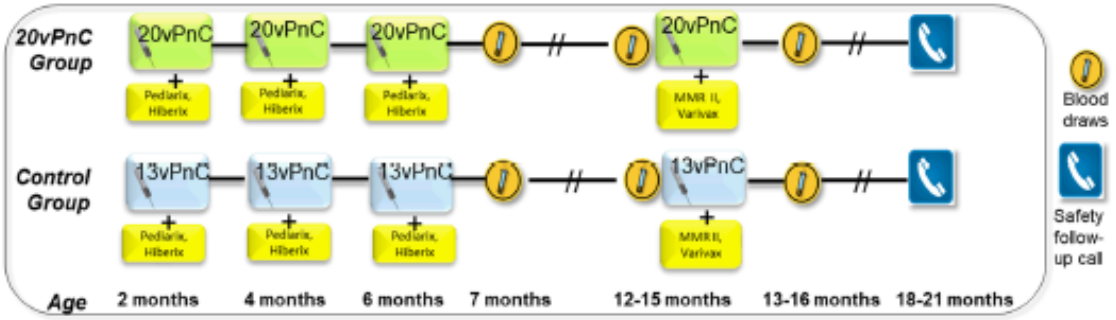
Sample size

Approximately 2000 participants were enrolled to achieve a target of 1600 evaluable participants (800 in each vaccine group) at the follow-up time point 1 month after Dose 3.

Randomisation and blinding (masking)

Participants were randomized in a 1:1 ratio to receive either 20vPnC or 13vPnC (control vaccine) at 2, 4, 6, and 12 to 15 months of age (Doses 1, 2, 3, and 4, respectively) by site-based randomization. Each participant participated in the trial for approximately 16 to 19 months (Figure 1).

Figure 1. Study Design B7471011



Statistical Methods

The primary safety objectives were evaluated by descriptive summary statistics for local reactions, systemic events, AEs (including SAEs) and NDCMCs. AEs were categorized according to the MedDRA.

The primary and key secondary 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 3 and 1 month after Dose 4. 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.

Results

Participant flow

Table 3. Disposition of All Participants – All Randomized Participants

	Vaccine Group (as Randomized)		
	20vPnC n[a] (%)	13vPnC n[a] (%)	Total n[a] (%)
Randomized[b]	1004 (100.0)	993 (100.0)	1997 (100.0)
Not vaccinated	3 (0.3)	3 (0.3)	6 (0.3)
Vaccinated			
Dose 1	1001 (99.7)	990 (99.7)	1991 (99.7)
Dose 2	966 (96.2)	949 (95.6)	1915 (95.9)
Dose 3	934 (93.0)	926 (93.3)	1860 (93.1)
Dose 4	853 (85.0)	844 (85.0)	1697 (85.0)
Completed 1-month follow-up after Dose 3	930 (92.6)	924 (93.1)	1854 (92.8)
Completed 1-month follow-up after Dose 4	851 (84.8)	839 (84.5)	1690 (84.6)
Completed 6-month follow-up telephone contact[c]	885 (88.1)	842 (84.8)	1727 (86.5)
Completed all visits per protocol	821 (81.8)	802 (80.8)	1623 (81.3)
Total withdrawn	183 (18.2)	191 (19.2)	374 (18.7)
Withdrawn before Dose 1	3 (0.3)	3 (0.3)	6 (0.3)
Withdrawn after Dose 1 and before 1-month follow-up after Dose 3	71 (7.1)	66 (6.6)	137 (6.9)
Withdrawn after 1-month follow-up after Dose 3 and before Dose 4	77 (7.7)	80 (8.1)	157 (7.9)
Withdrawn after Dose 4 and before 1-month follow-up after Dose 4	2 (0.2)	5 (0.5)	7 (0.4)
Withdrawn after 1-month follow-up after Dose 4 through 6-month follow-up telephone contact	30 (3.0)	37 (3.7)	67 (3.4)
Reason for withdrawal			
Lost to follow-up	48 (4.8)	63 (6.3)	111 (5.6)
Withdrawal by parent/guardian	50 (5.0)	56 (5.6)	106 (5.3)
No longer meets eligibility criteria	51 (5.1)	44 (4.4)	95 (4.8)
Protocol deviation	29 (2.9)	23 (2.3)	52 (2.6)
Adverse event	2 (0.2)	4 (0.4)	6 (0.3)
Physician decision	0	1 (0.1)	1 (0.1)
Other	3 (0.3)	0	3 (0.2)

a. n = Number of participants with the specified characteristic.
b. This value is the denominator for the percentage calculations.
c. The number of participants in the 6-month follow-up telephone contact includes participants who had previously withdrawn from vaccination but whose parent(s)/legal guardian(s) consented to the safety follow-up.
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Recruitment

Infants ≥42 to ≤98 days of age were eligible if they were naïve to pneumococcal vaccination. This study population was selected as this was the historical population studied for licensure of 13vPnC in infants. The participants were administered either 20vPnC or 13vPnC at 2, 4, 6, and 12 to 15 months of age. This was consistent with the pneumococcal vaccine recommendations for infants in the United States (including Puerto Rico).

Baseline data

Demographic and baseline characteristics of sex, race, ethnicity, geographic region (USA/Puerto Rico), and age for the safety population were similar in the 20vPnC and 13vPnC groups (Table 5). Most participants were White and non-Hispanic/non-Latino, approximately 25% of the study population was

non-White, with approximately 11% Black or African American and 7% multiracial, and approximately 30% were Hispanic/Latino. Demographic characteristics for the Dose 3 and Dose 4 evaluable immunogenicity populations were similar to those for the safety population.

Table 5. Demographic Characteristics – Safety Population

	Vaccine Group (as Administered)		
	20vPnC (N[a]=1001) n[b] (%)	13vPnC (N[a]=987) n[b] (%)	Total (N[a]=1988) n[b] (%)
Sex			
Male	518 (51.7)	505 (51.2)	1023 (51.5)
Female	483 (48.3)	482 (48.8)	965 (48-5)
Race			
White	754 (75.3)	742 (75.2)	1496 (75.3)
Black or African American	110 (11.0)	108 (10.9)	218 (11.0)
Asian	16 (1.6)	16 (1.6)	32 (1.6)
American Indian or Alaska Native	4 (0.4)	3 (0.3)	7 (0.4)
Native Hawaiian or other Pacific Islander	2 (0.2)	2 (0.2)	4 (0.2)
Multiracial	68 (6.8)	73 (7.4)	141 (7.1)
Not reported	47 (4.7)	43 (4.4)	90 (4.5)
Ethnicity			
Hispanic/Latino	312 (31.2)	293 (29.7)	605 (30.4)
Non-Hispanic/non-Latino	661 (66.0)	659 (66.8)	1320 (66.4)
Not reported	28 (2.8)	35 (3.5)	63 (3.2)
Geographic region USA	893 (89.2)	881 (89.3)	1774 (89.2)
Puerto Rico	108 (10.8)	106 (10.7)	214 (10.8)
Age at Dose 1 (days)			
Mean (SD)	65.9 (7.98)	65.6 (7.13)	65.8 (7.57)
Median	64.0	64.0	64.0
Min, max	(42, 97)	(43, 96)	(42, 97)
Age at Dose 4 (days)			
Mean (SD)	378.4 (15.75)	378.7 (15.47)	378.5 (15.61)
Median	372.0	373.0	372.0
Min, max	(365, 460)	(366, 455)	(365, 460)

a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations. Participants who received any incorrect study vaccination during the study are excluded.
b. n = Number of participants with the specified characteristic.

Numbers analysed

- There were 1991 (99.7%) participants included in the safety population: 1001 (99.7%) and 990 (99.7%) participants in the 20vPnC and 13vPnC groups, respectively.

- There were 1636 (81.9%) participants included in the Dose 3 evaluable immunogenicity population: 833 (83.0%) and 803 (80.9%) participants in the 20vPnC and 13vPnC groups, respectively.

- There were 1500 (75.1%) participants included in the Dose 4 evaluable immunogenicity population: 755 (75.2%) and 745 (75.0%) participants in the 20vPnC and 13vPnC groups, respectively.

Efficacy results

Immunogenicity Results

Primary and Key Secondary - Pneumococcal Immune Response (Relevant to 13vPnC)

- At 1 month after Dose 3 and 1 month after Dose 4, 13vPnC elicited serotype-specific IgG GMCs for all vaccine serotypes (Tables 8, 12).

- At 1 month after Dose 3, the percentages of participants with predefined serotype-specific IgG concentrations ranged from 67.6% (serotype 3) to 98.1% (serotype 19A) in the 13vPnC group (Table 9).

Supportive Results - Pneumococcal Immune Responses

- Strong boosting responses were observed between dose 3 and dose 4 for the vaccine serotypes in the 13 vPnC control group, as serotype-specific IgG responses increased between dose 3 and dose 4 when measured one month after respective doses (Tables 8, 12).

- 13vPnC also elicited functional opsonophagocytic activity (OPA) responses to all vaccine serotypes at 1 month after Dose 3 and 1 month after Dose 4, based on OPA geometric mean titers (GMTs), geometric mean fold rises (GMFRs), percentages of participants with ≥4-fold rise, and percentages of participants with OPA titers ≥ lower level of quantification (LLOQ). Evidence of OPA boosting was observed for all serotypes, similar to the boosting observed for the IgG responses. Results from serotypes 1, 3, 4 and 5 as an example can be seen in figures 14 and 15.

Table 8. Pneumococcal IgG GMCs and GMRs – 1 Month After Dose 4 – Dose 4 Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	20vPnC			13vPnC[a]			20vPnC/13vPnC	
Serotype	n[b]	GMC[c]	(95% CI[c])	n[b]	GMC[c]	(95% CI[c])	GMR[d]	(95% CI[d])
13vPnC								
1	755	1.47	(1.37, 1.57)	744	2.12	(1.97, 2.27)	0.69	(0.63, 0.76)
3	755	0.56	(0.53, 0.60)	745	0.85	(0.80, 0.90)	0.66	(0.61, 0.73)
4	754	3.77	(3.52, 4.04)	745	4.84	(4.50, 5.22)	0.78	(0.70, 0.86)
5	755	1.87	(1.74, 2.00)	745	2.51	(2.33, 2.70)	0.74	(0.67, 0.82)
6A	755	9.01	(8.45, 9.61)	745	11.69	(10.91, 12.53)	0.77	(0.70, 0.85)
6B	753	4.01	(3.70, 4.35)	744	5.74	(5.27, 6.24)	0.70	(0.62, 0.79)
7F	755	3.91	(3.70, 4.14)	745	5.18	(4.88, 5.49)	0.76	(0.70, 0.82)
9V	755	3.44	(3.23, 3.67)	744	4.30	(4.02, 4.59)	0.80	(0.73, 0.88)
14	755	5.68	(5.27, 6.12)	745	6.34	(5.88, 6.83)	0.90	(0.81, 1.00)
18C	755	3.46	(3.24, 3.70)	745	4.69	(4.34, 5.05)	0.74	(0.67, 0.82)
19A	754	3.53	(3.30, 3.77)	745	4.13	(3.84, 4.45)	0.85	(0.77, 0.94)
19F	755	5.01	(4.68, 5.36)	745	5.79	(5.36, 6.25)	0.86	(0.78, 0.96)
23F	755	3.95	(3.63, 4.31)	745	6.18	(5.66, 6.75)	0.64	(0.57, 0.72)
7 Additional								
8	755	3.97	(3.73, 4.22)	744	2.12	(1.97, 2.27)	1.87	(1.71, 2.06)
10A	755	6.22	(5.75, 6.72)	744	2.12	(1.97, 2.27)	2.94	(2.64, 3.26)
11A	755	3.53	(3.31, 3.78)	744	2.12	(1.97, 2.27)	1.67	(1.51, 1.84)
12F	755	1.85	(1.73, 1.99)	744	2.12	(1.97, 2.27)	0.88	(0.79, 0.97)
15B	755	12.59	(11.78, 13.45)	744	2.12	(1.97, 2.27)	5.95	(5.39, 6.55)
22F	755	10.60	(9.92, 11.33)	744	2.12	(1.97, 2.27)	5.01	(4.54, 5.52)
33F	755	9.31	(8.71, 9.96)	744	2.12	(1.97, 2.27)	4.40	(3.99, 4.85)

Abbreviations: GMC = geometric mean concentration; GMR = geometric mean ratio; IgG = immunoglobulin G; LLOQ = lower limit of quantitation.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
a. For the 13vPnC serotypes, the GMCs are from the corresponding serotype in the 13vPnC group. For the 7 additional serotypes, the GMCs are from serotype 1 (13vPnC serotype with the lowest GMC, not including serotype 3) in the 13vPnC group.
b. n = Number of participants with valid IgG concentrations for the specified serotype.
c. GMCs and 2-sided CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student t distribution).
d. 2-Sided CIs were calculated by exponentiating the mean differences of the logarithms of the IgG concentrations (20vPnC – 13vPnC) and the corresponding CIs (based on the Student t distribution).
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Table 12. Pneumococcal IgG GMCs and GMRs – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

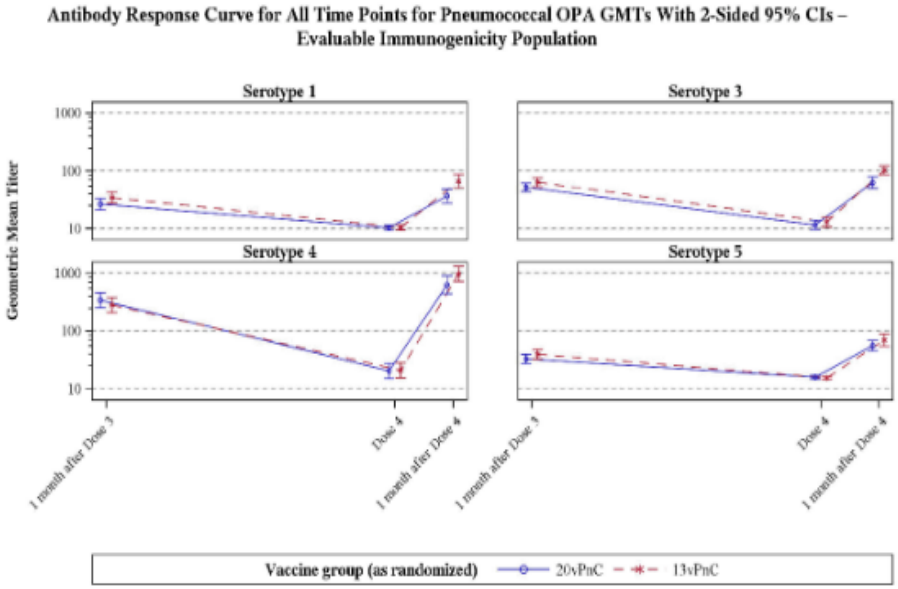
	Vaccine Group (as Randomized)							
	20vPnC			13vPnC[a]			20vPnC/13vPnC	
Serotype	n[b]	GMC[c]	(95% CI[c])	n[b]	GMC[c]	(95% CI[c])	GMR[a]	(95% CI[d])
13vPnC								
1	833	0.74	(0.70, 0.79)	802	1.14	(1.06, 1.22)	0.65	(0.59, 0.72)
3	833	0.36	(0.33, 0.38)	802	0.51	(0.48, 0.55)	0.70	(0.64, 0.76)
4	833	0.75	(0.70, 0.81)	802	1.08	(1.00, 1.17)	0.70	(0.63, 0.78)
5	833	0.66	(0.61, 0.71)	802	0.96	(0.88, 1.04)	0.69	(0.61, 0.77)
6A	833	1.95	(1.81, 2.10)	802	2.69	(2.48, 2.92)	0.72	(0.65, 0.81)
6B	831	0.61	(0.55, 0.68)	801	1.02	(0.91, 1.14)	0.60	(0.51, 0.70)
7F	833	1.71	(1.62, 1.81)	802	2.29	(2.16, 2.43)	0.75	(0.69, 0.81)
9V	833	0.87	(0.81, 0.93)	802	1.21	(1.12, 1.30)	0.72	(0.65, 0.80)
14	832	2.16	(2.01, 2.33)	802	2.72	(2.51, 2.95)	0.79	(0.71, 0.89)
18C	833	1.31	(1.23, 1.39)	802	1.71	(1.59, 1.84)	0.77	(0.70, 0.84)
19A	833	0.72	(0.67, 0.76)	802	0.91	(0.85, 0.97)	0.79	(0.72, 0.86)
19F	833	1.59	(1.50, 1.67)	802	2.00	(1.88, 2.12)	0.79	(0.73, 0.86)
23F	833	0.82	(0.75, 0.90)	802	1.25	(1.14, 1.37)	0.66	(0.58, 0.75)
7 Additional								
8	833	1.80	(1.70, 1.91)	802	0.91	(0.85, 0.97)	1.98	(1.81, 2.16)
10A	833	1.21	(1.09, 1.33)	802	0.91	(0.85, 0.97)	1.32	(1.18, 1.49)
11A	833	1.39	(1.30, 1.48)	802	0.91	(0.85, 0.97)	1.52	(1.39, 1.67)
12F	833	0.55	(0.50, 0.60)	802	0.91	(0.85, 0.97)	0.60	(0.54, 0.67)
15B	833	4.40	(4.11, 4.71)	802	0.91	(0.85, 0.97)	4.82	(4.39, 5.30)

Table 9. Comparison of the Percentage of Participants With Predefined Pneumococcal IgG Concentrations for Vaccine Serotypes – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)									
		20vPnC				13vPnC[a]				20vPnC – 13vPnC	
Serotype	Predefined Level	N[b]	n[c]	%	(95% CI[d])	N[b]	n[c]	%	(95% CI[d])	Difference[a] (%)	(95% CI[e])
13vPnC											
1	≥0.35 µg/mL	833	665	79.8	(76.9, 82.5)	802	709	88.4	(86.0, 90.5)	-8.6	(-12.1, -5.1)
3	≥0.35 µg/mL	833	434	52.1	(48.6, 55.5)	802	542	67.6	(64.2, 70.8)	-15.5	(-20.1, -10.8)
4	≥0.35 µg/mL	833	664	79.7	(76.8, 82.4)	802	707	88.2	(85.7, 90.3)	-8.4	(-12.0, -4.9)
5	≥0.23 µg/mL	833	687	82.5	(79.7, 85.0)	802	696	86.8	(84.2, 89.1)	-4.3	(-7.8, -0.8)
6A	≥0.35 µg/mL	833	779	93.5	(91.6, 95.1)	802	769	95.9	(94.3, 97.2)	-2.4	(-4.6, -0.2)
6B	≥0.10 µg/mL	831	734	88.3	(85.9, 90.4)	801	740	92.4	(90.3, 94.1)	-4.1	(-7.0, -1.2)
7F	≥0.35 µg/mL	833	805	96.6	(95.2, 97.8)	802	783	97.6	(96.3, 98.6)	-1.0	(-2.7, 0.7)
9V	≥0.35 µg/mL	833	682	81.9	(79.1, 84.4)	802	720	89.8	(87.5, 91.8)	-7.9	(-11.3, -4.6)
14	≥0.35 µg/mL	832	777	93.4	(91.5, 95.0)	802	755	94.1	(92.3, 95.7)	-0.8	(-3.1, 1.6)
18C	≥0.35 µg/mL	833	771	92.6	(90.6, 94.2)	802	747	93.1	(91.2, 94.8)	-0.6	(-3.1, 1.9)
19A	≥0.12 µg/mL	833	809	97.1	(95.7, 98.1)	802	787	98.1	(96.9, 98.9)	-1.0	(-2.6, 0.5)
19F	≥0.35 µg/mL	833	807	96.9	(95.5, 98.0)	802	775	96.6	(95.1, 97.8)	0.2	(-1.5, 2.0)
23F	≥0.35 µg/mL	833	649	77.9	(74.9, 80.7)	802	686	85.5	(82.9, 87.9)	-7.6	(-11.4, -3.9)
7 Additional											
8	≥0.35 µg/mL	833	806	96.8	(95.3, 97.9)	802	686	85.5	(82.9, 87.9)	11.2	(8.6, 14.0)
10A	≥0.35 µg/mL	833	685	82.2	(79.5, 84.8)	802	686	85.5	(82.9, 87.9)	-3.3	(-6.9, 0.3)
11A	≥0.35 µg/mL	833	772	92.7	(90.7, 94.4)	802	686	85.5	(82.9, 87.9)	7.1	(4.2, 10.2)
12F	≥0.35 µg/mL	833	562	67.5	(64.2, 70.6)	802	686	85.5	(82.9, 87.9)	-18.1	(-22.1, -14.0)
15B	≥0.35 µg/mL	833	818	98.2	(97.0, 99.0)	802	686	85.5	(82.9, 87.9)	12.7	(10.2, 15.4)
22F	≥0.35 µg/mL	833	819	98.3	(97.2, 99.1)	802	686	85.5	(82.9, 87.9)	12.8	(10.3, 15.5)
33F	≥0.35 µg/mL	833	722	86.7	(84.2, 88.9)	802	686	85.5	(82.9, 87.9)	1.1	(-2.2, 4.5)

Abbreviation: IgG = immunoglobulin G.
a. For the 13vPnC serotypes, the compared results are from the corresponding serotype in the 13vPnC group. For the 7 additional serotypes, the compared results are from serotype 23F (13vPnC serotype with the lowest percentage, not including serotype 3) in the 13vPnC group.
b. N = number of participants with valid assay results for the specified serotype. These values are the denominators for the percentage calculations.
c. n = Number of participants with an IgG concentration ≥ the predefined level for the given serotype.
d. Exact 2-sided CI, based on the Clopper and Pearson method.
e. 2-Sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
PFIZER CONFIDENTIAL SDTM Creation: 11SEP2022 (09:03) Source Data: adva Table Generation: 16SEP2022 (03:20)
(Snapshot date: 09SEP2022) Output File: ./B7471011_sec/B7471011_Final_CSR/adva_s006_13_1md3_eval

14.15. Antibody Response Curve for All Time Points for Pneumococcal OPA GMTs With 2-Sided 95% CIs – Evaluable Immunogenicity Population



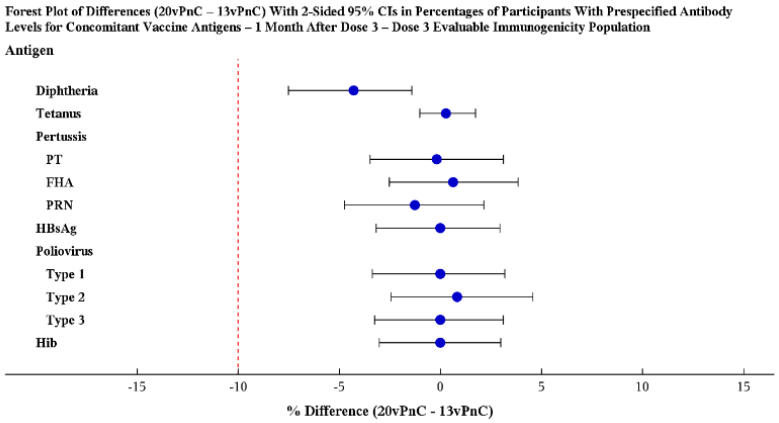
Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.
Note: Blood was collected 1 month after Dose 3 (approximately 7 months of age), prior to Dose 4 (12-15 months of age), and 1 month after Dose 4 (approximately 13 to 16 months of age).
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: OPA titers were determined on serum from randomly selected subsets of participants assuring equal representation of both vaccine groups.
Note: GMTs and 2-sided CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student t distribution).
PFIZER CONFIDENTIAL SDTM Creation: 11SEP2022 (09:03) Source Data: adva Table Generation: 16SEP2022 (21:32) (Snapshot date: 09SEP2022) Output File: ./B7471011_sec/B7471011_Final_CSR/adva_f001_ar_opa_8_eval

Immune Response to Concomitant Vaccines

- At 1 month after Dose 3, ≥95% participants had prespecified antibody levels to specific concomitant vaccine antigens (diphtheria toxoid, tetanus toxoid, pertussis antigens [PT, FHA, PRN], HBsAg, poliovirus strains 1, 2, and 3, and Hib) when given with 13vPnC (Fig. 6).

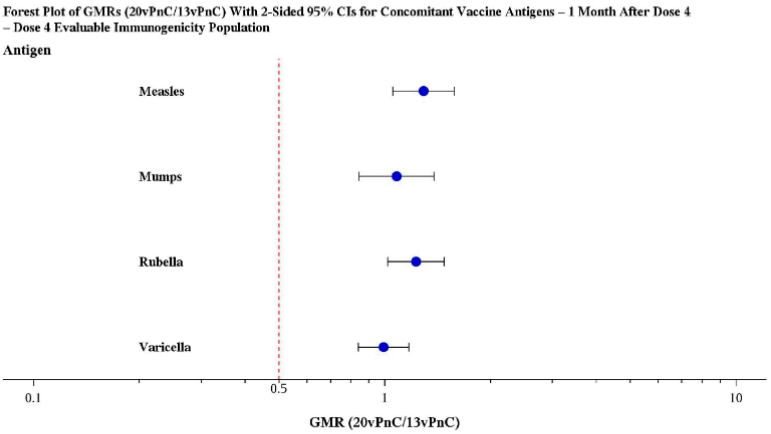
- At 1 month after Dose 4, antibody to concomitant vaccine antigens (measles, mumps, rubella, and varicella viruses) was elicited when given with 13vPnC (Fig. 7).

Figure 6. Forest Plot of Differences (20vPnC – 13vPnC) With 2-Sided 95% CIs in Percentages of Participants With Prespecified Antibody Levels for Concomitant Vaccine Antigens – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population



Abbreviations: HBsAg = hepatitis B surface antigen; mIU/mL = milli-international units per milliliter; PT = pertussis toxoid.
Note: The Dose 3 evaluable immunogenicity population was restricted to only those participants who received the appropriate concomitant vaccines with the first 3 doses.
Note: Antibody concentrations to the diphtheria, tetanus, pertussis, hepatitis B, poliovirus and Hib vaccine antigens were determined on sera collected 1 month after Dose 3 from randomly selected subsets of participants with sufficient sera volumes.
Note: The prespecified antibody thresholds for the concomitant vaccine antigens are: diphtheria and tetanus toxoids ≥0.1 IU/mL; PT ≥14.40 EU/mL; FHA ≥26.60 EU/mL; PRN ≥13.00 EU/mL; HBsAg ≥10 mIU/mL; Poliovirus strains (types 1, 2, and 3) ≥1:8; Hib ≥0.15 µg/mL. The prespecified antibody thresholds for the concomitant vaccine antigens PT, FHA, and PRN are the observed antipertussis antibody concentration achieved by 95% of participants receiving 13vPnC.
PFIZER CONFIDENTIAL SDTM Creation: 11SEP2022 (09:03) Source Data: adva Table Generation: 17SEP2022 (00:29) (Snapshot date: 09SEP2022) Output File: ./B7471011_sec/B7471011_Final_CSR/adva_f007_fr_conncm_1md3_eval

Figure 7. Forest Plot of GMRs (20vPnC / 13vPnC) With 2-Sided 95% CIs for Concomitant Vaccine Antigens – 1 Month After Dose 4 – Dose 4 Evaluable Immunogenicity Population



Abbreviations: GMR = geometric mean ratio; LLOQ = lower limit of quantitation.
Note: The Dose 4 evaluable immunogenicity population was restricted to only those participants who received the appropriate concomitant vaccines with Dose 4.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: Antibody concentrations to the measles, mumps, rubella, and varicella vaccine antigens were determined on sera collected 1 month after Dose 4 from a randomly selected subset of participants with sufficient sera volumes.
Note: GMR and 2-sided CIs were calculated by exponentiating the mean differences of the logarithms of each specific concomitant vaccine antibody level (20vPnC − 13vPnC) and the corresponding CIs (based on the Student t distribution).
PFIZER CONFIDENTIAL SDTM Creation: 11SEP2022 (09:03) Source Data: adva Table Generation: 17SEP2022 (00:29) (Snapshot date: 09SEP2022) Output File: ./B7471011_sec/B7471011_Final_CSR/adva_f007_fr_conncm_1md4_eval

Safety results

- The most frequently reported local reaction after any dose was pain at injection site (35.7% to 49.1% in the 20vPnC group and 35.8% to 45.3% in the 13vPnC group). There was no strong trend in frequency or severity of local reactions with each subsequent dose. Most local reactions were mild or moderate in severity and generally resolved with median durations between 1 to 2 days.

- The most frequently reported systemic event was irritability (61.0% to 71.6% in the 20vPnC group and 61.1% to 71.7% in the 13vPnC group), followed by drowsiness (39.5% to 67.2% in the 20vPnC group and 39.5% to 66.0% in the 13vPnC group, which decreased in frequency in both groups after each subsequent dose). Most systemic events were mild or moderate in severity and generally resolved with median durations between 1 to 3 days. The percentages of participants reporting any fever were similar in the 20vPnC and 13vPnC groups (7.5% to 17.3%), and fever of >38.9°C was reported infrequently.

- The percentages of participants with SAEs from Dose 1 to 6 months after Dose 4 were low and similar in the 20vPnC (4.5%) and 13vPnC (3.1%) 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 percentages of participants with NDCMCs from Dose 1 to 6 months after Dose 4 were low and similar in the 20vPnC (5.0%) and 13vPnC (5.9%) groups, and consistent with medical events that may occur in these populations.

- The percentages of participants with local reactions, systemic events, and AEs were generally similar after 20vPnC or 13vPnC administration across each of the sex, race, and coadministered influenza vaccine subgroups.

- No safety concerns were identified in this study.

2.3.3. Discussion on clinical aspects

In the current study “A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Infants”, the purpose was to evaluate the safety and efficacy of 20vPnC in infants and to provide key safety data to support licensure in this population. 20vPnC was compared with 13vPnC, where 13vPnC was included as a control group. Safety results from this study are consistent with the known profile of 13vPnC as reflected in the EU SmPC and support the continued use of 13vPnC. No changes are being proposed to the Prevenar 13 label in this submission. The study confirms what is already known about the safety profile of Prevenar 13 and the submitted study does not change the benefit-risk balance for Prevenar 13.

3. CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.