Amsterdam, 30 March 2023
EMA/CHMP/85386/2023
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/P46/069

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

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1. Introduction

On 10 January 2023, the MAH submitted a completed paediatric study for Prevenar 13, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Infants, B7471013 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The B7471013 study was the Phase 3 study in the paediatric population. The participants in the primary study population were administered either 20vPnC or 13vPnC in a 3-dose vaccination schedule. 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 CRM_{197} (a nontoxic variant of diphtheria toxin). 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 Prevanar 13, as it was manufactured according to the approved Prevnar 13 commercial drug product process using commercially released vaccine drug substances.

20vPnC and 13vPnC, supplied as syringes, were both white suspensions and have a matching appearance.

2.3. Clinical aspects

2.3.1 Introduction

The MAH submitted a final report for:

- B7471013 - A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Infants

2.3.2 Clinical study

B7471013 - A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Infants.

Description:

The purpose of this trial was to provide key safety data in infants receiving a 4-dose vaccine series of 20vPnC. The targeted enrollment age of the population for this study was infants ⩾34 weeks of gestation who were ⩾42 to 98 days of age, since the routinely recommended vaccination schedule for pneumococcal conjugate vaccines and other vaccines in infants starts at approximately 2 months of

age. The participants were administered either 20vPnC or 13vPnC at 2, 4, 6, and 12 to 15 months of age.

Methods

Treatments

Participants received a single 0.5-mL dose of either 20vPnC or 13vPnC at each vaccination visit (Doses 1, 2, 3, and 4 at Visits 1, 2, 3, and 5, respectively) administered intramuscularly into the anterolateral thigh muscle of the left leg by a designated site staff member. Other routine Pediatric vaccines were permitted according to official local recommendations/regulations at any time throughout study participation.

Objective and endpoints

Approximately 1500 infants were planned to be enrolled. Overall, a total of 1511 participants were randomized and 1447 (95.8%) completed all 3 infant doses. 1442 (95.4%) completed the follow-up visit after Dose 3, 1385 (91.7%) participants received all 4 doses, and 1357 (89.8%) completed all visits per protocol.

Study objectives, estimands, and endpoints are provided in Table 1.

Table 1: Study Objectives, Estimands, and Endpoints.

Objectives	Estimands	Endpoints
Primary Safety:	**Primary Safety:**	**Primary Safety:**
• To describe the safety profile of 20vPnC	In participants receiving at least 1 dose of investigational product and who have safety data reported after any vaccination: • The percentage of participants reporting prompted local reactions within 7 days after each dose in each group • The percentage of participants reporting prompted systemic events within 7 days after each dose in each group • The percentage of participants reporting AEs from Dose 1 through 1 month after Dose 3 in each group • The percentage of participants reporting AEs from Dose 4 through 1 month after Dose 4 in each group • The percentage of participants reporting SAEs up to 6 months after Dose 4 in each group • The percentage 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, irritability, and drowsiness/increased sleep) • AEs • SAEs • NDCMCs
Exploratory:	**Exploratory:**	**Exploratory:**
• To describe the safety profile of 20vPnC in subgroups	• Same as the estimands for the primary safety objective, for different race and sex subgroups	• Same as the primary safety endpoints

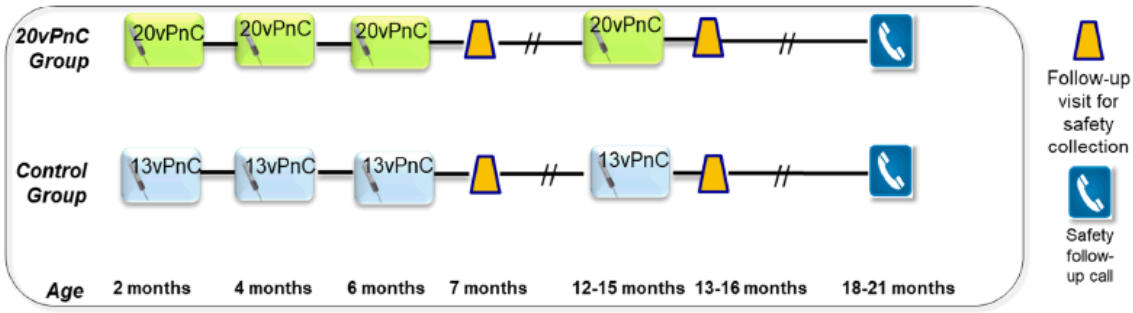
Study design / Randomisation

This was a Phase 3, multicenter, randomized, double-blind study with a 2-arm parallel design. Approximately 1500 infants ≥42 to ≤98 days of age were randomized (2:1) to receive either 20vPnC or

13vPnC at 2, 4, and 6 months of age (Doses 1 through 3) and 12 to 15 months of age (Dose 4). Participants received the same vaccine (20vPnC or 13vPnC) for all 4 doses. The targeted age of the population for this study was selected as this is the routinely recommended age for initial vaccination with pneumococcal conjugate vaccines and other vaccines in infants.

The duration of this trial for each participant was approximately 16 to 19 months.

An overview of the study design is presented below.



Statistical Methods

The primary safety objective was evaluated by descriptive summary statistics for prompted local reactions (redness, swelling, and pain at the injection site), prompted systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability), AEs (including SAEs) and NDCMCs.

AEs were categorized according to the MedDRA. Other exploratory safety objectives were evaluated by descriptive summary statistics for the same as the primary safety endpoints.

Results

Recruitment

Overall, a total of 1511 participants were randomized, 1447 (95.8%) participants completed all 3 infant doses, 1442 (95.4%) completed the follow-up visit after Dose 3, 1385 (91.7%) participants received all 4 doses, and 1357 (89.8%) completed all visits per protocol (Table 3). Disposition of all randomized participants was similar in the 20vPnC and 13vPnC groups.

Numbers analysed

Of the 150 (9.9%) participants that were withdrawn from the trial, the most common reasons were lost to follow-up (52 [3.4%] participants) and withdrawal by parent/legal guardian (51 [3.4%].

participants). For participants who were withdrawn because they no longer met eligibility criteria, the majority were because they relocated out of the area.

The numbers and percentages of participants included in the safety populations are summarized in Table 3. All participants who received at least 1 dose of 20vPnC or 13vPnC with safety follow-up after any dose were analysed in the safety population.

Table 3. Summary of Safety Population–All Randomized Participants

	Vaccine Group (as Randomized)		
	20vPnC n[a] (%)	13vPnC n[a] (%)	Total n[a] (%)
Randomized[b]	1006 (100.0)	505 (100.0)	1511 (100.0)
Vaccinated	1000 (99.4)	504 (99.8)	1504 (99.5)
Safety population[c]	1000 (99.4)	504 (99.8)	1504 (99.5)
Excluded from safety population	6 (0.6)	1 (0.2)	7 (0.5)
Reasons for exclusion			
Participant did not receive study vaccine	6 (0.6)	1 (0.2)	7 (0.5)

a. n = Number of participants with the specified characteristic in the specified group, or the total sample.
b. This value is the denominator for the percentage calculations.
c. One participant was randomized to 13vPnC but received 20vPnC at Dose 1. Data collected after the incorrect study vaccine administration are excluded from local reaction and systemic event summary tables and figures. Adverse events from participants who received any incorrect study vaccination in a specified reporting period are excluded from the summary tables and figures for that and all subsequent reporting periods. All data are included in the listings.

Baseline data

Demographic and baseline characteristics of sex, race, ethnicity, and age for the safety population were similar in the participants in the 20vPnC and 13vPnC groups (Table 4). The majority of the study population was White (87.4%) and non-Hispanic/non-Latino (61.5%).

Table 4. Demographic Characteristics – Safety Population

	Vaccine Group (as Administered)		
	20vPnC (N[a]=1000) n[b] (%)	13vPnC (N[a]=503) n[b] (%)	Total (N[a]=1503) n[b] (%)
Sex			
Male	517 (51.7)	244 (48.5)	761 (50.6)
Female	483 (48.3)	259 (51.5)	742 (49.4)
Race			
White	868 (86.8)	445 (88.5)	1313 (87.4)
Black or African American	55 (5.5)	15 (3.0)	70 (4.7)
Asian	21 (2.1)	10 (2.0)	31 (2.1)
American Indian or Alaska Native	4 (0.4)	1 (0.2)	5 (0.3)
Native Hawaiian or other Pacific Islander	2 (0.2)	2 (0.4)	4 (0.3)
Multiracial	35 (3.5)	21 (4.2)	56 (3.7)
Not reported	15 (1.5)	9 (1.8)	24 (1.6)
Ethnicity			
Hispanic/Latino	367 (36.7)	193 (38.4)	560 (37.3)
Non-Hispanic/non-Latino	621 (62.1)	303 (60.2)	924 (61.5)
Not reported	12 (1.2)	7 (1.4)	19 (1.3)
Country			
USA	323 (32.3)	155 (30.8)	478 (31.8)
Puerto Rico	12 (1.2)	7 (1.4)	19 (1.3)

Table 4. Demographic Characteristics – Safety Population

	Vaccine Group (as Administered)		
	20vPnC (N[a]=1000) n[b] (%)	13vPnC (N[a]=503) n[b] (%)	Total (N[a]=1503) n[b] (%)
Argentina	51 (5.1)	28 (5.6)	79 (5.3)
Canada	127 (12.7)	62 (12.3)	189 (12.6)
Chile	20 (2.0)	10 (2.0)	30 (2.0)
Czech Republic	20 (2.0)	9 (1.8)	29 (1.9)
Germany	32 (3.2)	17 (3.4)	49 (3.3)
Spain	212 (21.2)	108 (21.5)	320 (21.3)
Finland	11 (1.1)	6 (1.2)	17 (1.1)
Greece	20 (2.0)	11 (2.2)	31 (2.1)
Hungary	172 (17.2)	90 (17.9)	262 (17.4)
Age at Dose 1 (days)			
Mean (SD)	64.6 (8.51)	65.0 (8.95)	64.8 (8.66)
Median	64.0	64.0	64.0
Min, max	(43, 98)	(43, 97)	(43, 98)
Age at Dose 4 (days)			
Mean (SD)	379.8 (16.69)	380.4 (18.05)	380.0 (17.15)
Median	373.0	372.0	373.0
Min, max	(365, 455)	(366, 455)	(365, 455)
Gestational age (weeks)			
Mean (SD)	38.9 (1.50)	38.9 (1.46)	38.9 (1.49)
Median	39.0	39.0	39.0
Min, max	(34, 42)	(34, 42)	(34, 42)
≥34 to <37 Weeks	77 (7.7)	34 (6.8)	111 (7.4)
≥37 Weeks	923 (92.3)	469 (93.2)	1392 (92.6)

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.
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Efficacy results

N/A

Safety results

- Pain at the injection site was the most common local reaction in both groups. Most local reactions were mild or moderate in severity and generally resolved with median durations between 1 to 2 days.

- Irritability was reported most frequently in both groups. Most systemic events were mild or moderate in severity and generally resolved with median durations between 1 to 2 days. The percentage of participants with any fever were similar in both groups (9.3%–18.0% in the 20vPnC group and 9.8%–17.0% in the 13vPnC group). Fever of >38.9°C was reported infrequently.

- From Dose 1 to 1 month after Dose 3, at least 1 AE was reported in 29.6% of participants in the 20vPnC group and 27.6% of participants in the 13vPnC group, and from Dose 4 to 1 month after Dose 4, AEs were reported in 15.1% of participants in the 20vPnC group and 15.8 % of participants in the 13vPnC group. No safety concerns were identified.

- The percentages of participants with SAEs from Dose 1 to 6 months after Dose 4 were low and similar in the 20vPnC (4.4%) and 13vPnC (5.6%) groups. Most SAEs reported were consistent with medical events or conditions that may occur in this population, and all 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 (≤2.8%) and similar in the 20vPnC and 13vPnC groups, and consistent with medical conditions that may occur in these populations.

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

- The percentages of late preterm participants (infants born at ≥34 to <37 weeks of gestational age, N=111) with local reactions, systemic events, and overall AEs reported after 20vPnC or 13vPnC were generally similar between vaccine groups and to infants born full term.

Local reactions

The percentages of participants with local reactions at the injection site within 7 days after Doses 1 through 4 of 20vPnC or 13vPnC are presented in Table 7. The percentages of participants with any local reactions after Doses 1 through 4 were generally similar in the 20vPnC group (51.6%, 45.8%, 38.6%, and 40.6%, respectively) and 13vPnC group (53.6%, 49.1%, 40.0%, and 42.3%, respectively). The most frequently reported local reaction after any dose was pain at injection site (24.7%–40.5% in the 20vPnC group and 26.8%–42.0% in the 13vPnC group). Most local reactions were mild or moderate in severity. There was no strong trend in frequency or severity of local reactions across all 4 doses. Across Doses 1 through 4, the median day of onset for local reactions was between Day 1 and Day 2 (Day 1 was the day of vaccination) and local reactions resolved with a median duration between 1 to 2 days.

Table 7. Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Safety Population

		Vaccine Group (as Administered)							
		20vPnC			13vPnC			20vPnC–13vPnC	
Dose	Local Reaction	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])	Difference (%)	(95% CI[d])
Dose 1	Redness[e]	992			498				
	Any		216 (21.8)	(19.2, 24.5)		97 (19.5)	(16.1, 23.2)	2.3	(-2.1, 6.5)
	Mild		179 (18.0)	(15.7, 20.6)		82 (16.5)	(13.3, 20.0)	1.6	(-2.6, 5.5)
	Moderate		37 (3.7)	(2.6, 5.1)		15 (3.0)	(1.7, 4.9)	0.7	(-1.4, 2.5)
	Severe		0	(0.0, 0.4)		0	(0.0, 0.7)	0.0	(-0.8, 0.4)
	Swelling[e]	992			498				
	Any		198 (20.0)	(17.5, 22.6)		83 (16.7)	(13.5, 20.2)	3.3	(-0.9, 7.3)
	Mild		137 (13.8)	(11.7, 16.1)		56 (11.2)	(8.6, 14.4)	2.6	(-1.1, 6.0)
	Moderate		61 (6.1)	(4.7, 7.8)		27 (5.4)	(3.6, 7.8)	0.7	(-2.0, 3.1)
	Severe		0	(0.0, 0.4)		0	(0.0, 0.7)	0.0	(-0.8, 0.4)
	Pain at injection site[f]	992			498				
	Any		402 (40.5)	(37.5, 43.7)		209 (42.0)	(37.6, 46.4)	-1.4	(-6.8, 3.8)
	Mild		246 (24.8)	(22.1, 27.6)		126 (25.3)	(21.5, 29.4)	-0.5	(-5.3, 4.1)
	Moderate		154 (15.5)	(13.3, 17.9)		83 (16.7)	(13.5, 20.2)	-1.1	(-5.3, 2.7)
	Severe		2 (0.2)	(0.0, 0.7)		0	(0.0, 0.7)	0.2	(-0.6, 0.7)
	Any local reaction[g]	992	512 (51.6)	(48.5, 54.8)	498	267 (53.6)	(49.1, 58.1)	-2.0	(-7.3, 3.4)
Dose 2	Redness[e]	952			485				
	Any		224 (23.5)	(20.9, 26.4)		113 (23.3)	(19.6, 27.3)	0.2	(-4.5, 4.8)
	Mild		194 (20.4)	(17.9, 23.1)		94 (19.4)	(16.0, 23.2)	1.0	(-3.5, 5.2)
	Moderate		30 (3.2)	(2.1, 4.5)		19 (3.9)	(2.4, 6.1)	-0.8	(-3.1, 1.2)
	Severe		0	(0.0, 0.4)		0	(0.0, 0.8)	0.0	(-0.8, 0.4)
	Swelling[e]	952			485				
	Any		170 (17.9)	(15.5, 20.4)		92 (19.0)	(15.6, 22.7)	-1.1	(-5.5, 3.0)
	Mild		128 (13.4)	(11.3, 15.8)		65 (13.4)	(10.5, 16.8)	0.0	(-3.8, 3.6)
	Moderate		42 (4.4)	(3.2, 5.9)		27 (5.6)	(3.7, 8.0)	-1.2	(-3.8, 1.1)
	Severe		0	(0.0, 0.4)		0	(0.0, 0.8)	0.0	(-0.8, 0.4)
	Pain at injection site[f]	952			485				
	Any		307 (32.2)	(29.3, 35.3)		159 (32.8)	(28.6, 37.2)	-0.5	(-5.7, 4.5)
	Mild		198 (20.8)	(18.3, 23.5)		98 (20.2)	(16.7, 24.1)	0.6	(-3.9, 4.9)
	Moderate		102 (10.7)	(8.8, 12.9)		57 (11.8)	(9.0, 15.0)	-1.0	(-4.7, 2.3)
	Severe		7 (0.7)	(0.3, 1.5)		4 (0.8)	(0.2, 2.1)	-0.1	(-1.4, 0.8)
	Any local reaction[g]	952	436 (45.8)	(42.6, 49.0)	485	238 (49.1)	(44.5, 53.6)	-3.3	(-8.7, 2.2)
Dose 3	Redness[e]	940			477				
	Any		218 (23.2)	(20.5, 26.0)		97 (20.3)	(16.8, 24.2)	2.9	(-1.8, 7.3)
	Mild		182 (19.4)	(16.9, 22.0)		81 (17.0)	(13.7, 20.7)	2.4	(-2.0, 6.5)
	Moderate		36 (3.8)	(2.7, 5.3)		15 (3.1)	(1.8, 5.1)	0.7	(-1.5, 2.6)

Table 7. Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Safety Population

		Vaccine Group (as Administered)							
		20vPnC			13vPnC			20vPnC–13vPnC	
Dose	Local Reaction	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])	Difference (%)	(95% CI[d])
	Severe		0	(0.0, 0.4)		1 (0.2)	(0.0, 1.2)	-0.2	(-1.2, 0.2)
	Swelling[e]	940			477				
	Any		154 (16.4)	(14.1, 18.9)		78 (16.4)	(13.1, 20.0)	0.0	(-4.2, 4.0)
	Mild		115 (12.2)	(10.2, 14.5)		62 (13.0)	(10.1, 16.4)	-0.8	(-4.6, 2.8)
	Moderate		39 (4.1)	(3.0, 5.6)		15 (3.1)	(1.8, 5.1)	1.0	(-1.2, 2.9)
	Severe		0	(0.0, 0.4)		1 (0.2)	(0.0, 1.2)	-0.2	(-1.2, 0.2)
	Pain at injection site[f]	940			477				
	Any		232 (24.7)	(22.0, 27.6)		128 (26.8)	(22.9, 31.1)	-2.2	(-7.1, 2.6)
	Mild		153 (16.3)	(14.0, 18.8)		79 (16.6)	(13.3, 20.2)	-0.3	(-4.5, 3.7)
	Moderate		78 (8.3)	(6.6, 10.2)		49 (10.3)	(7.7, 13.4)	-2.0	(-5.4, 1.1)
	Severe		1 (0.1)	(0.0, 0.6)		0	(0.0, 0.8)	0.1	(-0.7, 0.6)
	Any local reaction[g]	940	363 (38.6)	(35.5, 41.8)	477	191 (40.0)	(35.6, 44.6)	-1.4	(-6.8, 3.9)
Dose 4	Redness[e]	892			454				
	Any		189 (21.2)	(18.5, 24.0)		99 (21.8)	(18.1, 25.9)	-0.6	(-5.4, 3.9)
	Mild		135 (15.1)	(12.8, 17.7)		88 (19.4)	(15.8, 23.3)	-4.2	(-8.7, -0.0)
	Moderate		53 (5.9)	(4.5, 7.7)		11 (2.4)	(1.2, 4.3)	3.5	(1.3, 5.6)
	Severe		1 (0.1)	(0.0, 0.6)		0	(0.0, 0.8)	0.1	(-0.7, 0.6)
	Swelling[e]	892			454				
	Any		132 (14.8)	(12.5, 17.3)		65 (14.3)	(11.2, 17.9)	0.5	(-3.7, 4.3)
	Mild		90 (10.1)	(8.2, 12.3)		52 (11.5)	(8.7, 14.7)	-1.4	(-5.1, 2.0)
	Moderate		42 (4.7)	(3.4, 6.3)		13 (2.9)	(1.5, 4.8)	1.8	(-0.4, 3.9)
	Severe		0	(0.0, 0.4)		0	(0.0, 0.8)	0.0	(-0.8, 0.4)
	Pain at injection site[f]	892			454				
	Any		275 (30.8)	(27.8, 34.0)		145 (31.9)	(27.7, 36.4)	-1.1	(-6.4, 4.1)
	Mild		177 (19.8)	(17.3, 22.6)		99 (21.8)	(18.1, 25.9)	-2.0	(-6.7, 2.5)
	Moderate		91 (10.2)	(8.3, 12.4)		46 (10.1)	(7.5, 13.3)	0.1	(-3.5, 3.4)
	Severe		7 (0.8)	(0.3, 1.6)		0	(0.0, 0.8)	0.8	(-0.1, 1.6)
	Any local reaction[g]	892	362 (40.6)	(37.3, 43.9)	454	192 (42.3)	(37.7, 47.0)	-1.7	(-7.3, 3.8)

Note: Local reactions were collected in the e-diary from Day 1 through Day 7 after each dose. If a severe reaction was identified by the investigator as a Grade 4 reaction at a follow-up assessment, it was also reported as an adverse event.
a. N = number of participants with any e-diary data reported after the specified dose. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
d. 2-Sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
e. Mild: >0.0 to 2.0 cm; moderate: >2.0 to 7.0 cm; severe: >7.0 cm.
f. Mild: hurts if gently touched; moderate: hurts if gently touched with crying; severe: causes limitation of limb movement.
g. Any local reaction: any redness >0.0 cm, any swelling >0.0 cm, or any pain at the injection site after the specified dose.
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Systemic Events

The percentages of participants with systemic events within 7 days after Doses 1 through 4 were generally similar in the 20vPnC and 13vPnC groups, and the most frequently reported systemic event was irritability (54.8 % to 68.2% in the 20vPnC group and 54.7% to 68.5% in the 13vPnC group), followed by drowsiness (35.3% to 64.8% in the 20vPnC group and 35.9% to 62.2% in the 13vPnC group). Both irritability and drowsiness frequencies decreased in both groups between Dose 1 and Dose 3, and Dose 4 frequencies for both events were similar to Dose 3. Most systemic events were mild or moderate in severity. The percentages of participants with any fever of ≥38.0°C were similar in the 20vPnC and 13vPnC groups (9.3%–18.0% in the 20vPnC group and 9.8%–17.0% in the 13vPnC group). Fever of >38.9°C was reported infrequently in both groups (≤3.8% and ≤3.3 % in the 20vPnC and 13vPnC groups, respectively), and fever >40°C was reported only at Dose 4 (1 participant in each vaccine group). There was no strong trend in frequency or severity of fever across the 4 doses.

Table 8. Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Safety Population

		Vaccine Group (as Administered)							
			20vPnC			13vPnC		20vPnC–13vPnC	
Dose	Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])	Difference (%)	(95% CI[d])
Dose 2	Fever	952			485				
	≥38.0°C		148 (15.5)	(13.3, 18.0)		55 (11.3)	(8.7, 14.5)	4.2	(0.4, 7.7)
	≥38.0°C to 38.4°C		101 (10.6)	(8.7, 12.7)		41 (8.5)	(6.1, 11.3)	2.2	(-1.2, 5.2)
	>38.4°C to 38.9°C		34 (3.6)	(2.5, 5.0)		13 (2.7)	(1.4, 4.5)	0.9	(-1.2, 2.7)
	>38.9°C to 40.0°C		13 (1.4)	(0.7, 2.3)		1 (0.2)	(0.0, 1.1)	1.2	(0.1, 2.2)
	>40.0°C		0	(0.0, 0.4)		0	(0.0, 0.8)	0.0	(-0.8, 0.4)
	Decreased appetite[e]	952			485				
	Any		226 (23.7)	(21.1, 26.6)		100 (20.6)	(17.1, 24.5)	3.1	(-1.5, 7.5)
	Mild		128 (13.4)	(11.3, 15.8)		58 (12.0)	(9.2, 15.2)	1.5	(-2.3, 5.0)
	Moderate		91 (9.6)	(7.8, 11.6)		40 (8.2)	(6.0, 11.1)	1.3	(-2.0, 4.3)
	Severe		7 (0.7)	(0.3, 1.5)		2 (0.4)	(0.0, 1.5)	0.3	(-0.8, 1.2)
	Drowsiness[f]	952			485				
	Any		468 (49.2)	(45.9, 52.4)		244 (50.3)	(45.8, 54.8)	-1.1	(-6.6, 4.3)
	Mild		336 (35.3)	(32.3, 38.4)		171 (35.3)	(31.0, 39.7)	0.0	(-5.2, 5.2)
	Moderate		128 (13.4)	(11.3, 15.8)		67 (13.8)	(10.9, 17.2)	-0.4	(-4.3, 3.3)
	Severe		4 (0.4)	(0.1, 1.1)		6 (1.2)	(0.5, 2.7)	-0.8	(-2.3, 0.1)
	Irritability[g]	952			485				
	Any		616 (64.7)	(61.6, 67.7)		328 (67.6)	(63.3, 71.8)	-2.9	(-8.0, 2.3)
	Mild		221 (23.2)	(20.6, 26.0)		96 (19.8)	(16.3, 23.6)	3.4	(-1.1, 7.8)
	Moderate		355 (37.3)	(34.2, 40.4)		207 (42.7)	(38.2, 47.2)	-5.4	(-10.8, -0.1)
	Severe		40 (4.2)	(3.0, 5.7)		25 (5.2)	(3.4, 7.5)	-1.0	(-3.5, 1.3)
	Any systemic event[h]	952	748 (78.6)	(75.8, 81.1)	485	385 (79.4)	(75.5, 82.9)	-0.8	(-5.1, 3.8)
	Use of antipyretic or pain medication[i]	952	338 (35.5)	(32.5, 38.6)	485	169 (34.8)	(30.6, 39.3)	0.7	(-4.6, 5.8)
Dose 3	Fever	940			477				
	≥38.0°C		109 (11.6)	(9.6, 13.8)		47 (9.9)	(7.3, 12.9)	1.7	(-1.8, 5.0)
	≥38.0°C to 38.4°C		70 (7.4)	(5.9, 9.3)		39 (8.2)	(5.9, 11.0)	-0.7	(-3.9, 2.1)
	>38.4°C to 38.9°C		27 (2.9)	(1.9, 4.2)		3 (0.6)	(0.1, 1.8)	2.2	(0.8, 3.6)
	>38.9°C to 40.0°C		12 (1.3)	(0.7, 2.2)		5 (1.0)	(0.3, 2.4)	0.2	(-1.2, 1.4)
	>40.0°C		0	(0.0, 0.4)		0	(0.0, 0.8)	0.0	(-0.8, 0.4)
	Decreased appetite[e]	940			477				
	Any		222 (23.6)	(20.9, 26.5)		82 (17.2)	(13.9, 20.9)	6.4	(2.0, 10.7)
	Mild		141 (15.0)	(12.8, 17.4)		50 (10.5)	(7.9, 13.6)	4.5	(0.8, 8.0)
	Moderate		77 (8.2)	(6.5, 10.1)		30 (6.3)	(4.3, 8.9)	1.9	(-1.1, 4.6)
	Severe		4 (0.4)	(0.1, 1.1)		2 (0.4)	(0.1, 1.5)	0.0	(-1.1, 0.7)
	Drowsiness[f]	940			477				
	Any		332 (35.3)	(32.3, 38.5)		173 (36.3)	(31.9, 40.8)	-0.9	(-6.3, 4.3)
	Mild		250 (26.6)	(23.8, 29.5)		130 (27.3)	(23.3, 31.5)	-0.7	(-5.6, 4.1)
	Moderate		80 (8.5)	(6.8, 10.5)		43 (9.0)	(6.6, 12.0)	-0.5	(-3.8, 2.5)
	Severe		2 (0.2)	(0.0, 0.8)		0	(0.0, 0.8)	0.2	(-0.6, 0.8)
	Irritability[g]	940			477				
	Any		515 (54.8)	(51.5, 58.0)		261 (54.7)	(50.1, 59.2)	0.1	(-5.4, 5.6)
	Mild		210 (22.3)	(19.7, 25.1)		106 (22.2)	(18.6, 26.2)	0.1	(-4.6, 4.6)
	Moderate		283 (30.1)	(27.2, 33.2)		142 (29.8)	(25.7, 34.1)	0.3	(-4.8, 5.3)
	Severe		22 (2.3)	(1.5, 3.5)		13 (2.7)	(1.5, 4.6)	-0.4	(-2.4, 1.3)
	Any systemic event[h]	940	645 (68.6)	(65.5, 71.6)	477	321 (67.3)	(62.9, 71.5)	1.3	(-3.8, 6.5)
	Use of antipyretic or pain medication[i]	940	243 (25.9)	(23.1, 28.8)	477	132 (27.7)	(23.7, 31.9)	-1.8	(-6.8, 3.0)
Dose 4	Fever	892			454				
	≥38.0°C		161 (18.0)	(15.6, 20.7)		77 (17.0)	(13.6, 20.7)	1.1	(-3.3, 5.2)
	≥38.0°C to 38.4°C		87 (9.8)	(7.9, 11.9)		43 (9.5)	(6.9, 12.5)	0.3	(-3.2, 3.5)
	>38.4°C to 38.9°C		40 (4.5)	(3.2, 6.1)		19 (4.2)	(2.5, 6.5)	0.3	(-2.2, 2.5)
	>38.9°C to 40.0°C		33 (3.7)	(2.6, 5.2)		14 (3.1)	(1.7, 5.1)	0.6	(-1.7, 2.5)
	>40.0°C		1 (0.1)	(0.0, 0.6)		1 (0.2)	(0.0, 1.2)	-0.1	(-1.1, 0.4)
	Decreased appetite[e]	892			454				
	Any		253 (28.4)	(25.4, 31.4)		117 (25.8)	(21.8, 30.1)	2.6	(-2.5, 7.5)

Dose	Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])	Difference (%)	(95% CI[d])
	Mild		144 (16.1)	(13.8, 18.7)		56 (12.3)	(9.5, 15.7)	3.8	(-0.2, 7.6)
	Moderate		94 (10.5)	(8.6, 12.7)		53 (11.7)	(8.9, 15.0)	-1.1	(-4.9, 2.3)
	Severe		15 (1.7)	(0.9, 2.8)		8 (1.8)	(0.8, 3.4)	-0.1	(-1.9, 1.3)
	Drowsiness[f]	892			454				
	Any		331 (37.1)	(33.9, 40.4)		163 (35.9)	(31.5, 40.5)	1.2	(-4.3, 6.6)
	Mild		216 (24.2)	(21.4, 27.2)		114 (25.1)	(21.2, 29.4)	-0.9	(-5.9, 3.9)
	Moderate		109 (12.2)	(10.1, 14.6)		48 (10.6)	(7.9, 13.8)	1.6	(-2.1, 5.1)
	Severe		6 (0.7)	(0.2, 1.5)		1 (0.2)	(0.0, 1.2)	0.5	(-0.6, 1.3)
	Irritability[g]	892			454				
	Any		493 (55.3)	(51.9, 58.6)		250 (55.1)	(50.4, 59.7)	0.2	(-5.4, 5.8)
	Mild		191 (21.4)	(18.8, 24.3)		100 (22.0)	(18.3, 26.1)	-0.6	(-5.4, 3.9)
	Moderate		280 (31.4)	(28.4, 34.5)		135 (29.7)	(25.6, 34.2)	1.7	(-3.6, 6.8)
	Severe		22 (2.5)	(1.6, 3.7)		15 (3.3)	(1.9, 5.4)	-0.8	(-3.1, 1.0)
	Any systemic event[h]	892	590 (66.1)	(62.9, 69.2)	454	309 (68.1)	(63.6, 72.3)	-1.9	(-7.1, 3.4)
	Use of antipyretic or pain medication[i]	892	331 (37.1)	(33.9, 40.4)	454	151 (33.3)	(28.9, 37.8)	3.8	(-1.6, 9.1)

Note: Systemic events and use of antipyretic/pain medication were collected in the e-diary from Day 1 through Day 7 after each dose. If a severe event was identified by the investigator as a Grade 4 event at a follow-up assessment, it was also reported as an adverse event.

a. N = number of participants with any e-diary data reported after the specified dose. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Exact 2-sided CI, based on the Clopper and Pearson method.
d. 2-Sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
e. Mild: decreased interest in eating; moderate: decreased oral intake; severe: refusal to feed.
f. Mild: increased or prolonged sleeping bouts; moderate: slightly subdued interfering with daily activity; severe: disabling not interested in usual daily activity.
g. Mild: easily consolable; moderate: requiring increased attention; severe: inconsolable; crying cannot be comforted.
h. Any systemic event: any fever ≥38.0°C, any decreased appetite, any drowsiness, or any irritability after the specified dose.
i. The numbers in the table reflect yes responses (ie, number of events reported).

Adverse events

From Dose 1 to 1 month after Dose 3, at least 1 AE was reported in 29.6% of participants in the 20vPnC group and 27.6% of participants in the 13vPnC group. As commonly seen in this population, AEs in the SOC of infections and infestations were reported most frequently in the 20vPnC (18.2%) and 13vPnC (15.9%) groups and included upper respiratory tract infection (4.1% and 3.0%, respectively) and nasopharyngitis (2.8% and 1.2%, respectively). From Dose 4 to 1 month after Dose 4, AEs were reported in 15.1% of participants in the 20vPnC group and 15.8 % of participants in the in the 13vPnC group. As with the AEs from Dose 1 to 1 month after Dose 3, AEs in the SOC infections and infestations were reported most frequently in participants in the 20vPnC (11.6%) and 13vPnC (13.4 %) groups and included upper respiratory tract infection (2.1% and 3.0%, respectively) and nasopharyngitis (2.3% and 1.1%, respectively).

Related adverse events: The frequencies of any reported related AEs from Dose 1 to 1 month after Dose 3 (≤0.4% and ≤1.0%) and from Dose 4 to 1 month after Dose 4 (≤0.2% and ≤0.2%) were low and similar in the 20vPnC and 13vPnC groups. The most frequently reported related AEs were in the General Disorders and Administration Site Conditions and Gastrointestinal Disorders SOCs.

Immediate Adverse Events: Immediate AEs were reported infrequently in the 20vPnC and 13vPnC groups (≤0.4% of participants after each dose; the same AE was not reported more than once per dose). Most immediate AEs belonged to the General Disorders and Administration Site Conditions SOC, and none of the immediate AEs represented serious allergic reactions to 20vPnC.

Severe Adverse Events Severe AEs were reported infrequently in both groups from Dose 1 to 1 month after Dose 3 (≤1.0%) and from Dose 4 to 1 month after Dose 4 (≤0.7%), and the percentages were similar in the 20vPnC and 13vPnC groups. No severe AEs were assessed by the investigators as related to study intervention. The severe AEs most often represented SAEs consistent with diseases and medical conditions that may occur in the baseline infant and toddler population.

Newly Diagnosed Chronic Medical Conditions The percentages of participants with newly diagnosed chronic medical conditions (NDMCMCs) after Dose 1 were low (2.8%) in both the 20vPnC and 13vPnC groups. From Dose 1 to 1 month after Dose 3 of 20vPnC or 13vPnC, NDCMCs were reported for 2.0% of

participants and from Dose 4 to 1 month after Dose 4 of 20vPnC or 13vPnC, for ≤0.4% of participants. The majority of NDMCs were new diagnoses of atopic dermatitis, eczema, or food and milk allergy.

Deaths: There were no deaths during the trial.

2.3.3 Discussion on clinical aspects

In the current study "A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Infants", the purpose was to evaluate the safety of 20vPnC in infants. 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. Overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.