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EMA/CHMP/495335/2020
Committee for Medicinal Products for Human Use (CHMP)

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/P46/063

Note

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

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1. Introduction

On 29th July 2020, 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 2, randomised, double-blind trial to evaluate the safety and immunogenicity of a multivalent pneumococcal conjugate vaccine in healthy infants, B7471003 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

All subjects received a single dose (0.5 mL) of 20vPnC or 13vPnC intramuscularly into the anterolateral thigh muscle of the left leg at the vaccination visits.

The 13vPnC supply is being manufactured specifically for this study and is not a marketed product; however, it is considered representative of Prevenar 13, as the polysaccharide intermediates and vaccine substances are manufactured according to the approved Prevenar 13 commercial process and the formulation and filling processes are similar but are performed at a different scale than the commercial process.

The investigational vaccine 20vPnC contains the same 13 serotypes as 13vPnC, plus conjugated capsular polysaccharides for 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F).

The vaccine is formulated with 5mM succinate buffer, 0.02% polysorbate 80, and 0.125mg of aluminium as aluminium phosphate, per 0.5-mL dose.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Phase 2, randomised, double-blind trial to evaluate the safety and immunogenicity of a multivalent pneumococcal conjugate vaccine in healthy infants, B7471003

2.3.2. Clinical study

Phase 2, randomised, double-blind trial to evaluate the safety and immunogenicity of a multivalent pneumococcal conjugate vaccine in healthy infants, B7471003

Description

Pfizer is developing a new 20vPnC candidate to expand protection against pneumococcal disease beyond that covered by current pneumococcal vaccines. 20vPnC has the same composition as 13vPnC, but contains an additional 7 pneumococcal conjugates to protect against serotypes responsible for a

substantial burden of remaining pneumococcal disease. A meta-analysis of serotypes causing invasive pneumococcal disease (IPD) in children <5 years of age showed that, overall, these 7 serotypes accounted for approximately 70% of disease not due to the 13vPnC vaccine types.

The purpose of this Phase 2 study was to describe the safety and immunogenicity of 20vPnC in infants administered vaccine (20vPnC or 13vPnC control) at 2, 4, 6, and 12 months of age and inform further clinical development of 20vPnC in the paediatric populations. The control group received 13vPnC prepared specifically for the study to provide context for the safety and immunogenicity of 20vPnC.

Methods

Objectives and endpoints

Table 1. Objectives and endpoints

Type	Objectives	Endpoint
Primary		
Safety	• To describe the safety profile of 20vPnC in healthy infants.	• Proportions of subjects reporting prompted local reactions (redness, swelling, and pain at the injection site) within 7 days of each dose. • Proportions of subjects reporting prompted systemic events (fever, decreased appetite, irritability, and drowsiness/increased sleep) within 7 days of each dose. • Proportions of subjects reporting AEs from Dose 1 to 1 month following Dose 3 and from Dose 4 to 1 month following Dose 4. • Proportions of subjects reporting SAEs and newly diagnosed chronic medical conditions (NDCMCs) from Dose 1 to 6 months following Dose 4.
Secondary		
Immunogenicity	• To describe the immunogenicity of 20vPnC in healthy infants.	• Pneumococcal serotype-specific IgG concentrations 1 month after Dose 3. • Pneumococcal serotype-specific IgG concentrations 1 month after Dose 4.
Exploratory		
Immunogenicity	• To further describe the immunogenicity of 20vPnC in healthy infants.	• Pneumococcal serotype-specific IgG concentrations at various study time points. • Pneumococcal serotype-specific OPA titers at various study time points.
Immunogenicity	• To describe the immune responses to concomitantly administered diphtheria and pertussis vaccine antigens.	• Diphtheria toxoid and pertussis antibody levels 1 month after Dose 3.

Study design

This was a Phase 2, multicenter, randomized, active-controlled, double-blind study with a 2-arm parallel design, conducted at investigator sites in the United States. Approximately 460 infants aged ≥42 to ≤98 days were to be randomized (1:1) to receive either 20vPnC or 13vPnC at 2, 4, and 6 months of age (infant series, Doses 1 through 3) and 12 months of age (Dose 4). Vaccine containing diphtheria, tetanus, and acellular pertussis, hepatitis B and polio antigens (Pediarix, GlaxoSmithKline) was administered concomitantly with Doses 1 to 3. Other routine paediatric vaccines (Haemophilus influenzae type b (Hib), measles, mumps, and rubella (MMR), rotavirus, meningococcal, influenza) could be administered as specified in the protocol as well. The study design is presented below in Figure 1.

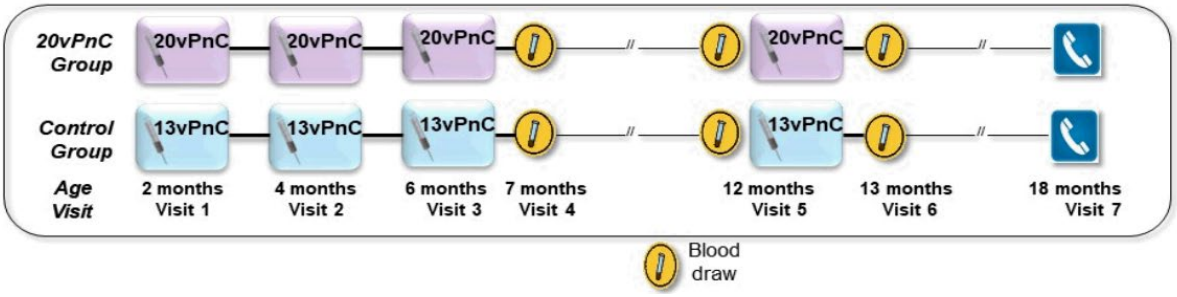

Figure 1. Study design

Study population /Sample size

Healthy male or female infants born at >36 weeks of gestation and aged 2 months (≥42 to ≤98 days) at the time of consent (the day of birth is considered day of life 1) were enrolled in this study.

A total of 460 participants were randomized across both vaccine groups (20vPnC; and 13vPnC) and 89.3% of participants completed the visit 1 month after Dose 3. The percentages of participants were similar in the 2 groups for all the categories in the disposition table. Of the 49 (10.7%) participants that were withdrawn from the study before the visit 1 month after Dose 3, the most common reason was withdrawal by parent/guardian (26 [5.7%] participants). Two participants (1 each in the 20vPnC and 13vPnC groups) were randomized but not vaccinated because the parents withdrew consent.

A total of 391 participants were vaccinated at Dose 4 and 82.8% of participants completed the visit 1 month after Dose 4. The percentages of participants were similar in the 2 groups for all the categories in the disposition table. Of the 10 (2.2%) participants that were withdrawn from the study after Dose 4 but before the visit 1 month after Dose 4, the most common reason for withdrawal was lost to follow-up (7 [1.5%] participants).

Treatments

All subjects received a single dose (0.5 mL) of 20vPnC or 13vPnC intramuscularly into the anterolateral thigh muscle of the left leg at the vaccination visits.

As stated in the Brief Licensing History, the 13vPnC supply is being manufactured specifically for this study and is not a marketed product; however, it is considered representative of Prevenar 13, as the polysaccharide intermediates and vaccine substances are manufactured according to the approved Prevenar 13 commercial process and the formulation and filling processes are similar but are performed at a different scale than the commercial process.

Diphtheria, tetanus, and acellular pertussis (DTaP)-containing vaccine (potentially in combination with other antigens such as poliomyelitis) will be administered concomitantly with the first 3 doses of 20vPnC or 13vPnC. If not in the combination, poliomyelitis, hepatitis B, and Haemophilus influenzae type b vaccines may be given with 20vPnC or 13vPnC. Measles, mumps, and rubella (MMR) vaccination will be administered concomitantly with 20vPnC or 13vPnC Dose 4.

Study Evaluations

Safety Evaluations

The legally acceptable representative (LAR) of the participants were asked to monitor and record local reactions, specific systemic events, and antipyretics/pain medication taken for 7 days, each evening after each dose of investigational product (20vPnC or 13vPnC) using an e-diary on a provisioned device or e-diary application on a personal device.

Local Reactions: For the first 7 days after each dose of investigational product from Day 1 through Day 7, the subject's LAR was asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary in the evening.

Systemic Events: For the first 7 days after each dose of investigational product from Day 1 through Day 7, the subject's LAR was asked to assess decreased appetite, drowsiness/increased sleep, and irritability and to record the symptoms in the e-diary in the evening. Temperature was recorded in the evening daily in the e-diary by the subject's LAR for 7 days after each dose of investigational product (Days 1 to 7, where Day 1 was the day of vaccination) and at any time during the 7 days that fever was suspected. The subject's LAR was asked to record the use of antipyretic/pain medication (yes/no) in the e-diary in the evening daily for 7 days after each dose of investigational product.

Adverse events (AEs), serious adverse events (SAEs), and newly diagnosed chronic medical conditions (NDCMCs): The time period for actively eliciting and collecting AEs, SAEs, and NDCMCs for each subject began from the time the subject's LAR provided informed consent, which was obtained before the subject's participation in the study (i.e., before undergoing any study-related procedure and/or receiving investigational product). AEs were collected through 1 month after Dose 3 and from Dose 4 through 1 month after Dose 4. NDCMCs and SAEs were collected through 6 months after Dose 4. An NDCMC was defined as a disease or medical condition, not previously identified, that is expected to be persistent or is otherwise long-lasting in its effects.

Acute reactions within the first 30 minutes after investigational product and concomitant vaccination administration were assessed and documented as an AE with or without an SAE in the case report form (CRF) and SAE form, as appropriate.

Immunogenicity Evaluations

Blood samples (approximately 5 mL/visit) for immunogenicity assessments were collected from all subjects 1 month after Dose 3, prior to Dose 4, and 1 month after Dose 4. Concentrations of anticapsular IgG for the 20 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) were determined in all subjects at the 3 time points.

Opsonophagocytic activity (OPA, functional neutralization assay) titers were determined on serum from randomly selected subsets of participants with equal representation of both groups in each subset. There were a small number of participants in each subset so conclusions are limited.

Assessor´s comment: the overall study design, objectives, endpoints and evaluation methods are appropriate.

Statistical Methods

The statistical analysis were descriptive.

Table 2. Analysis sets

Analysis Population	Description	Analysis Set applies to following endpoints
Safety Analysis Population	Overall safety population - all subjects who received at least 1 dose of study vaccine (20vPnC or 13vPnC) with safety follow-up in the study. Additional safety populations were defined for Doses 1 to 3 and Dose 4. The Dose 1 to 3 safety population was the primary analysis population for safety and reactogenicity data from Doses 1 to 3. The Dose 4 safety population was the primary analysis population for safety and reactogenicity data from Dose 4. Definitions of the additional safety populations: • Dose 1 to Dose 3 Safety Population - subjects receiving Dose 1 and having safety follow-up between Dose 1 and the blood draw visit 1 month after Dose 3 • Dose 4 Safety Population - subjects receiving Dose 4 and having safety follow-up between Dose 4 and 6 months after Dose 4 Subjects were included in the vaccine group corresponding to the vaccine actually received in the analyses based on safety populations.	Safety
Evaluable Immunogenicity Population	The evaluable immunogenicity population was defined for Dose 3 and Dose 4 separately. The Dose 3 evaluable immunogenicity population was the primary analysis population for immunogenicity results from the blood collected at 1 month after Dose 3. The Dose 3 evaluable immunogenicity population included any subject: • Who was eligible for the study. • Who was randomly assigned to receive the vaccine. • Who was 42 to 98 days of age, inclusive, on the day of first vaccination. • Who received the vaccine to which he or she was randomly assigned at the first 3 doses. • Who had a valid and determinate immunoglobulin G (IgG) concentration for at least 1 serotype from 1 month after Dose 3 visit (Visit 4). • Whose blood collection was within 27 to 56 days, inclusive, after Dose 3. • Who received no prohibited vaccines before the	Immunogenicity

Analysis Population	Description	Analysis Set applies to following endpoints
	blood draw at 1 month after Dose 3. • Who had no other major protocol deviations as determined by the clinician or medical monitor.	
	The Dose 4 evaluable immunogenicity population was the primary analysis population for immunogenicity results before and after Dose 4. The Dose 4 evaluable immunogenicity population included any subject: • Who was eligible for the study. • Who was randomly assigned to receive the vaccine. • Who was 42 to 98 days of age, inclusive, on the day of first vaccination. • Who received the assigned vaccine, as randomized, within the defined window for Dose 4. • Who received the vaccine to which he or she was randomly assigned at all 4 doses. • Who had a valid and determinate immunoglobulin (IgG) concentration for at least 1 serotype after Dose 4. • Whose blood collection was within 27 to 56 days, inclusive, after Dose 4. • Who received no prohibited vaccines before the blood draw at 1 month after Dose 4. • Who had no other major protocol deviations as determined by the clinician or medical monitor. Immunogenicity results were summarized according to the randomized vaccine group in the analyses based on • evaluable immunogenicity populations.	
All-Available Immunogenicity Population	The all-available immunogenicity population was defined for Dose 3 and Dose 4 separately. The all-available Dose 3 immunogenicity population included all randomized subjects who had at least 1 valid and determinate IgG concentration at the 1 month after Dose 3 blood draw. The all-available Dose 4 immunogenicity population included all randomized subjects who had at least 1 valid and determinate IgG concentration at the 1 month after Dose 4 blood draw. Immunogenicity results were summarized according to the randomized vaccine group in the analyses based on all-available immunogenicity populations.	Immunogenicity

Analysis Population	Description	Analysis Set applies to following endpoints
	If there was less than a 5% difference in sample size between the all-available and the corresponding evaluable immunogenicity populations, the immunogenicity data would be analyzed based on the evaluable immunogenicity population only.	

Results

Recruitment/ Number analysed

A total of 460 participants were randomized across both vaccine groups (20vPnC; and 13vPnC) and 89.3% of participants completed the visit 1 month after Dose 3. The percentages of participants were similar in the 2 groups for all the categories in the disposition table. Of the 49 (10.7%) participants that were withdrawn from the study before the visit 1 month after Dose 3, the most common reason was withdrawal by parent/guardian (26 [5.7%] participants). One participant from each vaccine group (20vPnC and 13vPnC) was randomized but not vaccinated because the parents withdrew consent.

A total of 391 participants were vaccinated at Dose 4 and 82.8% of participants completed the visit 1 month after Dose 4. The percentages of participants were similar in the 2 groups for all the categories in the disposition table. Of the 10 (2.2%) participants that were withdrawn from the study after Dose 4 but before the visit 1 month after Dose 4, the most common reason for withdrawal was lost to follow-up (7 [1.5%] participants).

Baseline data

The study population consisted of racially diverse, male and female participants aged 44 to 95 days, with a mean age of 64.5 days at Dose 1. The demographic characteristics in the 2 groups were similar.

Table 3: Demographics characteristics – All subjects

	Vaccine Group (as Randomized)		
	20vPnC (N[a]=232) n[b] (%)	13vPnC (N[a]=228) n[b] (%)	Total (N[a]=460) n[b] (%)
Sex			
Male	120 (51.7)	113 (49.6)	233 (50.7)
Female	112 (48.3)	115 (50.4)	227 (49.3)
Race[c]			
White	161 (69.4)	171 (75.0)	332 (72.2)
Black or African American	35 (15.1)	29 (12.7)	64 (13.9)
Asian	9 (3.9)	5 (2.2)	14 (3.0)
American Indian or Alaskan native	4 (1.7)	3 (1.3)	7 (1.5)
Native Hawaiian or other Pacific Islander	1 (0.4)	3 (1.3)	4 (0.9)
Multiracial	22 (9.5)	15 (6.6)	37 (8.0)
Not reported	0	2 (0.9)	2 (0.4)
Ethnicity			
Hispanic/Latino	41 (17.7)	40 (17.5)	81 (17.6)
Non-Hispanic/non-Latino	191 (82.3)	188 (82.5)	379 (82.4)
Age at Dose 1 (days)[d]			
Mean (SD)	64.5 (8.07)	64.5 (6.68)	64.5 (7.40)
Median	64.0	64.0	64.0
Min, max	(44, 95)	(45, 89)	(44, 95)

a. N = number of subjects in the vaccine group or the total sample. These values are used as the denominators for the percentage calculations.
b. n = Number of subjects in the specified category.
c. Subjects whose race is not in the listed categories are included in the "Not reported" category.
d. For subjects randomized but not vaccinated, age is calculated using enrollment date instead of the date of first dose.

Efficacy/ immunogenicity results

Subjects Achieving a Prespecified Level of Pneumococcal IgG Concentrations

Percentages and numbers of participants achieving the prespecified serotype-specific IgG concentrations are shown in Table 4.

Table 4: Subjects Achieving a Prespecified Level of Pneumococcal IgG Concentrations – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

Serotype	Comparison Level	Vaccine Group (as Randomized) 20vPnC Na	20vPnC nb	20vPnC %	20vPnC (95% CIc)	13vPnC Na	13vPnC nb	13vPnC %	(95% CIc)
1	≥0.35 µg/mL	189	166	87.8	(82.3, 92.1)	187	164	87.7	(82.1, 92.0)
3	≥0.35 µg/mL	189	123	65.1	(57.8, 71.9)	187	141	75.4	(68.6, 81.4)
4	≥0.35 µg/mL	189	166	87.8	(82.3, 92.1)	187	171	91.4	(86.5, 95.0)
5	≥0.23 µg/mL	189	166	87.8	(82.3,	187	168	89.8	(84.6, 93.8)

Serotype	Comparison Level	Vaccine Group (as Randomized) 20vPnC 13vPnC Na	nb	%	(95% CIc)	Na	nb	%	(95% CIc)
					92.1)				
6A	≥0.35 µg/mL	189	177	93.7	(89.2, 96.7)	187	173	92.5	(87.8, 95.8)
6B	≥0.10 µg/mL	189	164	86.8	(81.1, 91.3)	187	169	90.4	(85.2, 94.2)
7F	≥0.35 µg/mL	189	187	98.9	(96.2, 99.9)	187	183	97.9	(94.6, 99.4)
9V	≥0.35 µg/mL	189	169	89.4	(84.1, 93.4)	187	167	89.3	(84.0, 93.3)
14	≥0.35 µg/mL	189	178	94.2	(89.8, 97.1)	187	179	95.7	(91.7, 98.1)
18C	≥0.35 µg/mL	189	175	92.6	(87.9, 95.9)	187	178	95.2	(91.1, 97.8)
19A	≥0.12 µg/mL	189	186	98.4	(95.4, 99.7)	187	183	97.9	(94.6, 99.4)
19F	≥0.35 µg/mL	189	186	98.4	(95.4, 99.7)	187	181	96.8	(93.1, 98.8)
23F	≥0.35 µg/mL	189	151	79.9	(73.5, 85.4)	187	153	81.8	(75.5, 87.1)
Additional									
8	≥0.35 µg/mL	189	188	99.5	(97.1, 100.0)	187	7	3.7	(1.5, 7.6)
10A	≥0.35 µg/mL	189	166	87.8	(82.3, 92.1)	187	2	1.1	(0.1, 3.8)
11A	≥0.35 µg/mL	189	184	97.4	(93.9, 99.1)	187	3	1.6	(0.3, 4.6)
12F	≥0.35 µg/mL	189	156	82.5	(76.4, 87.7)	187	1	0.5	(0.0, 2.9)
15B	≥0.35 µg/mL	189	187	98.9	(96.2, 99.9)	187	8	4.3	(1.9, 8.3)
22F	≥0.35 µg/mL	189	187	98.9	(96.2, 99.9)	187	2	1.1	(0.1, 3.8)
33F	≥0.35 µg/mL	189	174	92.1	(87.2, 95.5)	187	3	1.6	(0.3, 4.6)

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

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

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

c. Exact 2-sided CI calculated using the Clopper and Pearson method.

Pneumococcal IgG GMCs

The IgG GMCs and geometric mean fold rises (GMFR) are shown in Table 5. The IgG GMCs were generally similar in the 2 groups but numerically lower in the 20vPnC group compared to the 13vPnC group.

For the 13 serotypes common to both 20vPnC and 13vPnC, the geometric mean fold rises (GMFRs) demonstrate a boost in response at 1 month after Dose 4 when compared to both 1 month after Dose 3 (Table 5) and before Dose 4. The GMFRs were generally similar in the 20vPnC and 13vPnC groups, both from before 1 month after Dose 3 to 1 month after Dose 4 and from before Dose 4 to 1 month after Dose 4.

Table 5(1): Summary of Pneumococcal IgG GMFRs From 1 Month After Dose 3 to 1 Month After Dose 4 – Evaluable Immunogenicity Population

		Sampling Time[a]						
		1 Month After Dose 3			1 Month After Dose 4		Fold Rise (1 Month After Dose 4/1 Month After Dose 3)	
Serotypes	Vaccine Group (as Randomized)	n[b]	GMC[c]	(95% CI[c])	GMC[c]	(95% CI[c])	GMFR[c]	(95% CI[c])
13vPnC								
1	20vPnC	157	0.86	(0.75, 0.99)	2.66	(2.34, 3.03)	3.09	(2.67, 3.58)
	13vPnC	159	1.17	(1.01, 1.37)	3.64	(3.20, 4.14)	3.10	(2.73, 3.53)
3	20vPnC	157	0.40	(0.35, 0.45)	1.17	(0.98, 1.39)	2.95	(2.47, 3.51)
	13vPnC	159	0.56	(0.49, 0.65)	1.50	(1.28, 1.76)	2.67	(2.27, 3.13)
4	20vPnC	157	1.22	(1.02, 1.46)	7.19	(6.22, 8.30)	5.87	(4.86, 7.11)
	13vPnC	159	1.71	(1.43, 2.05)	9.30	(8.00, 10.81)	5.44	(4.64, 6.38)
5	20vPnC	157	0.85	(0.71, 1.03)	3.40	(2.95, 3.93)	3.98	(3.35, 4.73)
	13vPnC	159	1.19	(0.99, 1.44)	4.87	(4.20, 5.65)	4.09	(3.48, 4.80)
6A	20vPnC	157	2.09	(1.76, 2.48)	14.04	(12.38, 15.92)	6.72	(5.69, 7.95)
	13vPnC	159	2.65	(2.18, 3.22)	18.80	(16.30, 21.67)	7.10	(5.95, 8.46)
6B	20vPnC	157	0.59	(0.45, 0.77)	6.50	(5.53, 7.65)	11.04	(8.77, 13.89)
	13vPnC	159	1.07	(0.80, 1.42)	9.84	(8.17, 11.85)	9.22	(7.53, 11.29)
7F	20vPnC	157	2.07	(1.85, 2.32)	6.24	(5.60, 6.96)	3.01	(2.66, 3.42)
	13vPnC	159	2.67	(2.34, 3.06)	9.25	(8.17, 10.47)	3.46	(3.08, 3.89)
9V	20vPnC	157	1.12	(0.95, 1.32)	5.59	(4.88, 6.41)	4.98	(4.20, 5.91)
	13vPnC	159	1.51	(1.26, 1.80)	7.78	(6.73, 8.99)	5.16	(4.43, 6.01)
14	20vPnC	157	2.83	(2.39, 3.36)	8.98	(7.63, 10.56)	3.17	(2.58, 3.89)
	13vPnC	159	3.69	(3.08, 4.41)	11.26	(9.64, 13.16)	3.06	(2.53, 3.69)
18C	20vPnC	157	1.48	(1.27, 1.73)	5.69	(4.98, 6.51)	3.85	(3.26, 4.54)
	13vPnC	159	2.10	(1.77, 2.49)	8.37	(7.13, 9.82)	3.99	(3.50, 4.53)

Table 5(2): Summary of Pneumococcal IgG GMFRs From 1 Month After Dose 3 to 1 Month After Dose 4 – Evaluable Immunogenicity Population

		Sampling Time[a]						
		1 Month After Dose 3			1 Month After Dose 4		Fold Rise (1 Month After Dose 4/1 Month After Dose 3)	
Serotypes	Vaccine Group (as Randomized)	n[b]	GMC[c]	(95% CI[c])	GMC[c]	(95% CI[c])	GMFR[c]	(95% CI[c])
19A	20vPnC	157	0.78	(0.67, 0.90)	5.97	(5.12, 6.96)	7.67	(6.41, 9.18)
	13vPnC	159	1.06	(0.91, 1.23)	7.05	(6.00, 8.28)	6.65	(5.63, 7.87)
19F	20vPnC	157	1.81	(1.60, 2.05)	8.01	(6.90, 9.29)	4.43	(3.73, 5.25)
	13vPnC	159	2.25	(1.94, 2.63)	9.22	(7.89, 10.79)	4.09	(3.54, 4.73)
23F	20vPnC	157	0.84	(0.69, 1.04)	6.23	(5.26, 7.38)	7.38	(6.14, 8.87)
	13vPnC	159	1.32	(1.04, 1.66)	9.89	(8.12, 12.05)	7.52	(6.31, 8.95)
Additional								
8	20vPnC	157	2.02	(1.82, 2.25)	3.14	(2.79, 3.53)	1.55	(1.35, 1.78)
	13vPnC	159	0.04	(0.03, 0.04)	0.05	(0.04, 0.06)	1.29	(1.08, 1.55)
10A	20vPnC	157	1.55	(1.23, 1.97)	10.11	(8.70, 11.74)	6.50	(5.21, 8.12)
	13vPnC	159	0.03	(0.03, 0.03)	0.03	(0.03, 0.04)	1.11	(0.98, 1.26)
11A	20vPnC	157	1.82	(1.59, 2.09)	5.76	(4.99, 6.64)	3.16	(2.71, 3.67)
	13vPnC	159	0.01	(0.01, 0.01)	0.01	(0.01, 0.02)	1.34	(1.04, 1.73)
12F	20vPnC	157	0.79	(0.66, 0.95)	1.98	(1.73, 2.27)	2.51	(2.10, 3.01)
	13vPnC	159	0.02	(0.02, 0.02)	0.02	(0.02, 0.03)	1.22	(1.11, 1.36)
15B	20vPnC	157	5.38	(4.64, 6.22)	18.75	(16.60, 21.19)	3.49	(3.00, 4.05)
	13vPnC	159	0.04	(0.04, 0.05)	0.04	(0.04, 0.05)	1.12	(0.95, 1.31)
22F	20vPnC	157	4.35	(3.72, 5.09)	14.86	(12.70, 17.38)	3.42	(2.96, 3.95)
	13vPnC	159	0.01	(0.01, 0.01)	0.01	(0.01, 0.01)	1.12	(0.90, 1.39)
33F	20vPnC	157	2.08	(1.74, 2.50)	4.79	(4.27, 5.39)	2.30	(1.91, 2.77)
	13vPnC	159	0.05	(0.04, 0.05)	0.05	(0.04, 0.05)	0.97	(0.84, 1.13)

Abbreviations: GMC = geometric mean concentration; GMFR = geometric mean fold rise; IgG = immunoglobulin G; LLOQ = lower limit of quantitation.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ.
Note: Analysis population includes subjects from both the Dose 3 evaluable immunogenicity population and the Dose 4 evaluable immunogenicity population.
a. Protocol-specified timing for blood draw.
b. n = Number of subjects with valid and determinate assay results for the given serotype at both the specified time points.
c. GMCs, GMFRs, and the corresponding 2-sided CIs were calculated by back transforming the mean logarithm of the concentrations or fold rises and the corresponding CIs based on the Student t distribution.
PFIZER CONFIDENTIAL SDTM Creation: 21MAR2020 (21:30) Source Data: ADVA Output File: ./nda1/B7471003_CSR/adva_s002_gm_cfr_1md3_1md4_evl Date of Generation: 06APR2020 (11:21)

Serotype-specific opsonophagocytic activity (OPA) Titers

For the 13 serotypes common to both 20vPnC and 13vPnC, the OPA geometric mean fold rise (GMFRs) indicate a boosting of response at 1 month after Dose 4 when compared to both 1 month after Dose 3 (Table 6) and before Dose 4 .

Table 6(1): Summary of pneumococcal OPA GMFRs from 1 month after dose 3 to 1 month after dose 4 – Evaluable Immunogenicity Population

			Sampling Time[a]					
			1 Month After Dose 3		1 Month After Dose 4		Fold Rise (1 Month After Dose 4/1 Month After Dose 3)	
Serotypes	Vaccine Group (as Randomized)	n[b]	GMT[c]	(95% CI[c])	GMT[c]	(95% CI[c])	GMFR[c]	(95% CI[c])
13vPnC								
1	20vPnC	42	15.3	(11.7, 20.0)	55.5	(37.4, 82.5)	3.62	(2.54, 5.16)
	13vPnC	41	28.7	(20.5, 40.2)	97.3	(66.1, 143.0)	3.38	(2.55, 4.50)
3	20vPnC	38	48.4	(34.9, 67.3)	95.1	(71.4, 126.5)	1.96	(1.51, 2.54)
	13vPnC	46	62.6	(49.9, 78.5)	110.2	(92.2, 131.7)	1.76	(1.39, 2.22)
4	20vPnC	44	422.2	(278.1, 641.0)	468.8	(285.2, 770.4)	1.11	(0.70, 1.76)
	13vPnC	40	323.8	(177.6, 590.5)	795.4	(478.2, 1322.9)	2.46	(1.45, 4.17)
5	20vPnC	34	31.0	(22.6, 42.5)	77.7	(56.0, 107.7)	2.51	(1.86, 3.38)
	13vPnC	46	45.1	(34.6, 58.7)	108.2	(80.4, 145.7)	2.40	(1.89, 3.05)
6A	20vPnC	36	719.7	(468.1, 1106.7)	1778.4	(1202.8, 2629.7)	2.47	(1.77, 3.46)
	13vPnC	45	922.3	(714.7, 1190.1)	2053.7	(1600.0, 2636.2)	2.23	(1.69, 2.93)
6B	20vPnC	36	433.9	(254.5, 739.5)	1548.3	(1078.8, 2222.1)	3.57	(2.32, 5.48)
	13vPnC	45	769.3	(558.7, 1059.2)	1695.5	(1167.5, 2462.4)	2.20	(1.47, 3.30)
7F	20vPnC	42	1338.9	(1034.1, 1733.6)	2557.3	(2076.2, 3150.0)	1.91	(1.45, 2.51)
	13vPnC	44	1254.5	(941.7, 1671.3)	3199.9	(2424.5, 4223.2)	2.55	(1.93, 3.37)
9V	20vPnC	41	427.2	(284.1, 642.3)	1272.8	(940.5, 1722.4)	2.98	(2.03, 4.38)
	13vPnC	42	524.9	(329.3, 836.5)	1968.3	(1366.2, 2835.9)	3.75	(2.53, 5.56)
14	20vPnC	36	624.1	(407.6, 955.7)	1012.9	(755.3, 1358.2)	1.62	(1.14, 2.32)
	13vPnC	46	405.9	(262.2, 628.5)	1121.1	(800.1, 1570.9)	2.76	(1.72, 4.45)
18C	20vPnC	40	1127.9	(869.2, 1463.7)	2059.3	(1586.7, 2672.7)	1.83	(1.32, 2.52)
	13vPnC	39	1362.2	(947.8, 1957.7)	2937.7	(2030.7, 4249.9)	2.16	(1.52, 3.05)
19A	20vPnC	43	89.9	(59.5, 135.8)	655.2	(513.4, 836.1)	7.29	(5.11, 10.40)
	13vPnC	42	122.8	(81.9, 184.3)	883.3	(653.2, 1194.5)	7.19	(5.18, 9.98)
19F	20vPnC	38	93.4	(62.9, 138.9)	580.3	(375.7, 896.2)	6.21	(3.87, 9.96)
	13vPnC	45	129.7	(92.9, 181.2)	724.9	(514.8, 1020.6)	5.59	(4.06, 7.70)
23F	20vPnC	36	217.8	(139.5, 340.3)	770.8	(554.6, 1071.2)	3.54	(2.39, 5.24)
	13vPnC	39	218.4	(116.0, 411.2)	1347.1	(919.2, 1974.3)	6.17	(3.93, 9.69)

Immune Response to Concomitant Vaccines

Table 6(2): Summary of pneumococcal OPA GMFRs from 1 month after dose 3 to 1 month after dose 4 – Evaluable Immunogenicity Population

		Sampling Time[a]						
		1 Month After Dose 3			1 Month After Dose 4		Fold Rise (1 Month After Dose 4/1 Month After Dose 3)	
Serotypes	Vaccine Group (as Randomized)	n[b]	GMT[c]	(95% CI[c])	GMT[c]	(95% CI[c])	GMFR[c]	(95% CI[c])
Additional								
8	20vPnC	43	485.0	(346.1, 679.7)	1709.2	(1195.6, 2443.4)	3.52	(2.55, 4.86)
	13vPnC	43	16.5	(14.7, 18.6)	38.0	(23.6, 61.1)	2.30	(1.42, 3.72)
10A	20vPnC	50	1741.9	(1216.6, 2494.1)	2726.3	(2030.2, 3661.0)	1.57	(1.16, 2.12)
	13vPnC	42	38.2	(31.0, 47.1)	60.9	(40.5, 91.4)	1.59	(0.99, 2.56)
11A	20vPnC	48	540.9	(356.6, 820.7)	5563.7	(4087.4, 7573.2)	10.29	(6.72, 15.75)
12F	20vPnC	47	5463.9	(3947.9, 7561.9)	8372.3	(5764.5, 12160)	1.53	(0.93, 2.52)
	13vPnC	43	24.0	(24.0, 24.0)	28.2	(22.4, 35.6)	1.18	(0.93, 1.48)
15B	20vPnC	47	993.5	(605.0, 1631.7)	2855.2	(2029.5, 4016.8)	2.87	(1.73, 4.76)
	13vPnC	43	19.7	(16.4, 23.5)	30.4	(19.3, 47.8)	1.54	(0.94, 2.54)
22F	20vPnC	45	5830.5	(3874.2, 8774.6)	7922.2	(5172.7, 12133)	1.36	(0.82, 2.24)
	13vPnC	45	10.6	(8.3, 13.7)	16.3	(10.6, 25.2)	1.53	(0.91, 2.58)
33F	20vPnC	44	6966.5	(4471.3, 10854)	8293.8	(5433.1, 12661)	1.19	(0.65, 2.17)
	13vPnC	39	50.7	(32.0, 80.5)	130.9	(72.1, 237.8)	2.58	(1.24, 5.37)

Abbreviations: GMFR = geometric mean fold rise; GMT = geometric mean titer; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ.
Note: Analysis population includes subjects from both the Dose 3 evaluable immunogenicity population and the Dose 4 evaluable immunogenicity population.
Note: OPA titers were determined on serum from a randomly selected subset of subjects assuring equal representation of both vaccine series in each subset.
a. Protocol-specified timing for blood draw.
b. n = Number of subjects with valid and determinate assay results for the given serotype at both the specified time points.
c. GMTs, GMFRs, and the corresponding 2-sided CIs were calculated by back transforming the mean logarithm of the titers or fold rises and the corresponding CIs based on the Student t distribution.
PFIZER CONFIDENTIAL SDTM Creation: 21MAR2020 (21:30) Source Data: ADVA Output File: ./nda1/B7471003_CSR_OPA/adva_s002_gm_tfr_1md3_1md4_evl Date of Generation: 02JUN2020 (15:57)

Antibody concentrations to the diphtheria and pertussis vaccine antigens were determined on sera collected 1 month after Dose 3 from a randomly selected subset of participants with sufficient serum volumes.

Overall, ≥94.0% and ≥95.8% of the tested participants in the 20vPnC group and 13vPnC group, respectively, achieved the prespecified antibody concentrations for diphtheria and pertussis. The diphtheria and pertussis GMCs are similar in the vaccine groups (data not shown in this report).

Immunogenicity Conclusions

- 20vPnC induced robust pneumococcal immune responses to all 20 serotypes 1 month after Dose 3 as measured by both the percentages of participants with prespecified serotype-specific IgG concentrations and the IgG GMCs.
- After Dose 4, strong boosting responses were observed for all serotypes when compared the serotype-specific IgG concentrations from 1 month after Dose 4 to responses both 1 month after Dose 3 and before Dose 4.
- 20vPnC also elicited functional OPA responses to all 20 serotypes at 1 month afterDose 3 and 1 month after Dose 4 as measured by OPA GMTs. Evidence of boosting was observed for all serotypes similar to the IgG responses.
- Immune responses to concomitant vaccines as measured by percentages of participants with prespecified antibody concentrations and GMCs for diphtheria and pertussis were similar between vaccine groups.

Assessors comment: we agree with the MAH immunogenicity conclusions. No specific conclusions regarding Prevenar 13 can be drawn. The results are in agreement with previously presented results.

Safety results

Local reactions

Most local reactions were mild or moderate, and the proportions of participants reporting any local reaction in the 20vPnC group were generally similar to the 13vPnC group. The most frequent local reaction reported was pain at injection site. The frequency and severity of reported events was comparable with a slight tendency to decrease after subsequent doses (Table 7).

Table 7: Summary of Subjects Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose – Overall Safety Population.

		Vaccine Group (as Administered)					
		20vPnC			13vPnC		
Dose	Local Reaction	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
1	Redness[d]						
	Any	229	57 (24.9)	(19.4, 31.0)	224	57 (25.4)	(19.9, 31.7)
	Mild	229	51 (22.3)	(17.1, 28.2)	224	53 (23.7)	(18.3, 29.8)
	Moderate	229	6 (2.6)	(1.0, 5.6)	224	4 (1.8)	(0.5, 4.5)
	Severe	229	0	(0.0, 1.6)	224	0	(0.0, 1.6)
	Swelling[d]						
	Any	229	29 (12.7)	(8.6, 17.7)	224	32 (14.3)	(10.0, 19.6)
	Mild	229	23 (10.0)	(6.5, 14.7)	224	29 (12.9)	(8.8, 18.1)
	Moderate	229	5 (2.2)	(0.7, 5.0)	224	3 (1.3)	(0.3, 3.9)
	Severe	229	1 (0.4)	(0.0, 2.4)	224	0	(0.0, 1.6)
	Pain at injection site[e]						
	Any	229	117 (51.1)	(44.4, 57.7)	224	120 (53.6)	(46.8, 60.2)
	Mild	229	74 (32.3)	(26.3, 38.8)	224	80 (35.7)	(29.4, 42.4)
	Moderate	229	42 (18.3)	(13.5, 24.0)	224	40 (17.9)	(13.1, 23.5)
	Severe	229	1 (0.4)	(0.0, 2.4)	224	0	(0.0, 1.6)
	Any local reaction[f]	229	139 (60.7)	(54.0, 67.1)	224	140 (62.5)	(55.8, 68.9)
2	Redness[d]						
	Any	215	53 (24.7)	(19.0, 31.0)	204	58 (28.4)	(22.4, 35.2)
	Mild	215	47 (21.9)	(16.5, 28.0)	204	49 (24.0)	(18.3, 30.5)
	Moderate	215	6 (2.8)	(1.0, 6.0)	204	9 (4.4)	(2.0, 8.2)
	Severe	215	0	(0.0, 1.7)	204	0	(0.0, 1.8)
	Swelling[d]						

	Any	215	35 (16.3)	(11.6, 21.9)	204	38 (18.6)	(13.5, 24.7)
	Mild	215	27 (12.6)	(8.4, 17.7)	204	27 (13.2)	(8.9, 18.7)
	Moderate	215	8 (3.7)	(1.6, 7.2)	204	11 (5.4)	(2.7, 9.4)
	Severe	215	0	(0.0, 1.7)	204	0	(0.0, 1.8)
	Pain at injection site[e]						
	Any	215	92 (42.8)	(36.1, 49.7)	204	99 (48.5)	(41.5, 55.6)
	Mild	215	56 (26.0)	(20.3, 32.5)	204	59 (28.9)	(22.8, 35.7)
	Moderate	215	34 (15.8)	(11.2, 21.4)	204	40 (19.6)	(14.4, 25.7)
	Severe	215	2 (0.9)	(0.1, 3.3)	204	0	(0.0, 1.8)
	Any local reaction[f]	215	109 (50.7)	(43.8, 57.6)	204	121 (59.3)	(52.2, 66.1)
3	Redness[d]						
	Any	201	54 (26.9)	(20.9, 33.6)	204	54 (26.5)	(20.6, 33.1)
	Mild	201	53 (26.4)	(20.4, 33.0)	204	47 (23.0)	(17.4, 29.4)
	Moderate	201	1 (0.5)	(0.0, 2.7)	204	7 (3.4)	(1.4, 6.9)
	Severe	201	0	(0.0, 1.8)	204	0	(0.0, 1.8)
	Swelling[d]						
	Any	201	36 (17.9)	(12.9, 23.9)	204	40 (19.6)	(14.4, 25.7)
	Mild	201	34 (16.9)	(12.0, 22.8)	204	32 (15.7)	(11.0, 21.4)
	Moderate	201	2 (1.0)	(0.1, 3.5)	204	7 (3.4)	(1.4, 6.9)
	Severe	201	0	(0.0, 1.8)	204	1 (0.5)	(0.0, 2.7)
	Pain at injection site[e]						
	Any	201	89 (44.3)	(37.3, 51.4)	204	83 (40.7)	(33.9, 47.8)
	Mild	201	58 (28.9)	(22.7, 35.6)	204	57 (27.9)	(21.9, 34.6)
	Moderate	201	30 (14.9)	(10.3, 20.6)	204	26 (12.7)	(8.5, 18.1)
	Severe	201	1 (0.5)	(0.0, 2.7)	204	0	(0.0, 1.8)
	Any local reaction[f]	201	110 (54.7)	(47.6, 61.7)	204	104 (51.0)	(43.9, 58.0)
4	Redness[d]						
	Any	186	48 (25.8)	(19.7, 32.7)	185	56 (30.3)	(23.7, 37.4)
	Mild	186	45 (24.2)	(18.2, 31.0)	185	47 (25.4)	(19.3, 32.3)
	Moderate	186	3 (1.6)	(0.3, 4.6)	185	9 (4.9)	(2.2, 9.0)
	Severe	186	0	(0.0, 2.0)	185	0	(0.0, 2.0)
	Swelling[d]						
	Any	186	32 (17.2)	(12.1, 23.4)	185	26 (14.1)	(9.4, 19.9)
	Mild	186	28 (15.1)	(10.2, 21.0)	185	23 (12.4)	(8.0, 18.1)
	Moderate	186	4 (2.2)	(0.6, 5.4)	185	3 (1.6)	(0.3, 4.7)
	Severe	186	0	(0.0, 2.0)	185	0	(0.0, 2.0)
	Pain at injection site[e]						
	Any	186	66 (35.5)	(28.6, 42.8)	185	66 (35.7)	(28.8, 43.0)
	Mild	186	50 (26.9)	(20.7, 33.9)	185	53 (28.6)	(22.3, 35.7)
	Moderate	186	16 (8.6)	(5.0, 13.6)	185	13 (7.0)	(3.8, 11.7)
	Severe	186	0	(0.0, 2.0)	185	0	(0.0, 2.0)
	Any local reaction[f]	186	91 (48.9)	(41.5, 56.3)	185	88 (47.6)	(40.2, 55.0)

a. N = number of subjects with any e-diary data reported after the specified dose.
b. n = Number of subjects with the specified characteristic.
c. Exact 2-sided CI calculated using the Clopper and Pearson method.
d. Mild is >0.0 to 2.0 cm, moderate is >2.0 to 7.0 cm, severe is >7.0 cm.
e. Mild = hurts if gently touched (eg, whimpers, winces, protests, or withdraws); moderate = hurts if gently touched, with crying; severe = causes limitation of limb movement.
f. Any local reaction = any redness, any swelling, or any pain at the injection site within Day 1 to Day 7 after the specified dose.

Systemic events

Most events were mild or moderate and the percentage of participants reporting systemic events in the 20vPnC group was similar to the 13vPnC group. The most frequent systemic event reported was irritability. The pattern of reported events was comparable with a slight tendency to decrease after subsequent doses, and with the older age of the infant.

Table 8: Summary of Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose – Overall Safety Population

Dose	Systemic Event	Vaccine Group (as Administered) 20vPnC N[a]	20vPnC n[b] (%)	20vPnC (95% CI[c])	13vPnC N[a]	13vPnC n[b] (%)	13vPnC (95% CI[c])
1	Fever						
	≥38.0°C	229	33 (14.4)	(10.1, 19.6)	224	22 (9.8)	(6.3, 14.5)
	≥38.0°C to 38.4°C	229	23 (10.0)	(6.5, 14.7)	224	14 (6.3)	(3.5, 10.3)
	>38.4°C to 38.9°C	229	9 (3.9)	(1.8, 7.3)	224	5 (2.2)	(0.7, 5.1)
	>38.9°C to 40.0°C	229	1 (0.4)	(0.0, 2.4)	224	3 (1.3)	(0.3, 3.9)
	>40.0°C	229	0	(0.0, 1.6)	224	0	(0.0, 1.6)
	Decreased appetite (loss of appetite)[d]						
	Any	229	58 (25.3)	(19.8, 31.5)	224	68 (30.4)	(24.4, 36.8)
	Mild	229	37 (16.2)	(11.6, 21.6)	224	43 (19.2)	(14.3, 25.0)
	Moderate	229	21 (9.2)	(5.8, 13.7)	224	24 (10.7)	(7.0, 15.5)
	Severe	229	0	(0.0, 1.6)	224	1 (0.4)	(0.0, 2.5)
	Drowsiness (increased sleep)[e]						
	Any	229	156 (68.1)	(61.7, 74.1)	224	159 (71.0)	(64.6, 76.8)
	Mild	229	117 (51.1)	(44.4, 57.7)	224	123 (54.9)	(48.1, 61.5)
	Moderate	229	38 (16.6)	(12.0, 22.1)	224	32 (14.3)	(10.0, 19.6)
	Severe	229	1 (0.4)	(0.0, 2.4)	224	4 (1.8)	(0.5, 4.5)
	Irritability (fussiness)[f]						
	Any	229	182 (79.5)	(73.7, 84.5)	224	174 (77.7)	(71.7, 83.0)
	Mild	229	54 (23.6)	(18.2, 29.6)	224	58 (25.9)	(20.3, 32.1)
	Moderate	229	116 (50.7)	(44.0, 57.3)	224	106 (47.3)	(40.6, 54.1)
	Severe	229	12 (5.2)	(2.7, 9.0)	224	10 (4.5)	(2.2, 8.1)
	Any systemic event[g]	229	200 (87.3)	(82.3, 91.4)	224	204 (91.1)	(86.5, 94.5)
	Use of antipyretic/pain medication[h]	229	87 (38.0)	(31.7, 44.6)	224	99 (44.2)	(37.6, 51.0)
2	Fever						
	≥38.0°C	215	37 (17.2)	(12.4, 22.9)	204	47 (23.0)	(17.4, 29.4)
	≥38.0°C to 38.4°C	215	22 (10.2)	(6.5, 15.1)	204	26 (12.7)	(8.5, 18.1)
	>38.4°C to 38.9°C	215	9 (4.2)	(1.9, 7.8)	204	16 (7.8)	(4.5, 12.4)
	>38.9°C to 40.0°C	215	6 (2.8)	(1.0, 6.0)	204	5 (2.5)	(0.8, 5.6)
	>40.0°C	215	0	(0.0, 1.7)	204	0	(0.0, 1.8)
	Decreased appetite (loss of appetite)[d]						
	Any	215	50 (23.3)	(17.8, 29.5)	204	55 (27.0)	(21.0, 33.6)
	Mild	215	31 (14.4)	(10.0, 19.8)	204	30 (14.7)	(10.1, 20.3)
	Moderate	215	17 (7.9)	(4.7, 12.4)	204	24 (11.8)	(7.7, 17.0)
	Severe	215	2 (0.9)	(0.1, 3.3)	204	1 (0.5)	(0.0, 2.7)
	Drowsiness (increased sleep)[e]						
	Any	215	123 (57.2)	(50.3, 63.9)	204	115 (56.4)	(49.3, 63.3)
	Mild	215	80 (37.2)	(30.7, 44.0)	204	77 (37.7)	(31.1, 44.8)
	Moderate	215	38 (17.7)	(12.8, 23.4)	204	34 (16.7)	(11.8, 22.5)
	Severe	215	5 (2.3)	(0.8, 5.3)	204	4 (2.0)	(0.5, 4.9)
	Irritability (fussiness)[f]						
	Any	215	153 (71.2)	(64.6, 77.1)	204	163 (79.9)	(73.7, 85.2)
	Mild	215	43 (20.0)	(14.9, 26.0)	204	46 (22.5)	(17.0, 28.9)
	Moderate	215	105 (48.8)	(42.0, 55.7)	204	107 (52.5)	(45.4, 59.5)
	Severe	215	5 (2.3)	(0.8, 5.3)	204	10 (4.9)	(2.4, 8.8)
	Any systemic event[g]	215	175 (81.4)	(75.5, 86.4)	204	183 (89.7)	(84.7, 93.5)
	Use of antipyretic/pain medication[h]	215	85 (39.5)	(33.0, 46.4)	204	99 (48.5)	(41.5, 55.6)
3	Fever						
	≥38.0°C	201	36 (17.9)	(12.9, 23.9)	204	37 (18.1)	(13.1, 24.1)
	≥38.0°C to 38.4°C	201	20 (10.0)	(6.2, 14.9)	204	20 (9.8)	(6.1, 14.7)
	>38.4°C to 38.9°C	201	9 (4.5)	(2.1, 8.3)	204	10 (4.9)	(2.4, 8.8)
	>38.9°C to 40.0°C	201	7 (3.5)	(1.4, 7.0)	204	7 (3.4)	(1.4, 6.9)
	>40.0°C	201	0	(0.0, 1.8)	204	0	(0.0, 1.8)
	Decreased appetite (loss of appetite)[d]						
	Any	201	62 (30.8)	(24.5, 37.7)	204	68 (33.3)	(26.9, 40.3)
	Mild	201	42 (20.9)	(15.5, 27.2)	204	39 (19.1)	(14.0, 25.2)
	Moderate	201	19 (9.5)	(5.8, 14.4)	204	28 (13.7)	(9.3, 19.2)
	Severe	201	1 (0.5)	(0.0, 2.7)	204	1 (0.5)	(0.0, 2.7)
	Drowsiness (increased sleep)[e]						
	Any	201	83 (41.3)	(34.4, 48.4)	204	93 (45.6)	(38.6, 52.7)
	Mild	201	58 (28.9)	(22.7, 35.6)	204	61 (29.9)	(23.7, 36.7)
	Moderate	201	23 (11.4)	(7.4, 16.7)	204	32 (15.7)	(11.0, 21.4)
	Severe	201	2 (1.0)	(0.1, 3.5)	204	0	(0.0, 1.8)
	Irritability (fussiness)[f]						
	Any	201	146 (72.6)	(65.9, 78.7)	204	142 (69.6)	(62.8, 75.8)
	Mild	201	58 (28.9)	(22.7, 35.6)	204	56 (27.5)	(21.5, 34.1)
	Moderate	201	82 (40.8)	(33.9, 47.9)	204	77 (37.7)	(31.1, 44.8)
	Severe	201	6 (3.0)	(1.1, 6.4)	204	9 (4.4)	(2.0, 8.2)
	Any systemic event[g]	201	156 (77.6)	(71.2, 83.2)	204	166 (81.4)	(75.3, 86.5)
	Use of antipyretic/pain medication[h]	201	86 (42.8)	(35.8, 49.9)	204	96 (47.1)	(40.1, 54.2)

a. N = number of subjects with any e-diary data reported after the specified dose.
b. n = Number of subjects with the specified characteristic.
c. Exact 2-sided CI calculated using the Clopper and Pearson method.
d. Mild = decreased interest in eating; moderate = decreased oral intake; severe = refusal to feed.
e. Mild = increased or prolonged sleeping bouts; moderate = slightly subdued, interfering with daily activity; severe = disabling, not interested in usual daily activity.
f. Mild = easily consolable; moderate = requiring increased attention; severe = inconsolable, crying cannot be comforted.
g. Any systemic event = any fever ≥38.0°C, any decreased appetite (loss of appetite), any drowsiness (increased sleep), or any irritability (fussiness).
h. Severity was not collected for use of antipyretic or pain medication.
PFIZER CONFIDENTIAL SDTM Creation: 21MAR2020 (21:29) Source Data: ADFACEVD Output File: ./nda1/B7471003_CSR/adce_s020_se_maxsev_d13_saf Date of Generation: 17APR2020 (18:44)

Adverse Events

At least 1 AE was reported in 61.0% of participants in the 20vPnC group and 56.4% of participants in the 13vPnC group from Dose 1 to 1 month after Dose 3. AEs in the SOC of infections and infestations were reported most frequently and included upper respiratory tract infection (16.0% and 18.5% of participants in the 20vPnC and 13vPnC groups, respectively) and otitis media (9.1% and 7.5%). These events are common in infants and young children.

At least 1 AE was reported in 18.3% of participants in the 20vPnC group and 25.3% of participants in the 13vPnC group from Dose 4 to 1 month after Dose 4. As with the AEs from Dose 1 to 1 month after Dose 3, AEs in the SOC of infections and infestations were reported most frequently and included otitis media (3.0% and 3.1% of participants in the 20vPnC and 13vPnC groups, respectively) and upper respiratory tract infection (2.5% and 3.1%).

Overall during the study period, SAEs were reported by 12 (5.2%) participants in the 20vPnC group and 5 (2.2%) participants in the 13vPnC group. SAEs included hospitalizations for infections commonly seen in this age group. No SAEs reported were considered related to vaccine. There were no deaths during the study.

Safety conclusions

- Proportions of participants reporting local reactions and systemic events after vaccination with 20vPnC or 13vPnC were similar. Most were mild or moderate in severity and resolved within 1 to 3 days.
- Proportions of participants reporting any AE were similar in the 20vPnC and 13vPnC groups. Upper respiratory tract infection and otitis media were the most frequently reported AEs.
- Few participants reported AEs that were considered related to vaccination. The most frequently reported related AEs were in the SOC of general disorders and administration site conditions. Few severe AEs were reported. Immediate AEs were uncommon.
- None of the SAEs or NDCMCs reported during the study were considered related to vaccination. One participant was withdrawn from the study due to an unrelated SAE of failure to thrive and there were no deaths during the study.

Assessors comment: we agree with the MAH safety conclusions.

2.4. Discussion on clinical aspects

In the current study, a Phase 2, randomised, double-blind trial to evaluate the safety and immunogenicity of a multivalent pneumococcal conjugate vaccine in healthy infants, Prevenar 13 was used as comparator vaccine. There was no hypothesis testing, but the novel vaccine immunogenicity and safety were compared to the already licensed vaccines Prevenar 13 immunogenicity and safety. The study size and design were suitable for a Phase 2 vaccine study.

The administration of 20vPnC was well tolerated, and AEs reported in the study were consistent with medical events or conditions that are common in this age group. The 20vPnC safety profile was similar to 13vPnC, and there were no safety signals identified in this Phase 2 study. The data demonstrate that 20vPnC induces robust and functional immune responses for all 20 serotypes which were boosted after Dose 4. The GMTs were somewhat lower in 20vPnC serotypes common with 13vPc, but were still above the threshold of seroprotection. Safety and immunogenicity results from this study support further clinical development of 20vPnC for the paediatric population.

There data collected for Prevenar 13 in the current study did not provide any new information regarding immunogenicity, and no new safety signal was detected.

3. CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.