17 September 2020
EMA/523288/2020
Human Medicines Division

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/P46/062

Note

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

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Table of contents

1. Introduction

On 29th June 2020, 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 4, randomised, open-label trial to describe the safety, tolerability, and immunogenicity of 13-valent pneumococcal conjugate vaccine formulated in multidose vials when given with routine paediatric vaccines in healthy infants in India, protocol B4671004 is a stand-alone study.

The current EU-approved indications for the use of Prevenar 13 are:

- Active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by Streptococcus pneumoniae in infants, children and adolescents from 6 weeks to 17 years of age;
- Active immunisation for the prevention of invasive disease and pneumonia caused by Streptococcus pneumoniae in adults ≥ 18 years of age and the elderly

The 4 dose multidose vial (MDV) with a new formulation of Prevenar 13 containing the additional preservative 2-phenoxyethanol (2-PE) was submitted to the European Medicines Agency(EMA) as a grouped Type II variation (EMEA/H/C/001104/II/0130/G) on the 11 November 2015 and received a positive Committee for Medicinal Products for Human Use (CHMP) Opinion on the 01 April 2016.

2.2. Information on the pharmaceutical formulation used in the study

Suspension for Injection, 1 dose (0.5 mL) contains Streptococcus pneumoniae saccharides conjugated to diphtheria CRM197 protein:

Serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F ..... 2.2 µg

Serotype 6B .....4.4 µg

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. 13vPnC multidose vials (MDVs) will also contain 4 mg of 2-PE per 0.5-mL dose.

For this study, the investigational products are 13vPnC with 2-PE in multidose vials (MDVs) and 13vPnC without 2-PE in prefilled syringes (PFSs). Four (4) doses of 13vPnC (2.0 mL) will be contained within each MDV. For the purposes of this study, only a single 0.5-mL dose will be administered from each of the MDVs.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

A phase 4, randomised, open-label trial to describe the safety, tolerability, and immunogenicity of 13-valent pneumococcal conjugate vaccine formulated in multidose vials when given with routine paediatric vaccines in healthy infants in India, Protocol B4671004.

2.3.2. Clinical study

A Phase 4, Randomized, Open-Label Trial to Describe the Safety, Tolerability, and Immunogenicity of 13-valent Pneumococcal Conjugate Vaccine Formulated in Multidose Vials When Given with Routine Pediatric Vaccines in Healthy Infants in India, Protocol B4671004

Description

Diseases caused by Streptococcus pneumoniae are a public health problem affecting all age groups worldwide. Pneumonia, febrile bacteraemia, and meningitis are the most common manifestations of invasive pneumonia disease (IPD). Pneumococcal meningitis is a severe disease with high mortality and high incidence of neurologic sequelae. S pneumoniae also causes non-invasive pneumococcal disease, including otitis media, sinusitis, bronchitis, and nonbacteraemic pneumonia. Of the estimated 8.8 million global annual deaths among children <5 years of age in 2008, the WHO estimated that 476,000 (333,000 to 529,000) were caused by pneumococcal infections. Disease rates and mortality are higher in developing regions than in industrialized regions, with the majority of deaths occurring in Africa and Asia.

The preservative, 2-PE, added to 13vPnC in MDVs is a phenolic derivative used in vaccine production. It was studied at high concentrations in animal studies and did not result in adverse effects (AEs). Furthermore, a study published by Khandke *et al* demonstrated that 2-PE at 5.0 mg per dose in the Prevenar 13 multidose formulation met the antimicrobial effectiveness requirements of the European Pharmacopoeia. Currently, 2-PE is the preservative used in a number of commercially available vaccines, e.g., diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (Daptacel; Infanrix) and hepatitis A inactivated and hepatitis B (recombinant) vaccine (Twinrix). In the earlier open-label, randomized study (B4671001) in healthy infants in the Gambia, the 13vPnC MDV formulation with 2-PE as preservative demonstrated immunogenicity and safety profiles comparable to those of the approved formulation of 13vPnC without 2-PE (provided in PFSs).

Prevenar 13 and the MDV 13vPnC+2-PE formulation are licensed in India for active immunization for the prevention of disease caused by S pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (including sepsis, meningitis, bacteraemia, pneumonia, and acute otitis media) in infants and children from 6 weeks to 5 years of age. Prevenar 13 is also licensed in India for active immunization for the prevention of pneumonia and invasive disease caused by S pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in children of 6 years to 17 years of age and adults 50 years of age and older.

This clinical study report (CSR) describes the safety, tolerability, and immunogenicity of 13vPnC with 2-PE presented in MDVs in infants and toddlers in India. This study is defined as a post-authorisation safety study (PASS).

Methods

Objectives and endpoints

The primary objective of this study was to describe the safety profile of the13vPnC multidose vial (MDV) formulation. The secondary objective pertains to the evaluation of the immune responses induced by this formulation, which were assessed through IgG as well as opsonophagocytic assay (OPA), which is a biological assay designed to measure functional pneumococcal serotype-specific antibodies present in human serum.

Table 1 Objectives and Endpoints of the study

Type	Objective	Endpoint
Primary		

Safety	• To describe the safety profile of 13vPnC with 2-PE in the MDV group and without 2-PE in the PFS group.	• Incidence of local reactions and systemic events at the following time periods in the MDV group and in the PFS group:
		  • Within the 7 days after the first dose of the infant series.
		  • Within the 7 days after the second dose of the infant series.
		  • Within the 7 days after the third dose of the infant series.
		  • Within the 7 days after the toddler dose.
		• Incidence of AEs in the MDV group and in the PFS group from the first dose up to 1 month after the infant series.
		• Incidence of AEs in the MDV group and in the PFS group from the toddler dose up to 1 month after the toddler dose.
		• Incidence of SAEs in the MDV group and in the PFS group from the first dose up to 1 month after the toddler dose.
		• Incidence of NDCMCs* in the MDV group and in the PFS group from 1 month after the infant series up to the toddler dose.

Secondary		

Immunogenicity	• To describe the pneumococcal immune responses induced by 13vPnC with 2-PE in the MDV group and in the PFS group.	• The proportion of subjects with IgG concentrations equal to or above the defined threshold for each of the pneumococcal serotypes measured:
		  • 1 month after the infant series in the MDV group and in the PFS group.
		  • 1 month after the toddler dose in the MDV group and in the PFS group.
		• The serotype-specific IgG GMC for each of the pneumococcal serotypes measured:
		  • 1 month after the infant series in the MDV group and in the PFS group.
		  • 1 month after the toddler dose in the MDV group and in the PFS group.
		• The serotype-specific OPA GMT for each of the pneumococcal serotypes measured:
		  • 1 month after the infant series in the MDV group and in the PFS group.
		  • 1 month after the toddler dose in the MDV group and in the PFS group.
		• The proportion of subjects achieving a serotype-specific OPA titer ≥ the LLOQ for each of the pneumococcal serotypes measured:
		  • 1 month after the infant series in the MDV group and in the PFS group.
		  • 1 month after the toddler dose in the MDV group and in the PFS group.

Note: The defined thresholds for IgG are listed below:

- ≥0.35 μg/mL was used for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19F, and 23F.
- ≥0.23 μg/mL was used for serotype 5.
- ≥0.10 μg/mL was used for serotype 6B.
- ≥0.12 μg/mL was used for serotype 19A.

* NDCMC: No newly diagnosed chronical medical conditions

Study design

This was a randomised, multi-centre and open-label phase 4 study. The subjects were randomised in a 1:1 ratio to receive either 13vPnC with 2-PE from an MDV or 13vPnC without 2-PE in a PFS. Subjects were allocated to vaccine groups through the use of an interactive web-based response system.

Approximately 300 subjects (150 subjects per group) at 7 sites were randomized. The subjects were vaccinated in a 3-dose infant series at 6, 10, and 14 weeks of age followed by a toddler dose at 12 months of age. Subjects had 2 blood draws of up to 5 mL approximately 1 month after the infant series and approximately 1 month after the toddler dose. The approximate duration of the study was 20 months, assuming a 6-month recruitment period.

Study population /Sample size

Approximately 300 Indian boys and girls (150 subjects per group) who were vaccinated in a 3-dose infant series at 6, 10, and 14 weeks of age followed by a toddler dose at 12 months of age.

Treatments

At Visits 1, 2, 3, and 5, all subjects were administered 13vPnC (MDV or PFS) intramuscularly by injecting 0.5 mL into the left anterolateral thigh muscle. Concomitant vaccines were given in a different limb from that used to administer 13vPnC.

Outcomes/endpoints

As reflected in Table 1 above.

Safety evaluations

Local reactions (i.e., redness, swelling, and pain) at the 13vPnC injection site were monitored for the first 7 days (Days 1 to 7) following vaccination. Local reactions were measured in caliper units (range: 1 to 14) and recorded in the e-diary.

The e-diary was used also to record the presence of systemic events (i.e., loss of or decreased appetite, increased sleep, and irritability) daily for 7 days (Days 1 to 7) after each vaccination using the grading scale. A digital thermometer was given to the subject's parent(s)/legal guardian(s) with instructions on how to measure the child's axillary temperature at home. Axillary temperature was collected at evening bedtime daily for 7 days (Days 1 to 7) after each vaccination, and at any time during the 7 days if fever was suspected. The highest temperature for each day was recorded in the e-diary. Fever was defined as a temperature of ≥38.0°C. Temperature was recorded to 1 decimal place and then categorized according to the scale for fever.

AEs, including serious adverse effects (SAEs) were recorded on the AE page(s) of the case report form (CRF) from the time the subject/ parent(s)/ legal guardian(s) provided informed consent through and including Visit 6 (28 to 42 Days After Visit 5).

Immunogenicity Evaluations

Blood samples were obtained from all subjects 1 month after the infant series and 1 month after the toddler dose of 13vPnC. A high-throughput, multiplex direct Luminex-based immunoassay (dLIA) was performed on these samples to measure the concentration of antibodies elicited by the 13 pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F present in the vaccine.

Pfizer's 13-plex dLIA was validated using immunized human serum that contained IgG antibodies to the 13 serotypes in 13vPnC.

Serotype-specific OPA assays for the 13 pneumococcal serotypes were performed on blood samples taken from all subjects 1 month after the infant series and 1 month after the toddler dose of 13vPnC, where sufficient sera were available.

Statistical Methods

Evaluable Immunogenicity Population:

The evaluable immunogenicity population was defined for the 3-dose infant series and the toddler dose separately.

The infant evaluable immunogenicity population included all subjects who:

- met all eligibility criteria
- were aged 6 weeks (42 to 72 days, inclusive) at the time of the first vaccination
- had received 3 doses of vaccine that was randomly assigned to them
- had post–Dose 3 blood drawn within 27 to 49 days, inclusive, after the third vaccination
- had at least 1 valid and determinate post–Dose 3 assay result, and had no other major protocol violations

The toddler evaluable immunogenicity population included all subjects who:

- had received 3 doses in the infant series and 1 toddler dose of randomly assigned vaccine
- had post–Dose 4 blood drawn within 27 to 49 days, inclusive, after the fourth vaccination
- had at least 1 valid and determinate post–Dose 4 assay result, and had no other major protocol violations.

The infant and toddler evaluable immunogenicity populations were primary immunogenicity populations for the infant and toddler analyses.

All- Available Immunogenicity Populations:

The all-available immunogenicity population were defined for the 3-dose infant series and the toddler dose separately. The infant all-available immunogenicity population included all subjects who had at least 1 valid and determinate assay result after Dose 3. The toddler all-available immunogenicity population included all subjects who had at least 1valid and determinate assay result after Dose 4.

Safety Analysis Populations:

Separate safety populations were defined for the infant series and the toddler dose. Each safety population included all subjects who received at least 1dose of the investigational product for the indicated regimen.

Analysis of Demographic Characteristics:

The demographic characteristics that will be summarized using descriptive statistics include sex, ethnicity, and age at each vaccination.

Efficacy Analysis:

The proportions of subjects with IgG ≥the defined threshold was accompanied by 2-sided 95% confidence of intervals (CIs). The Clopper-Pearson method was used. GMCs were obtained by log transformation of concentrations, averaging the transformed values, then exponentiating the results. 95% confidence was obtained for CIs. The CIs were calculated in the log scale with reference to the appropriate t-distribution. Then the lower and upper limits were exponentiated. Empirical reverse cumulative distribution curves (RCDCs) were compiled for each serotype at each blood sampling time point. Two (2)-sided 95% CIs comparing the 2 vaccine groups were compiled in order to quantify the differences between the 2 vaccine groups. For the proportions of subjects with IgG ≥the defined threshold for each of the pneumococcal serotypes measured, the 2-sided 95% CI on MDV minus PFS were compiled. For the GMC, the 2-sided 95% CI on MDV minus PFS were compiled, using the log concentrations, as a 2-sample CI on the difference between means. The t-distribution was used. The lower and upper limits were exponentiated, so the results described the ratio of MDV to PFS. Assay results below the limit of quantification were set to the limit of detection before analysis. Missing data will not be replaced or imputed.

Safety Analysis:

Local injection site reactions, systemic events, and AEs were summarized by vaccine group and by vaccination.

The proportions of subjects with local reactions at the injection site and systemic events reported on any day within the 7-day period after each vaccination were estimated for each vaccine group. Local reactions were not compiled for concurrent vaccinations.

Local reactions and systemic events that persist beyond Day 7 were listed in the CSR. AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA). AEs within 1 month after vaccination were summarized by vaccine group for each vaccination separately. AEs were also summarized from the first dose up to 1 month after the infant series. SAEs were summarized from the first dose up to 1 month after the toddler dose. Newly diagnosed chronic medical conditions were summarized from 1 month after the infant series up to the toddler dose. All safety analyses were performed on the safety population. Subjects were assigned to the vaccine actually received.

Assessors comment: We endorse MAH study design and chosen methods.

Results

Recruitment/ Number analysed

A total of 301 participants were randomized with 151 participants in the MDV group and 150 participants in the PFS group. The majority of participants completed the blood draws after the third dose of the infant series (18 -week visit,285 [94.7%]) and after the toddler dose (13-month visit, 276 [91.7%]). The percentages of participants were similar in the 2 groups for all the categories in the disposition table. One participant in the MDV group was withdrawn prior to vaccination. Seven participants in the MDV group and 8 in the PFS group were withdrawn before the blood draw at the 18-week visit (Visit 4). In addition, 4 participants in the MDV group and 3 participants in the PFS group were withdrawn between the 18-week blood draw and the toddler dose (Vaccination 4, Visit 5). Reasons for withdrawal before Visit 5 included AEs (0 participants MDV; 2 participants PFS), lost to follow-up (2 participants MDV; 1 participant PFS), no longer meets eligibility criteria (1 participant MDV, 0 participants PFS), and withdrawal by parent/guardian (8 participants MDV; 8 participants PFS). During the toddler dose, 1 participant each was withdrawn from the MDV and PFS groups by the parent/guardian.

Baseline data

The demographical characteristics were well balanced between study arms.

Table 2 Demographics- infant Series Safety Population

	MDV N=150 n (%)	PFS N=150 n (%)	Total N=300 n (%)
Male	76 (50.7)	83 (55.3)	159 (53.0)
Female	74 (49.3)	67 (44.7)	141 (47.0)
Asian Race (100%)	150 (100.0)	150 (100.0)	300 (100.0)
Age at Vaccination 1 (weeks)			
N	150	150	300
Median	7.0	7.0	7.0
Mean (SD)	6.9 (0.95)	6.9 (0.99)	6.9 (0.97)
Min, max	6.0, 10.0	5.0, 10.0	5.0, 10.0
Age at Vaccination 2 (weeks)			
N	144	144	288
Median	11.0	11.0	11.0
Mean (SD)	11.3 (1.11)	11.4 (1.33)	11.3 (1.22)
Min, max	10.0, 15.0	10.0, 19.0	10.0, 19.0
Age at Vaccination 3 (weeks)			
N	144	141	285
Median	15.0	15.0	15.0
Mean (SD)	15.8 (1.43)	15.9 (1.56)	15.8 (1.49)
Min, max	14.0, 21.0	14.0, 24.0	14.0, 24.0

Table 3 Demographics- Toddler Dose Safety population

	MDV N=139 n (%)	PFS N=139 n (%)	Total N=278 n (%)
Male	73 (52.5)	75 (54.0)	148 (53.2)
Female	66 (47.5)	64 (46.0)	130 (46.8)
Asian Race, n (%)	139 (100.0)	139 (100.0)	278 (100.0)
Age at toddler dose (months)			
N	139	139	278
Median	12.2	12.3	12.3
Mean (SD)	12.4 (0.46)	12.4 (0.41)	12.4 (0.43)
Min, max	12.1, 15.9	11.9, 13.8	11.9, 15.9

Efficacy results

Serotype-Specific IgG GMCs and IgG Concentrations Equal to or Above the Defined Threshold: Results were generally comparable for the MDV and PFS groups. After the toddler dose, there was a clear boosting of immune response induced by 13vPnC and the percentage of subjects with serotype-specific IgG concentrations at or above the defined thresholds were very similar for the MDV and PFS groups.

Table 4 Number (%) of Subjects With Serotype-Specific IgG Concentrations (µg/mL) ≥ Defined Threshold 1 Month After the Infant Series – Infant Series Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)									
	MDV				PFS					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
1	136	124	91.2	(85.1, 95.4)	133	113	85.0	(77.7, 90.6)	6.2	(-1.6, 14.4)
3	136	125	91.9	(86.0, 95.9)	133	114	85.7	(78.6, 91.2)	6.2	(-1.6, 14.2)
4	136	124	91.2	(85.1, 95.4)	133	121	91.0	(84.8, 95.3)	0.2	(-7.0, 7.5)
5	136	115	84.6	(77.4, 90.2)	133	109	82.0	(74.4, 88.1)	2.6	(-6.6, 11.9)
6A	136	114	83.8	(76.5, 89.6)	133	95	71.4	(63.0, 78.9)	12.4	(1.7, 22.4)
6B	136	105	77.2	(69.2, 84.0)	133	100	75.2	(67.0, 82.3)	2.0	(-8.3, 12.4)
7F	136	131	96.3	(91.6, 98.8)	133	124	93.2	(87.5, 96.9)	3.1	(-2.5, 9.2)
9V	136	116	85.3	(78.2, 90.8)	133	111	83.5	(76.0, 89.3)	1.8	(-7.0, 10.8)
14	136	120	88.2	(81.6, 93.1)	133	110	82.7	(75.2, 88.7)	5.5	(-3.1, 14.3)
18C	136	126	92.6	(86.9, 96.4)	133	112	84.2	(76.9, 90.0)	8.4	(0.6, 16.5)
19A	136	136	100.0	(97.3, 100.0)	133	131	98.5	(94.7, 99.8)	1.5	(-1.4, 5.4)
19F	136	133	97.8	(93.7, 99.5)	133	127	95.5	(90.4, 98.3)	2.3	(-2.4, 7.6)
23F	136	115	84.6	(77.4, 90.2)	133	102	76.7	(68.6, 83.6)	7.9	(-1.7, 17.6)

Abbreviation: IgG = immunoglobulin G.
Note: The defined threshold for IgG for each serotype was set as follows: 0.35 µg/mL for serotypes 1, 3, 4, 6A, 7F, 9V, 14, 18C, 19F, and 23F; 0.23 µg/mL for serotype 5; 0.10 µg/mL for serotype 6B; and 0.12 µg/mL for serotype 19A.
a. N = number of subjects with a valid and determinate IgG concentration for the specified serotype. These values are the denominators for the percentage calculations.
b. n = Number of subjects with IgG concentration ≥ defined threshold for the given serotype.
c. Exact 2-sided CI, calculated using the Clopper and Pearson method.
d. Difference in proportions, MDV – PFS, expressed as a percentage.
e. Exact 2-sided CI (based on the Chan and Zhang method) for the difference in proportions, expressed as a percentage.
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Table 5 Number (%) of Subjects With Serotype-Specific IgG Concentrations (µg/mL) ⩾ Defined Threshold 1 Month After the Toddler Dose – Toddler Dose Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)									
	MDV				PFS					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
1	132	131	99.2	(95.9, 100.0)	129	129	100.0	(97.2, 100.0)	-0.8	(-4.3, 2.2)
3	132	128	97.0	(92.4, 99.2)	129	127	98.4	(94.5, 99.8)	-1.5	(-6.2, 3.0)
4	132	131	99.2	(95.9, 100.0)	129	129	100.0	(97.2, 100.0)	-0.8	(-4.3, 2.2)
5	132	131	99.2	(95.9, 100.0)	129	129	100.0	(97.2, 100.0)	-0.8	(-4.3, 2.2)
6A	132	127	96.2	(91.4, 98.8)	129	125	96.9	(92.3, 99.1)	-0.7	(-6.0, 4.5)
6B	132	130	98.5	(94.6, 99.8)	129	125	96.9	(92.3, 99.1)	1.6	(-2.7, 6.5)
7F	132	131	99.2	(95.9, 100.0)	129	128	99.2	(95.8, 100.0)	0.0	(-3.6, 3.8)
9V	132	130	98.5	(94.6, 99.8)	129	128	99.2	(95.8, 100.0)	-0.7	(-4.7, 3.0)
14	132	129	97.7	(93.5, 99.5)	129	124	96.1	(91.2, 98.7)	1.6	(-3.1, 6.8)
18C	132	128	97.0	(92.4, 99.2)	129	128	99.2	(95.8, 100.0)	-2.3	(-6.9, 1.6)
19A	132	131	99.2	(95.9, 100.0)	129	128	99.2	(95.8, 100.0)	0.0	(-3.6, 3.8)
19F	132	130	98.5	(94.6, 99.8)	129	129	100.0	(97.2, 100.0)	-1.5	(-5.4, 1.5)
23F	132	131	99.2	(95.9, 100.0)	129	125	96.9	(92.3, 99.1)	2.3	(-1.5, 7.1)

Serotype-Specific OPA GMTs and titers ≥ lower limit of quantitation (LLOQ): Results were generally comparable for the MDV and PFS groups. After the toddler dose, there was a clear boosting of immune response induced by 13vPnC and serotype-specific IgG GMTs were very similar for the MDV and PFS groups.

Table 6 Summary of Serotype-Specific OPA GMTs – Infant Series Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)									
		MDV				PFS				MDV/PFS	
Serotype	Sampling Time Point[a]	N[b]	n[c]	GMT[d]	(95% CI[e])	N[b]	n[c]	GMT[d]	(95% CI[e])	GMR[f]	(95% CI[g])
1	1 Month after the infant series	136	111	21.8	(18.1, 26.2)	133	106	22.5	(18.1, 27.9)	0.97	(0.73,1.28)
3	1 Month after the infant series	136	109	79.7	(68.8, 92.3)	133	107	72.8	(62.7, 84.6)	1.09	(0.89,1.35)
4	1 Month after the infant series	136	105	1158.8	(938.3, 1431.1)	133	101	1159.2	(948.3, 1417.0)	1.00	(0.75,1.34)
5	1 Month after the infant series	136	114	37.0	(31.4, 43.5)	133	107	40.9	(34.0, 49.3)	0.90	(0.71,1.15)
6A	1 Month after the infant series	136	113	1211.7	(896.4, 1638.0)	133	107	1321.9	(1026.7, 1701.9)	0.92	(0.62,1.36)
6B	1 Month after the infant series	136	109	1145.8	(870.4, 1508.3)	133	104	957.6	(708.2, 1294.8)	1.20	(0.80,1.79)
7F	1 Month after the infant series	136	96	1743.3	(1436.6, 2115.5)	133	93	1178.8	(952.6, 1458.6)	1.48	(1.11,1.97)
9V	1 Month after the infant series	136	103	643.9	(498.6, 831.7)	133	100	683.3	(522.6, 893.3)	0.94	(0.65,1.36)
14	1 Month after the infant series	136	111	496.9	(344.2, 717.3)	133	108	341.8	(236.0, 495.0)	1.45	(0.87,2.44)
18C	1 Month after the infant series	136	103	3055.8	(2378.5, 3926.0)	133	99	2183.9	(1686.9, 2827.3)	1.40	(0.98,2.00)
19A	1 Month after the infant series	136	101	219.3	(169.4, 283.9)	133	92	275.7	(212.0, 358.6)	0.80	(0.55,1.15)
19F	1 Month after the infant series	136	107	236.1	(191.6, 291.1)	133	105	272.7	(219.1, 339.4)	0.87	(0.64,1.17)
23F	1 Month after the infant series	136	99	1036.4	(746.9, 1438.0)	133	98	926.8	(673.9, 1274.7)	1.12	(0.71,1.76)

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.

Note: LLOQ for OPA titers for each serotype was set as follows: serotype 1, 18; serotype 3, 12; serotype 4, 21; serotype 5, 29; serotype 6A, 37; serotype 6B, 43; serotype 7F, 113; serotype 9V, 141; serotype 14, 35; serotype 18C, 31; serotype 19A, 18; serotype 19F, 48; and serotype 23F, 13.

a. Protocol-specified timing for blood sample collection.

b. N = number of subjects in the vaccine group with a blood sample collected at the specified sampling time point.

c. n = Number of subjects with valid and determinate assay results for the specified serotype at the given sampling time point.

d. GMTs were calculated as the mean of the logarithmically transformed titers and then transformed back to its original units from all subjects with available data for the specified blood sample collection. Assay results below the LLOQ were set to 0.5 × LLOQ for the analysis.

e. CIs were constructed by obtaining CIs for the mean of the logarithmically transformed titers using student's t distribution and transforming the confidence limits back to the original units.

f. GMRs were calculated as the mean of the difference (MDV – PFS) of the logarithmically transformed titers and then transformed back to its original units.

g. CIs were constructed by obtaining CIs for the mean of the differences (MDV – PFS) of the logarithmically transformed titers using student's t distribution and transforming the confidence limits back to the original units.

PFIZER CONFIDENTIAL SDTM Creation: 01APR2020 (03:39) Source Data: adva Output File: ./nda2_cdisc/B4671004_IMMUNO/adva_s001i_opa2 Date of Generation: 21APR2020 (22:28)

Table 7 Summary of Serotype-Specific OPA GMTs – Toddler Dose Evaluable Immunogenicity Population

		Vaccine Group (as Randomized)									
		MDV				PFS				MDV/PFS	
Serotype	Sampling Time Point[a]	N[b]	n[c]	GMT[d]	(95% CI[e])	N[b]	n[c]	GMT[d]	(95% CI[e])	GMR[f]	(95% CI[g])
1	1 Month after the toddler dose	132	105	204.2	(164.7, 253.3)	130	102	217.0	(176.4, 266.9)	0.94	(0.70,1.27)
3	1 Month after the toddler dose	132	106	121.0	(104.4, 140.3)	130	101	129.8	(111.7, 150.8)	0.93	(0.76,1.15)
4	1 Month after the toddler dose	132	102	2991.4	(2437.5, 3671.3)	130	99	2519.0	(2098.7, 3023.6)	1.19	(0.90,1.56)
5	1 Month after the toddler dose	132	105	157.6	(131.9, 188.3)	130	102	153.4	(126.6, 185.8)	1.03	(0.79,1.33)
6A	1 Month after the toddler dose	132	104	2945.7	(2376.0, 3652.1)	130	101	3092.5	(2493.5, 3835.4)	0.95	(0.70,1.29)
6B	1 Month after the toddler dose	132	101	1948.9	(1521.4, 2496.7)	130	101	1750.1	(1360.9, 2250.8)	1.11	(0.78,1.58)
7F	1 Month after the toddler dose	132	97	4161.5	(3498.0, 4950.9)	130	90	4353.8	(3706.5, 5114.0)	0.96	(0.75,1.21)
9V	1 Month after the toddler dose	132	100	6927.5	(5765.9, 8323.2)	130	98	6460.4	(5277.3, 7908.7)	1.07	(0.82,1.41)
14	1 Month after the toddler dose	132	106	1505.8	(1246.5, 1819.0)	130	101	1302.2	(1106.1, 1533.2)	1.16	(0.90,1.48)
18C	1 Month after the toddler dose	132	100	8028.3	(6233.7, 10339.7)	130	100	7830.0	(5998.5, 10220.7)	1.03	(0.71,1.48)
19A	1 Month after the toddler dose	132	97	1848.9	(1472.0, 2322.2)	130	96	1832.5	(1454.9, 2308.1)	1.01	(0.73,1.39)
19F	1 Month after the toddler dose	132	102	808.8	(633.0, 1033.5)	130	99	766.0	(609.2, 963.2)	1.06	(0.76,1.47)
23F	1 Month after the toddler dose	132	102	3125.0	(2450.8, 3984.7)	130	96	3348.8	(2639.5, 4248.5)	0.93	(0.67,1.31)

Table 8 Number (%) of Subjects With Serotype-Specific OPA Titers ⩾ LLOQ 1 Month After the Infant Series – Infant Series Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	MDV				PFS			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
1	111	57	51.4	(41.7, 61.0)	106	49	46.2	(36.5, 56.2)
3	109	107	98.2	(93.5, 99.8)	107	105	98.1	(93.4, 99.8)
4	105	103	98.1	(93.3, 99.8)	101	100	99.0	(94.6, 100.0)
5	114	71	62.3	(52.7, 71.2)	107	67	62.6	(52.7, 71.8)
6A	113	103	91.2	(84.3, 95.7)	107	101	94.4	(88.2, 97.9)
6B	109	103	94.5	(88.4, 98.0)	104	96	92.3	(85.4, 96.6)
7F	96	95	99.0	(94.3, 100.0)	93	90	96.8	(90.9, 99.3)
9V	103	91	88.3	(80.5, 93.8)	100	88	88.0	(80.0, 93.6)
14	111	92	82.9	(74.6, 89.4)	108	83	76.9	(67.8, 84.4)
18C	103	101	98.1	(93.2, 99.8)	99	97	98.0	(92.9, 99.8)
19A	101	93	92.1	(85.0, 96.5)	92	88	95.7	(89.2, 98.8)
19F	107	96	89.7	(82.3, 94.8)	105	96	91.4	(84.4, 96.0)
23F	99	94	94.9	(88.6, 98.3)	98	93	94.9	(88.5, 98.3)

Table 9 Number (%) of Subjects With Serotype-Specific OPA Titers ⩾ LLOQ 1 Month After the Toddler Dose – Toddler Dose Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	MDV				PFS			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
1	105	102	97.1	(91.9, 99.4)	102	99	97.1	(91.6, 99.4)
3	106	104	98.1	(93.4, 99.8)	101	101	100.0	(96.4, 100.0)
4	102	102	100.0	(96.4, 100.0)	99	99	100.0	(96.3, 100.0)
5	105	100	95.2	(89.2, 98.4)	102	99	97.1	(91.6, 99.4)
6A	104	104	100.0	(96.5, 100.0)	101	100	99.0	(94.6, 100.0)
6B	101	98	97.0	(91.6, 99.4)	101	96	95.0	(88.8, 98.4)
7F	97	97	100.0	(96.3, 100.0)	90	90	100.0	(96.0, 100.0)
9V	100	100	100.0	(96.4, 100.0)	98	97	99.0	(94.4, 100.0)
14	106	106	100.0	(96.6, 100.0)	101	101	100.0	(96.4, 100.0)
18C	100	99	99.0	(94.6, 100.0)	100	99	99.0	(94.6, 100.0)
19A	97	97	100.0	(96.3, 100.0)	96	95	99.0	(94.3, 100.0)
19F	102	98	96.1	(90.3, 98.9)	99	96	97.0	(91.4, 99.4)
23F	102	101	99.0	(94.7, 100.0)	96	95	99.0	(94.3, 100.0)

Immunogenicity conclusions

Results were generally comparable in the MDV and PFS groups for all immunogenicity endpoints as measured 1 month after the infant series of 13vPnC. Results were similar for the MDV and PFS groups as measured 1 month also after the toddler dose and, as expected, there was a clear boosting of the immune response induced by 13vPnC.

Assessor's comment: We endorse MAH conclusions. After the toddler dose close to 100 % of children responded with protective antibody levels for all serotypes regardless which vaccine vial type (multidose with 2-PE preservative or single shot vial without 2-PE) was used. This indicates that 2-PE do not affect immunogenicity of Prevenar 13.

Safety results

Local reactions

The proportions of subjects reporting local reactions were similar for the MDV and PFS groups. The most frequent local reaction reported was pain at injection site, and most local reactions were mild or moderate in severity. The median durations of redness, swelling, and pain at the injection site were ≤2 days following each dose of the infant series and 1 day following the toddler dose. Durations were similar for the MDV and PFS groups. Reported local reactions by day were similar for the MDV and PFS groups.

Table 10 Summary of Subjects Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Infant Series Vaccination - Infant Series Safety Population

		Vaccine Group (as Administered)					
		MDV			PFS		
Vaccination	Local Reaction	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
1	Redness[d]	147			148		
	Any		29 (19.7)	(13.6, 27.1)		25 (16.9)	(11.2, 23.9)
	Mild		26 (17.7)	(11.9, 24.8)		19 (12.8)	(7.9, 19.3)
	Moderate		3 (2.0)	(0.4, 5.8)		6 (4.1)	(1.5, 8.6)
	Severe		0	(0.0, 2.5)		0	(0.0, 2.5)
	Swelling[d]	147			148		
	Any		41 (27.9)	(20.8, 35.9)		50 (33.8)	(26.2, 42.0)
	Mild		32 (21.8)	(15.4, 29.3)		35 (23.6)	(17.1, 31.3)
	Moderate		9 (6.1)	(2.8, 11.3)		15 (10.1)	(5.8, 16.2)
	Severe		0	(0.0, 2.5)		0	(0.0, 2.5)
	Pain at the injection site[e]	147			148		
	Any		91 (61.9)	(53.5, 69.8)		100 (67.6)	(59.4, 75.0)
	Mild		42 (28.6)	(21.4, 36.6)		49 (33.1)	(25.6, 41.3)
	Moderate		45 (30.6)	(23.3, 38.7)		43 (29.1)	(21.9, 37.1)
	Severe		4 (2.7)	(0.7, 6.8)		8 (5.4)	(2.4, 10.4)
	Any local reaction[f]	147	99 (67.3)	(59.1, 74.8)	148	104 (70.3)	(62.2, 77.5)
2	Redness[d]	141			140		
	Any		24 (17.0)	(11.2, 24.3)		27 (19.3)	(13.1, 26.8)
	Mild		23 (16.3)	(10.6, 23.5)		25 (17.9)	(11.9, 25.2)
	Moderate		1 (0.7)	(0.0, 3.9)		2 (1.4)	(0.2, 5.1)
	Severe		0	(0.0, 2.6)		0	(0.0, 2.6)
	Swelling[d]	141			140		
	Any		35 (24.8)	(17.9, 32.8)		39 (27.9)	(20.6, 36.1)
	Mild		30 (21.3)	(14.8, 29.0)		32 (22.9)	(16.2, 30.7)
	Moderate		5 (3.5)	(1.2, 8.1)		7 (5.0)	(2.0, 10.0)
	Severe		0	(0.0, 2.6)		0	(0.0, 2.6)
	Pain at the injection site[e]	141			140		
	Any		84 (59.6)	(51.0, 67.7)		87 (62.1)	(53.6, 70.2)
	Mild		46 (32.6)	(25.0, 41.0)		41 (29.3)	(21.9, 37.6)
	Moderate		29 (20.6)	(14.2, 28.2)		37 (26.4)	(19.3, 34.5)
	Severe		9 (6.4)	(3.0, 11.8)		9 (6.4)	(3.0, 11.9)
	Any local reaction[f]	141	87 (61.7)	(53.1, 69.8)	140	92 (65.7)	(57.2, 73.5)
3	Redness[d]	139			140		
	Any		28 (20.1)	(13.8, 27.8)		32 (22.9)	(16.2, 30.7)
	Mild		28 (20.1)	(13.8, 27.8)		28 (20.0)	(13.7, 27.6)
	Moderate		0	(0.0, 2.6)		4 (2.9)	(0.8, 7.2)
	Severe		0	(0.0, 2.6)		0	(0.0, 2.6)
	Swelling[d]	139			140		
	Any		32 (23.0)	(16.3, 30.9)		38 (27.1)	(20.0, 35.3)
	Mild		29 (20.9)	(14.4, 28.6)		33 (23.6)	(16.8, 31.5)
	Moderate		3 (2.2)	(0.4, 6.2)		4 (2.9)	(0.8, 7.2)
	Severe		0	(0.0, 2.6)		1 (0.7)	(0.0, 3.9)
	Pain at the injection site[e]	139			140		
	Any		77 (55.4)	(46.7, 63.8)		76 (54.3)	(45.7, 62.7)
	Mild		42 (30.2)	(22.7, 38.6)		39 (27.9)	(20.6, 36.1)
	Moderate		32 (23.0)	(16.3, 30.9)		30 (21.4)	(14.9, 29.2)
	Severe		3 (2.2)	(0.4, 6.2)		7 (5.0)	(2.0, 10.0)

Any local reaction[f]	139	80 (57.6)	(48.9, 65.9)	140	81 (57.9)	(49.2, 66.1)

Abbreviation: e-diary = electronic diary.
Note: Reactions were collected in the e-diary from Day 1 to Day 7 after vaccination.
a. N = number of subjects reporting at least 1 yes or no response for the specified reaction after the specified vaccination. These values are the denominators for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
c. Exact 2-sided CI, calculated using the Clopper and Pearson method.
d. Mild: 0.5 to 2.0 cm; moderate: 2.5 to 7.0 cm; or severe: >7 cm.
e. Mild: hurts if gently touched (eg, whimpers, winces, protests, or withdraws); moderate: hurts if gently touched (with crying); or severe: causes limitation of limb movement.
f. Any local reaction = any redness, any swelling, or any pain at the injection site.
PFIZER CONFIDENTIAL SDTM Creation: 12FEB2020 (01:54) Source Data: adfacevd Output File: ./nda2_cdisc/B4671004/adce_s010i Date of Generation: 20FEB2020 (09:33)

Table 11 Summary of Subjects Reporting Local Reactions, by Maximum Severity, Within 7 Days After the Toddler Dose – Toddler Dose Safety Population

	Vaccine Group (as Administered)					
	MDV			PFS		
Local Reaction	**N[a]**	**n[b] (%)**	**(95% CI[c])**	**N[a]**	**n[b] (%)**	**(95% CI[c])**
Redness[d]	132			132		
Any		11 (8.3)	(4.2, 14.4)		15 (11.4)	(6.5, 18.0)
Mild		11 (8.3)	(4.2, 14.4)		14 (10.6)	(5.9, 17.2)
Moderate		0	(0.0, 2.8)		1 (0.8)	(0.0, 4.1)
Severe		0	(0.0, 2.8)		0	(0.0, 2.8)
Swelling[d]	132			132		
Any		12 (9.1)	(4.8, 15.3)		16 (12.1)	(7.1, 18.9)
Mild		9 (6.8)	(3.2, 12.5)		15 (11.4)	(6.5, 18.0)
Moderate		3 (2.3)	(0.5, 6.5)		1 (0.8)	(0.0, 4.1)
Severe		0	(0.0, 2.8)		0	(0.0, 2.8)
Pain at the injection site[e]	132			132		
Any		33 (25.0)	(17.9, 33.3)		26 (19.7)	(13.3, 27.5)
Mild		25 (18.9)	(12.6, 26.7)		18 (13.6)	(8.3, 20.7)
Moderate		8 (6.1)	(2.7, 11.6)		7 (5.3)	(2.2, 10.6)
Severe		0	(0.0, 2.8)		1 (0.8)	(0.0, 4.1)
Any local reaction[f]	132	40 (30.3)	(22.6, 38.9)	132	36 (27.3)	(19.9, 35.7)

Systemic events

The proportions of subjects reporting systemic events were similar for the MDV and PFS groups. For the infant series, the most frequent systemic events reported were increased sleep and irritability. For the toddler dose, the most frequent systemic event reported was irritability. Most systemic events were mild or moderate in severity for both the infant series and the toddler dose. The median durations of fever, decreased appetite, increased sleep, and irritability, were ≤2 days following each dose of the infant series and ≤3 days following the toddler dose. Durations were similar for the MDV and PFS groups.

Table 12 Summary of Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Infant Series Vaccination – Infant Series Safety Population

		Vaccine Group (as Administered)					
		MDV			PFS		
Vaccination	Systemic Event	N[a]	n[b] (%)	(95% CI[c])	N[a]	n[b] (%)	(95% CI[c])
1	Fever	147			148		
	≥38.0°C		22 (15.0)	(9.6, 21.8)		16 (10.8)	(6.3, 17.0)
	38.0°C to 38.4°C		16 (10.9)	(6.4, 17.1)		12 (8.1)	(4.3, 13.7)
	38.5°C to 38.9°C		2 (1.4)	(0.2, 4.8)		4 (2.7)	(0.7, 6.8)
	39.0°C to 40.0°C		2 (1.4)	(0.2, 4.8)		0	(0.0, 2.5)
	>40.0°C		2 (1.4)	(0.2, 4.8)		0	(0.0, 2.5)
	Decreased appetite[d]	147			148		
	Any		62 (42.2)	(34.1, 50.6)		79 (53.4)	(45.0, 61.6)
	Mild		35 (23.8)	(17.2, 31.5)		45 (30.4)	(23.1, 38.5)
	Moderate		26 (17.7)	(11.9, 24.8)		32 (21.6)	(15.3, 29.1)
	Severe		1 (0.7)	(0.0, 3.7)		2 (1.4)	(0.2, 4.8)
	Increased sleep[e]	147			148		
	Any		81 (55.1)	(46.7, 63.3)		98 (66.2)	(58.0, 73.8)
	Mild		43 (29.3)	(22.0, 37.3)		49 (33.1)	(25.6, 41.3)
	Moderate		37 (25.2)	(18.4, 33.0)		46 (31.1)	(23.7, 39.2)
	Severe		1 (0.7)	(0.0, 3.7)		3 (2.0)	(0.4, 5.8)
	Irritability[f]	147			148		
	Any		95 (64.6)	(56.3, 72.3)		97 (65.5)	(57.3, 73.2)
	Mild		55 (37.4)	(29.6, 45.8)		48 (32.4)	(25.0, 40.6)
	Moderate		32 (21.8)	(15.4, 29.3)		39 (26.4)	(19.5, 34.2)
	Severe		8 (5.4)	(2.4, 10.4)		10 (6.8)	(3.3, 12.1)
	Any systemic event[g]	147	122 (83.0)	(75.9, 88.7)	148	125 (84.5)	(77.6, 89.9)
2	Fever	141			140		
	≥38.0°C		12 (8.5)	(4.5, 14.4)		12 (8.6)	(4.5, 14.5)
	38.0°C to 38.4°C		9 (6.4)	(3.0, 11.8)		8 (5.7)	(2.5, 10.9)
	38.5°C to 38.9°C		3 (2.1)	(0.4, 6.1)		3 (2.1)	(0.4, 6.1)
	39.0°C to 40.0°C		0	(0.0, 2.6)		0	(0.0, 2.6)
	>40.0°C		0	(0.0, 2.6)		1 (0.7)	(0.0, 3.9)
	Decreased appetite[d]	141			140		
	Any		57 (40.4)	(32.3, 49.0)		54 (38.6)	(30.5, 47.2)
	Mild		38 (27.0)	(19.8, 35.1)		35 (25.0)	(18.1, 33.0)
	Moderate		17 (12.1)	(7.2, 18.6)		17 (12.1)	(7.2, 18.7)
	Severe		2 (1.4)	(0.2, 5.0)		2 (1.4)	(0.2, 5.1)
	Increased sleep[e]	141			140		
	Any		71 (50.4)	(41.8, 58.9)		73 (52.1)	(43.5, 60.7)
	Mild		33 (23.4)	(16.7, 31.3)		31 (22.1)	(15.6, 29.9)
	Moderate		36 (25.5)	(18.6, 33.6)		37 (26.4)	(19.3, 34.5)
	Severe		2 (1.4)	(0.2, 5.0)		5 (3.6)	(1.2, 8.1)
	Irritability[f]	141			140		
	Any		80 (56.7)	(48.1, 65.0)		84 (60.0)	(51.4, 68.2)
	Mild		41 (29.1)	(21.7, 37.3)		53 (37.9)	(29.8, 46.4)
	Moderate		35 (24.8)	(17.9, 32.8)		25 (17.9)	(11.9, 25.2)
	Severe		4 (2.8)	(0.8, 7.1)		6 (4.3)	(1.6, 9.1)
	Any systemic event[g]	141	108 (76.6)	(68.7, 83.3)	140	109 (77.9)	(70.1, 84.4)
3	Fever	139			140		
	≥38.0°C		10 (7.2)	(3.5, 12.8)		13 (9.3)	(5.0, 15.4)
	38.0°C to 38.4°C		6 (4.3)	(1.6, 9.2)		9 (6.4)	(3.0, 11.9)
	38.5°C to 38.9°C		3 (2.2)	(0.4, 6.2)		2 (1.4)	(0.2, 5.1)
	39.0°C to 40.0°C		0	(0.0, 2.6)		2 (1.4)	(0.2, 5.1)

Vaccination	Systemic Event	Vaccine Group (as Administered) MDV N[a]	MDV n[b] (%)	MDV (95% CI[c])	PFS N[a]	PFS n[b] (%)	PFS (95% CI[c])
	>40.0°C		1 (0.7)	(0.0, 3.9)		0	(0.0, 2.6)
	Decreased appetite[d]	139			140		
	Any		48 (34.5)	(26.7, 43.1)		51 (36.4)	(28.5, 45.0)
	Mild		28 (20.1)	(13.8, 27.8)		33 (23.6)	(16.8, 31.5)
	Moderate		16 (11.5)	(6.7, 18.0)		14 (10.0)	(5.6, 16.2)
	Severe		4 (2.9)	(0.8, 7.2)		4 (2.9)	(0.8, 7.2)
	Increased sleep[e]	139			140		
	Any		50 (36.0)	(28.0, 44.5)		55 (39.3)	(31.1, 47.9)
	Mild		29 (20.9)	(14.4, 28.6)		27 (19.3)	(13.1, 26.8)
	Moderate		19 (13.7)	(8.4, 20.5)		25 (17.9)	(11.9, 25.2)
	Severe		2 (1.4)	(0.2, 5.1)		3 (2.1)	(0.4, 6.1)
	Irritability[f]	139			140		
	Any		76 (54.7)	(46.0, 63.1)		84 (60.0)	(51.4, 68.2)
	Mild		44 (31.7)	(24.0, 40.1)		53 (37.9)	(29.8, 46.4)
	Moderate		27 (19.4)	(13.2, 27.0)		22 (15.7)	(10.1, 22.8)
	Severe		5 (3.6)	(1.2, 8.2)		9 (6.4)	(3.0, 11.9)
	Any systemic event[g]	139	91 (65.5)	(56.9, 73.3)	140	93 (66.4)	(58.0, 74.2)

Table 13 Summary of Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After the Toddler Dose – Toddler Dose Safety Population

Systemic Event	Vaccine Group (as Administered) MDV N[a]	MDV n[b] (%)	MDV (95% CI[c])	PFS N[a]	PFS n[b] (%)	PFS (95% CI[c])
Fever	132			132		
≥38.0°C		4 (3.0)	(0.8, 7.6)		6 (4.5)	(1.7, 9.6)
38.0°C to 38.4°C		2 (1.5)	(0.2, 5.4)		5 (3.8)	(1.2, 8.6)
38.5°C to 38.9°C		0	(0.0, 2.8)		0	(0.0, 2.8)
39.0°C to 40.0°C		0	(0.0, 2.8)		1 (0.8)	(0.0, 4.1)
>40.0°C		2 (1.5)	(0.2, 5.4)		0	(0.0, 2.8)
Decreased appetite[d]	132			132		
Any		20 (15.2)	(9.5, 22.4)		22 (16.7)	(10.7, 24.1)
Mild		14 (10.6)	(5.9, 17.2)		9 (6.8)	(3.2, 12.5)
Moderate		6 (4.5)	(1.7, 9.6)		13 (9.8)	(5.3, 16.3)
Severe		0	(0.0, 2.8)		0	(0.0, 2.8)
Increased sleep[e]	132			132		
Any		10 (7.6)	(3.7, 13.5)		25 (18.9)	(12.6, 26.7)
Mild		5 (3.8)	(1.2, 8.6)		17 (12.9)	(7.7, 19.8)
Moderate		5 (3.8)	(1.2, 8.6)		8 (6.1)	(2.7, 11.6)
Severe		0	(0.0, 2.8)		0	(0.0, 2.8)
Irritability[f]	132			132		
Any		32 (24.2)	(17.2, 32.5)		31 (23.5)	(16.5, 31.6)
Mild		21 (15.9)	(10.1, 23.3)		22 (16.7)	(10.7, 24.1)
Moderate		10 (7.6)	(3.7, 13.5)		7 (5.3)	(2.2, 10.6)
Severe		1 (0.8)	(0.0, 4.1)		2 (1.5)	(0.2, 5.4)
Any systemic event[g]	132	46 (34.8)	(26.8, 43.6)	132	44 (33.3)	(25.4, 42.1)

Adverse Events

The incidence of AEs, SAEs, and related AEs was similar in the MDV and PFS groups. The total incidence of any event was 71 (47.3%) in the MDV group and 74 (49.3%) in the PFS group from the first vaccination until 1 month after the infant series. The total incidence of any event was 11 (7.9%) in the MDV group and 12 (8.6%) in the PFS group from the toddler dose until 1month after the toddler dose. No newly diagnosed chronical medical conditions (NDCMCs) were reported in either group. The distribution of AEs by system organ class and preferred term was similar in the MDV and PFS groups from the first vaccination until 1 month after the infant series and from the toddler dose until 1 month after the toddler dose. During the infant series, the most frequently reported AE by preferred term was injection site pain in both groups (44 [29.3%] in the MDV and 46 [30.7%] in the PFS groups). These reactions were local in nature. Injection site swelling and upper respiratory tract infection were also frequently reported. After the toddler dose, the most frequently reported AE by preferred term was upper respiratory tract infection (5 [3.6%] in the MDV and 2 [1.4%] in the PFS groups).

Two subjects, both in the PFS group, had AEs that led to withdrawal from the study; urinary tract infection and vesicoureteric reflux was reported for 1 subject and seizure was reported for the other subject. One participant was withdrawn prior to vaccination due to an AE. None of the AEs leading to withdrawal were assessed as related to the investigational product by the investigator.

The incidence of SAEs was similar between the MDV and PFS groups. From the first vaccination until 1 month after the infant series, SAEs were reported by 5 (3.3%) participants in the MDV group and 4 (2.7%) participants in the PFS group. From 1 month after the infant series until the toddler dose, SAEs were reported by 6 (4.0%) participants in the MDV group and 3 (2.0%) participants in the PFS group. From the toddler dose until 1 month after the toddler dose, SAEs were reported by 1 (0.7%) participants in the MDV group and no participants in the PFS group. One SAE was considered related to the investigational product by the investigator, a Grade 1 seizure occurring on the day of Vaccination 1 for a participant in the PFS group.

Table 14 Summary of Adverse Events After Vaccination (All, Severe, Related, Serious, NDCMC, Leading to Withdrawal)

	MDV				PFS			
	Infant Series Interval[a] (N[c]=150)		Toddler Dose Interval[b] (N[c]=139)		Infant Series Interval[a] (N[c]=150)		Toddler Dose Interval[b] (N[c]=139)	
Adverse Event Type	n[d](%)	No. of Events[e]	n[d](%)	No. of Events[e]	n[d](%)	No. of Events[e]	n[d](%)	No. of Events[e]
Any event	71 (47.3)	154	11 (7.9)	16	74 (49.3)	167	12 (8.6)	15
Serious	5 (3.3)	5	1 (0.7)	2	4 (2.7)	6	0	0
Severe	4 (2.7)	4	1 (0.7)	2	1 (0.7)	2	0	0
Related	7 (4.7)	11	0	0	8 (5.3)	11	1 (0.7)	1
NDCMCs	0	0	0	0	0	0	0	0
AE leading to withdrawal	0	0	0	0	2 (1.3)	3	0	0

Abbreviation: NDCMC = newly diagnosed chronic medical condition.
Note: MedDRA (v22.1) coding dictionary applied.
a. Infant series interval is defined as the first vaccination to 1 month after third vaccination.
b. Toddler dose interval is defined as the fourth vaccination to 1 month after fourth vaccination.
c. N = number of subjects in the specified group. These values were used as the denominators for the percentage calculations.
d. n = Number of subjects reporting at least 1 occurrence of the specified adverse event type. For "any event", n = the number of subjects reporting at least 1 occurrence of any adverse event.
e. The total number of occurrences of the event specified. Subjects can be represented more than once. Event counts are the sum of individual occurrences within that category.
PFIZER CONFIDENTIAL SDTM Creation: 11FEB2020 (21:48) Source Data: adae Output File: ./nda2_cdisc/B4671004/adae_s015 Date of Generation: 17FEB2020 (06:04)

Table 15 Summary of Adverse Events Reported From First Vaccination Until 1Month After the Infant Series, by System Organ Class and Preferred Term – Infant Series Safety Population

	Vaccine Group (as Administered)					
	MDV (N[a]=150)			PFS (N[a]=150)		
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	No. of Events[d]	n[b] (%)	(95% CI[c])	No. of Events[d]
Any event	71 (47.3)	(39.1, 55.6)	154	74 (49.3)	(41.1, 57.6)	167
General disorders and administration site conditions	55 (36.7)	(29.0, 44.9)	95	52 (34.7)	(27.1, 42.9)	104
Injection site pain	44 (29.3)	(22.2, 37.3)	59	46 (30.7)	(23.4, 38.7)	71
Injection site swelling	17 (11.3)	(6.7, 17.5)	18	16 (10.7)	(6.2, 16.7)	16
Pyrexia	12 (8.0)	(4.2, 13.6)	14	7 (4.7)	(1.9, 9.4)	10
Injection site erythema	4 (2.7)	(0.7, 6.7)	4	7 (4.7)	(1.9, 9.4)	7
Infections and infestations	28 (18.7)	(12.8, 25.8)	32	23 (15.3)	(10.0, 22.1)	32
Upper respiratory tract infection	16 (10.7)	(6.2, 16.7)	16	10 (6.7)	(3.2, 11.9)	10
Bronchiolitis	5 (3.3)	(1.1, 7.6)	5	3 (2.0)	(0.4, 5.7)	3
Nasopharyngitis	3 (2.0)	(0.4, 5.7)	3	3 (2.0)	(0.4, 5.7)	3
Respiratory tract infection	3 (2.0)	(0.4, 5.7)	3	4 (2.7)	(0.7, 6.7)	7
Rhinitis	2 (1.3)	(0.2, 4.7)	2	2 (1.3)	(0.2, 4.7)	2
Bronchitis	1 (0.7)	(0.0, 3.7)	1	0	(0.0, 2.4)	0
Lower respiratory tract infection	1 (0.7)	(0.0, 3.7)	1	0	(0.0, 2.4)	0
Otitis externa	1 (0.7)	(0.0, 3.7)	1	1 (0.7)	(0.0, 3.7)	1
Cellulitis of male external genital organ	0	(0.0, 2.4)	0	1 (0.7)	(0.0, 3.7)	1
Hand-foot-and-mouth disease	0	(0.0, 2.4)	0	1 (0.7)	(0.0, 3.7)	1
Otitis media acute	0	(0.0, 2.4)	0	1 (0.7)	(0.0, 3.7)	1
Umbilical sepsis	0	(0.0, 2.4)	0	1 (0.7)	(0.0, 3.7)	1
Urinary tract infection	0	(0.0, 2.4)	0	2 (1.3)	(0.2, 4.7)	2
Gastrointestinal disorders	10 (6.7)	(3.2, 11.9)	10	6 (4.0)	(1.5, 8.5)	7
Diarrhoea	7 (4.7)	(1.9, 9.4)	7	5 (3.3)	(1.1, 7.6)	5
Abdominal pain	2 (1.3)	(0.2, 4.7)	2	0	(0.0, 2.4)	0
Constipation	1 (0.7)	(0.0, 3.7)	1	2 (1.3)	(0.2, 4.7)	2
Respiratory, thoracic and mediastinal disorders	4 (2.7)	(0.7, 6.7)	4	7 (4.7)	(1.9, 9.4)	7
Nasal congestion	2 (1.3)	(0.2, 4.7)	2	3 (2.0)	(0.4, 5.7)	3
Cough	1 (0.7)	(0.0, 3.7)	1	4 (2.7)	(0.7, 6.7)	4
Rhinorrhoea	1 (0.7)	(0.0, 3.7)	1	0	(0.0, 2.4)	0
Skin and subcutaneous tissue disorders	4 (2.7)	(0.7, 6.7)	4	5 (3.3)	(1.1, 7.6)	5
Dry skin	1 (0.7)	(0.0, 3.7)	1	0	(0.0, 2.4)	0

	Vaccine Group (as Administered)					
	MDV (N[a]=150)			PFS (N[a]=150)		
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	No. of Events[d]	n[b] (%)	(95% CI[c])	No. of Even
Eczema	1 (0.7)	(0.0, 3.7)	1	1 (0.7)	(0.0, 3.7)	1
Rash papular	1 (0.7)	(0.0, 3.7)	1	0	(0.0, 2.4)	0
Urticaria papular	1 (0.7)	(0.0, 3.7)	1	0	(0.0, 2.4)	0
Dermatitis diaper	0	(0.0, 2.4)	0	1 (0.7)	(0.0, 3.7)	1
Rash	0	(0.0, 2.4)	0	1 (0.7)	(0.0, 3.7)	1
Skin discolouration	0	(0.0, 2.4)	0	2 (1.3)	(0.2, 4.7)	2
Psychiatric disorders	3 (2.0)	(0.4, 5.7)	3	1 (0.7)	(0.0, 3.7)	1
Irritability	2 (1.3)	(0.2, 4.7)	2	1 (0.7)	(0.0, 3.7)	1
Breath holding	1 (0.7)	(0.0, 3.7)	1	0	(0.0, 2.4)	0
Nervous system disorders	2 (1.3)	(0.2, 4.7)	2	3 (2.0)	(0.4, 5.7)	3
Somnolence	2 (1.3)	(0.2, 4.7)	2	0	(0.0, 2.4)	0
Lethargy	0	(0.0, 2.4)	0	1 (0.7)	(0.0, 3.7)	1
Seizure	0	(0.0, 2.4)	0	2 (1.3)	(0.2, 4.7)	2
Congenital, familial and genetic disorders	1 (0.7)	(0.0, 3.7)	2	0	(0.0, 2.4)	0
Hydrocele	1 (0.7)	(0.0, 3.7)	1	0	(0.0, 2.4)	0
Phimosis	1 (0.7)	(0.0, 3.7)	1	0	(0.0, 2.4)	0
Ear and labyrinth disorders	1 (0.7)	(0.0, 3.7)	1	2 (1.3)	(0.2, 4.7)	2
Excessive cerumen production	1 (0.7)	(0.0, 3.7)	1	1 (0.7)	(0.0, 3.7)	1
Otorrhoea	0	(0.0, 2.4)	0	1 (0.7)	(0.0, 3.7)	1
Reproductive system and breast disorders	1 (0.7)	(0.0, 3.7)	1	1 (0.7)	(0.0, 3.7)	1
Female genital tract fistula	1 (0.7)	(0.0, 3.7)	1	0	(0.0, 2.4)	0
Balanoposthitis	0	(0.0, 2.4)	0	1 (0.7)	(0.0, 3.7)	1
Blood and lymphatic system disorders	0	(0.0, 2.4)	0	1 (0.7)	(0.0, 3.7)	1
Anaemia	0	(0.0, 2.4)	0	1 (0.7)	(0.0, 3.7)	1
Eye disorders	0	(0.0, 2.4)	0	2 (1.3)	(0.2, 4.7)	2
Dacryostenosis acquired	0	(0.0, 2.4)	0	1 (0.7)	(0.0, 3.7)	1
Lacrimation increased	0	(0.0, 2.4)	0	1 (0.7)	(0.0, 3.7)	1
Immune system disorders	0	(0.0, 2.4)	0	1 (0.7)	(0.0, 3.7)	1
Allergy to arthropod bite	0	(0.0, 2.4)	0	1 (0.7)	(0.0, 3.7)	1
Renal and urinary disorders	0	(0.0, 2.4)	0	1 (0.7)	(0.0, 3.7)	1
Vesicoureteric reflux	0	(0.0, 2.4)	0	1 (0.7)	(0.0, 3.7)	1

Table 16 Summary of Adverse Events Reported From Toddler Dose Until 1 Month After the Toddler Dose, by System Organ Class and Preferred Term –Toddler Dose Safety Population

	Vaccine Group (as Administered)					
	MDV (N[a]=139)			PFS (N[a]=139)		
System Organ Class Preferred Term	n[b] (%)	(95% CI[c])	No. of Events[d]	n[b] (%)	(95% CI[c])	No. of Events[d]
Any event	11 (7.9)	(4.0, 13.7)	16	12 (8.6)	(4.5, 14.6)	15
Infections and infestations	11 (7.9)	(4.0, 13.7)	13	6 (4.3)	(1.6, 9.2)	7
Upper respiratory tract infection	5 (3.6)	(1.2, 8.2)	5	2 (1.4)	(0.2, 5.1)	2
Gastroenteritis	2 (1.4)	(0.2, 5.1)	2	2 (1.4)	(0.2, 5.1)	2
Escherichia urinary tract infection	1 (0.7)	(0.0, 3.9)	1	0	(0.0, 2.6)	0
Impetigo	1 (0.7)	(0.0, 3.9)	1	0	(0.0, 2.6)	0
Nasopharyngitis	1 (0.7)	(0.0, 3.9)	1	1 (0.7)	(0.0, 3.9)	1
Otitis media acute	1 (0.7)	(0.0, 3.9)	1	1 (0.7)	(0.0, 3.9)	1
Respiratory tract infection	1 (0.7)	(0.0, 3.9)	1	1 (0.7)	(0.0, 3.9)	1
Viral infection	1 (0.7)	(0.0, 3.9)	1	0	(0.0, 2.6)	0
General disorders and administration site conditions	1 (0.7)	(0.0, 3.9)	1	2 (1.4)	(0.2, 5.1)	2
Pyrexia	1 (0.7)	(0.0, 3.9)	1	1 (0.7)	(0.0, 3.9)	1
Xerosis	0	(0.0, 2.6)	0	1 (0.7)	(0.0, 3.9)	1
Nervous system disorders	1 (0.7)	(0.0, 3.9)	1	0	(0.0, 2.6)	0
Febrile convulsion	1 (0.7)	(0.0, 3.9)	1	0	(0.0, 2.6)	0
Skin and subcutaneous tissue disorders	1 (0.7)	(0.0, 3.9)	1	1 (0.7)	(0.0, 3.9)	1
Rash	1 (0.7)	(0.0, 3.9)	1	0	(0.0, 2.6)	0
Rash maculo-papular	0	(0.0, 2.6)	0	1 (0.7)	(0.0, 3.9)	1
Blood and lymphatic system disorders	0	(0.0, 2.6)	0	1 (0.7)	(0.0, 3.9)	1
Deficiency anaemia	0	(0.0, 2.6)	0	1 (0.7)	(0.0, 3.9)	1
Gastrointestinal disorders	0	(0.0, 2.6)	0	2 (1.4)	(0.2, 5.1)	2
Diarrhoea	0	(0.0, 2.6)	0	2 (1.4)	(0.2, 5.1)	2
Injury, poisoning and procedural complications	0	(0.0, 2.6)	0	1 (0.7)	(0.0, 3.9)	1
Anal injury	0	(0.0, 2.6)	0	1 (0.7)	(0.0, 3.9)	1
Respiratory, thoracic and mediastinal disorders	0	(0.0, 2.6)	0	1 (0.7)	(0.0, 3.9)	1
Wheezing	0	(0.0, 2.6)	0	1 (0.7)	(0.0, 3.9)	1

Safety conclusions

The proportions of participants reporting local reactions and systemic events within 7 days after vaccination were similar for the MDV and PFS groups. Most were mild or moderate in severity.

The proportions of participants reporting AEs were similar for the MDV and PFS groups. During the infant series, injection site pain, injection site swelling, and upper respiratory tract infection were the most frequently reported AEs. After the toddler dose, the most frequently reported AE was upper respiratory tract infection.

There were no deaths or NDCMCs reported during the study. Of the SAEs reported during the study period (14 in MDV group and 9 in PFS group), only 1 SAE was considered related to the investigational product by the investigator (seizure, PFS group). Two participants in the PFS group were withdrawn from the study for AEs assessed as unrelated to the investigational product (seizure, urinary tract infection and vesicoureteric reflux). One participant in the MDV group was withdrawn prior to vaccination due to an AE.

Assessors comment: We endorse MAH conclusions. Addition of 2-PE to the vaccine did not affect the safety of Prevenar 13.

2.3.3. Discussion on clinical aspects

Present study confirmed immunogenicity and safety of Prevenar 13 MDV formulation among Indian infants and toddlers at age 6 weeks-12 month. Immunogenicity of 13vPnC was comparable for the MDV and PFS groups as measured 1 month after the infant series and 1 month after the toddler dose. The immunogenicity results are in agreement with previously reported studies.

The administration of 13vPnC in both MDV and PFS was well tolerated. The safety profile of 13vPnC in a MDV was similar to a PFS and consistent with prior studies. The study population was small (N= 300) and therefore the chance to detect rare AEs and SAEs is low. No new efficacy or safety concern is raised from this study.

3. CHMP overall conclusion and recommendation

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

☒ **Fulfilled:**

No regulatory action required.