21 May 2015
EMA/393028/2015
Procedure Management and Committees Support 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/P46/058

Note

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

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Administrative information

Invented name of the medicinal product:	Prevenar 13
INN (or common name) of the active substance(s):	pneumococcal polysaccharide type 4, pneumococcal polysaccharide type 23F, pneumococcal polysaccharide type 7F, pneumococcal polysaccharide type 6A, pneumococcal polysaccharide type 5, pneumococcal polysaccharide type 9V, pneumococcal polysaccharide type 1, pneumococcal polysaccharide type 18C, pneumococcal polysaccharide type 19F, pneumococcal polysaccharide type 3, pneumococcal polysaccharide type 14, pneumococcal polysaccharide type 19A, pneumococcal polysaccharide type 6B
MAH:	Pfizer Limited
Currently approved Indication(s)	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 use of Prevenar 13 should be determined on the basis of official recommendations taking into consideration the risk of invasive disease and pneumonia in different age groups, underlying comorbidities as well as the variability of serotype epidemiology in different geographical areas.
Pharmaco-therapeutic group (ATC Code):	J07AL02
Pharmaceutical form(s) and strength(s):	Suspension for injection

1. Introduction

On February 23, 2015, 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 study B4671001 "A Phase 3, Randomized, Open-Label Trial to Evaluate the Safety, Tolerability, and Immunogenicity of 13-valent Pneumococcal Conjugate Vaccine Formulated in Multidose Vials Given With Routine Pediatric Vaccinations in Healthy Infants is part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

The study compared a new formulation of 13-valent pneumococcal conjugate vaccine containing the preservative 2-phenoxyethanol, presented in multidose vials, with the currently available formulation.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- study B4671001 "A Phase 3, Randomized, Open-Label Trial to Evaluate the Safety, Tolerability, and Immunogenicity of 13-valent Pneumococcal Conjugate Vaccine Formulated in Multidose Vials Given With Routine Pediatric Vaccinations in Healthy Infants

2.3.2. Clinical study

Study B4671001 "A Phase 3, Randomized, Open-Label Trial to Evaluate the Safety, Tolerability, and Immunogenicity of 13-valent Pneumococcal Conjugate Vaccine Formulated in Multidose Vials Given With Routine Pediatric Vaccinations in Healthy Infants

Description

Methods

Objectives

Primary Objective:

The primary objective of this study was to demonstrate that the immune response induced by 13-valent pneumococcal conjugate vaccine (13vPnC) with 2-phenoxyethanol (2-PE) was noninferior to the immune response induced by 13vPnC without 2-PE as measured by serotype-specific immunoglobulin G (IgG) concentrations 1 month after the infant series.

Primary Safety Objective:

The primary safety objective of the study was to evaluate the safety profile of 13vPnC with 2-PE as measured by the incidence rates of local reactions, systemic events, and adverse events (AEs).

Secondary Objective:

The secondary objective of this study was to assess the immune response induced by 13vPnC with 2-PE relative to the immune response induced by 13vPnC without 2-PE as measured by serotype-specific opsonophagocytic activity (OPA).

Study design

B4671001 was a randomized open-label Phase 3 study conducted at a single site in The Gambia to compare the safety, tolerability, and immunogenicity of 13vPnC with 2-PE presented in a multidose (4 doses) vial (13vPnC MDV) to that of 13vPnC without 2-PE presented in a prefilled single dose syringe (13vPnC SDS) when given concomitantly with routine paediatric vaccinations given as part of routine care in healthy infants at approximately 8, 12, and 16 weeks of age (Visits 1, 2, and 3, respectively) (Table 1). Approximately 500 subjects aged approximately 8 weeks at enrolment were randomized in a 1:1 ratio to 1 of the 2 vaccine groups (13vPnC with 2-PE or 13vPnC without 2-PE); The approximate duration of subjects participation in the study 4 months; the total duration of the study was approximately 9 months.

Table 1. Study Design

Visit No.	**1**	**2**	**3**	**4**
Approximate age	8 weeks	12 weeks	16 weeks	20 weeks
Vaccination	13vPnC (MDV or SDS)	13vPnC (MDV or SDS)	13vPnC (MDV or SDS)	
Blood draw				Up to 5 mL

Abbreviations: MDV = multidose vial; SDS = single-dose syringe.

Study population /Sample size

Inclusion Criteria: Subjects were eligible to participate in the study if they met all of the following inclusion criteria:

1. Evidence of a personally signed and dated informed consent document (ICD) indicating that the subject's parent(s)/legal guardian(s) had been informed of all pertinent aspects of the study. If the subject's parent(s)/legal guardian(s) was illiterate they must have added a thumbprint to the ICD and it must have been signed and dated by an impartial witness who was present throughout the entire informed consent process.
2. Aged 42 to 70 days at time of enrollment.
3. Available for entire study period.

4. Healthy infant as determined by medical history, physical examination, and judgment of the investigator.
5. Parent(s)/legal guardian(s) was willing and able to comply with scheduled visits and other study procedures.
6. Weight of 3.5 kg or greater at the time of enrollment.

Exclusion Criteria: Subjects were ineligible to participate in this study if they met any of the following exclusion criteria:

1. Previous vaccination with licensed or investigational pneumococcal vaccine.
2. A previous anaphylactic reaction to any vaccine or vaccine-related component.
3. Contraindication to vaccination with pneumococcal conjugate vaccine.
4. Bleeding diathesis or condition associated with prolonged bleeding time that would have contraindicated intramuscular injection.
5. Known or suspected immune deficiency or suppression.
6. History of culture-proven invasive disease caused by *Streptococcus pneumoniae*.
7. Major known congenital malformation or serious chronic disorder.
8. Significant neurological disorder or history of seizure including febrile seizure, or significant stable or evolving disorders such as cerebral palsy, encephalopathy, hydrocephalus, or other significant disorders. Did not include resolving syndromes due to birth trauma, such as Erb's palsy.
9. Receipt of blood products or gamma-globulin since birth and until the blood draw approximately 1 month after the last dose of 13vPnC.
10. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, made the subject inappropriate for entry into this study.
11. Participation in other studies within 28 days before the current study began and/or during study participation. Participation in observational studies, and interventional studies such as those where a nasopharyngeal swab or urine sample may have been collected, were permitted.
12. Subjects who were direct descendants (child or grandchild) of investigational site staff members or Pfizer employees directly involved in the conduct of the trial.

Treatments

Subjects received 1 dose (0.5 mL) of either 13vPnC with 2-PE or 13vPnC without 2-PE according to their randomization assignment, at approximately 8, 12, and 16 weeks of age (Visits 1, 2, and 3, respectively) (Table 1). Each dose of vaccine was administered intramuscularly into the anterolateral thigh muscle of the left leg.

Per local practice, routine pediatric vaccines required by local recommendations were to be administered concomitantly with 13vPnC but were given in a different limb (as applicable) at Visits 1, 2, and 3.

Outcomes/endpoints

Immunogenicity Evaluations: One (1) blood sample of approximately 5 mL was collected post–infant series at Visit 4 (approximately 1 month after the third dose of 13vPnC) from each subject for the assessment of pneumococcal immune responses. Immune response as measured by serotype-specific IgG geometric mean concentrations (GMCs) for the 13 pneumococcal serotypes was determined for each available blood sample by enzyme-linked immunosorbent assay (ELISA). In addition, immune response as measured by OPA geometric mean titers (GMTs) for the 13 pneumococcal serotypes was determined for each available blood sample in a subset of predefined subjects from both vaccine groups.

Safety Evaluations:

On Day 2 to Day 6 after each vaccination, the reactogenicity events (local reactions and systemic events) were recorded in electronic diaries (e-diaries). Local reactions included redness, swelling, and tenderness at the injection site. Systemic events included fever (temperature ≥38.0°C), loss of appetite or decreased appetite, drowsiness (synonymous with increased sleep), and irritability (fussiness) (synonymous with restless sleep; decreased sleep). In addition, the use of antipyretic medication was recorded daily for 5 days in the e-diary after each vaccination.

Field workers were required to record the outcomes of these assessments in the e-diary each day, on Days 2 to 6 following vaccination. For events persisting at Day 6 and use of antipyretic medication continuing at Day 6, the field worker continued to visit the subject daily and completed the e-diary until resolution.

AEs were recorded on the case report form (CRF) from the signing of the ICD to Visit 4 (postvaccination blood draw). Withdrawal due to an AE was distinguished from withdrawal due to insufficient response and was recorded on the appropriate AE CRF page. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative began from the time that the subject's parent(s)/legal guardian(s) provided informed consent, which was obtained prior to the subject's participation in the study, through and including Visit 4 but no less than 28 days after the last administration of the investigational product.

SAEs experienced by a subject after the active reporting period had ended were reported to the sponsor if the investigator became aware of them; at a minimum, all SAEs that the investigator believed had at least a reasonable possibility of being related to investigational product were reported to the sponsor.

AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA). The relationship between AEs and the actual study vaccine received was characterized as related or not related.

Assessor's comment: Reactogenicity was assessed on Day 2-6, and vaccinations were given on Day 1. Thus reactions occurring only on the day of vaccination, and resolving before Day 2 were not recorded. Considering that these reactions are likely to be very mild, they are of less importance. Each child was also observed for 30 minutes after each vaccination.

Statistical Methods

Immunogenicity:

For each of the pneumococcal serotypes for each vaccine group, the primary endpoint was the proportion of subjects achieving a serotype-specific IgG concentration ≥0.35 µg/mL 1 month after the infant series and the coprimary endpoint was the serotype specific IgG GMC 1 month after the infant series. For primary endpoint, noninferiority for a serotype (MDV relative to SDS) was achieved if the lower limit of the 97.5% confidence interval (CI) of difference in proportions (MDV – SDS) was greater than -10%. For the coprimary endpoint (IgG GMC), noninferiority for a serotype (MDV relative to SDS) was claimed if the lower limit of the 97.5% CI of geometric mean ratio (GMR) (MDV relative to SDS) was greater than 0.5. If noninferiority for either the primary endpoint or the coprimary endpoint was achieved for all the 13 serotypes, then the noninferiority of immunogenicity response of 13vPnC MDV group to 13vPnC SDS group for this study was declared.

The secondary endpoints for OPA analysis included, for each of the pneumococcal serotypes and for each vaccine group, the proportion of subjects achieving a serotype-specific OPA titer ≥LLOQ and serotype-specific OPA GMTs 1 month after the infant series.

The proportion of subjects achieving IgG concentration or OPA titer at the prespecified level for each of the pneumococcal serotypes were computed at the proposed analysis endpoints for each vaccine group. In addition, exact, unconditional, 2-sided, 95% CIs on the proportion were computed using the F distribution. The differences in proportions for the 2 vaccine groups were calculated along with the 97.5% CIs for IgG (and 95% CIs for OPA) with the following methods:

- For IgG, to assess 2 population differences in proportions, exact, unconditional, 2-sided, 97.5% CIs on the difference in proportions (MDV – SDS) were calculated. The CIs for the difference in proportions were computed using the noninferiority procedure of Chan and Zhang, using the standardized test statistic and gamma=0.000001. This method constructed the CIs by inverting two 1-sided tests using a standardized (score) statistic. For OPA, exact, unconditional, 2-sided, 95% (instead of 97.5%) CIs on the difference in proportions (MDV – SDS) were calculated in the same way.
- Within each vaccine group and for IgG concentrations or OPA titers, the GMCs or GMTs at the proposed analysis endpoints were calculated with 2-sided 95% CIs constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using the Student t distribution.

The GMRs were calculated along with the 97.5% CIs for IgG (and 95% CIs for OPA) with the methods as follows:

- For IgG, 2-sided 97.5% CIs for the ratio of 2 geometric means (MDV – SDS) were constructed by back transformation of the CIs for the difference of the 2 logarithmically transformed assay results computed using the Student t distribution. The mean difference of the logarithmically transformed results was equivalent to the ratio of the 2 geometric means on the logarithmic scale: GMR = antilog [(1/n)Σlog (*xi*) - (1/m)Σlog (*yi*)], where *xi* and *yi* were the IgG concentration or OPA titer from MDV and SDS, respectively. Similarly for OPA, 2-sided 95% (instead of 97.5%) CIs for the ratio of 2 geometric means (MDV – SDS reference) were constructed.
- For each serotype separately, the proportions of subjects achieving an IgG concentration ≥0.35 µg/mL and subjects achieving an OPA titer □ LLOQ were computed. For each serotype,

exact, unconditional, 2-sided 97.5% for IgG (or 95% for OPA) CIs on the proportion were calculated.

Reverse cumulative distribution curves (RCDCs) are presented graphically for each serotype-specific IgG concentration or OPA titer.

Safety:

The safety endpoints were the number of subjects reporting local reactions and systemic events (and antipyretic medication use) in the 5 days after each vaccination (from Days 2 to 6) in the 13vPnC MDV group and 13vPnC SDS group, and the number of subjects reporting AEs in the 13vPnC MDV group and 13vPnC SDS group. AEs, SAEs, related AEs, and related SAEs were summarized for the infant series by vaccine group and total sample and for each vaccination. AEs and SAEs that were reported prior to Dose 1 of the infant series were also summarized. In addition, tables for related events, events that caused study discontinuation, events of mild or moderate severity, and events characterized as severe or life threatening were tabulated by vaccine group for those events occurring during the study. Pfizer has recently adopted a 3-tier approach for summarizing AEs in Phase 2 to 4 studies. AEs for the study were summarized by this approach as additional analyses of the AEs.

Results

Recruitment / Number analysed

500 subjects were screened and randomized and received Dose 1 (250 per group), 497 subjects (249 in the 13vPnC MDV group and 248 in the 13vPnC SDS group) received Dose 2, and 491 subjects (247 in the 13vPnC MDV group and 244 in the 13vPnC SDS group) received Dose 3 (Table 2). Of the 500 subjects enrolled, 489 (97.8%) subjects completed the blood draw 1 month after Dose 3 and completed the study; the percentages of subjects were similar across groups (Table 2).

Of the 500 randomised and enrolled subjects, 489 (97.8%) subjects (245 in the 13vPnC MDV group and 244 in 13vPnC SDS group) were included in both the evaluable immunogenicity population and all-available immunogenicity population. A total of 11 (2.2%) subjects (5 in the 13vPnC MDV group and 6 in 13vPnC SDS group) were excluded from the all-available population because they had no valid and determinate assay result 1 month after Dose 3 for any pneumococcal serotype; in each instance, the subject had been withdrawn from the study before Visit 4; therefore blood samples were not collected. These 11 subjects were also excluded from the evaluable immunogenicity population because they were not in the all-available immunogenicity population. 99.8% of the subjects also received their routine paediatric vaccines (non-study vaccines) during the course of the study.

In the safety population, there were no notable differences in the percentages of demographic characteristics between vaccine groups. Of the 500 subjects enrolled and vaccinated in the vaccine groups, 51.8% were female and 48.2% were male. All subjects were black and of non-Hispanic and non-Latino ethnicity; 44.8% of subjects were from the Mandinka tribe. Subjects had a mean age of 57.1 days at Dose 1 and mean weight of 4.9 kg.

Table 2. Vaccine Administration and Timing

	Vaccine Group (as Randomized)					
	13vPnC MDV		13vPnC SDS		Total	
	n	%	n	%	n	%
Randomised[a]	250	100.0	250	100.0	500	100.0
Vaccinated at dose 1 at 42-70 days of age[b] (~ 8 weeks)	250	100.0	250	100.0	500	100.0
Vaccinated at Dose 2 on[c] 28-42 days after Visit 1[b] (~12 weeks)	249	99.6	248	99.2	497	99.4
Vaccinated at Dose 3 on[c] (~ 16 weeks)						
28-42 days after Visit 2[b #]	246	98.4	244	97.6	490	98.0
>42 days after Visit 2	1	0.4	0	0.0	1	0.2

a. The values in this row are used as the denominators for percentages.
b. Protocol-specified time frame.
One subject in the 13vPnC MDV group was outside this time frame
c. Days calculated since previous dose.
Program ID: Study B4671001/CP CS_VAX_TIMING.SAS. Runtime ID: 09DEC2014 17:17 Date of Reporting Dataset Creation: 09DEC2014_

Immunogenicity results

A comparison of subjects in the evaluable immunogenicity population who achieved a pneumococcal IgG concentration ≥0.35 μg/mL 1 month after Dose 3 of the infant series are shown in Table 3. The proportion of subjects achieving an IgG concentration ≥0.35 μg/mL 1 month after Dose 3 was ≥95.1% in both vaccine groups for all 13 serotypes.

For the primary endpoint (the proportion of subjects achieving an IgG concentration ≥0.35 μg/mL), the non-inferiority criterion was met for all 13 serotypes in the 13vPnC MDV group compared with the 13vPnC SDS group 1 month after Dose 3 of the infant series (lower limit of the 97.5% CI of the difference was greater than -10%).

Table 3. Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 μg/mL 1 Month After Dose 3 – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC MDV				13vPnC SDS					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(97.5% CI[e])
1	245	243	99.2	(97.1, 99.9)	244	244	100.0	(98.5, 100.0)	-0.8	(-3.4, 1.2)
3	245	242	98.8	(96.5, 99.7)	243	242	99.6	(97.7, 100.0)	-0.8	(-3.7, 1.6)
4	245	244	99.6	(97.7, 100.0)	244	243	99.6	(97.7, 100.0)	0.0	(-2.3, 2.4)
5	245	235	95.9	(92.6, 98.0)	244	237	97.1	(94.2, 98.8)	-1.2	(-5.4, 2.8)

Table 3. Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL 1 Month After Dose 3 – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC MDV				13vPnC SDS					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(97.5% CI[e])
6A	243	234	96.3	(93.1, 98.3)	244	238	97.5	(94.7, 99.1)	-1.2	(-5.3, 2.6)
6B	245	233	95.1	(91.6, 97.4)	244	232	95.1	(91.6, 97.4)	0.0	(-4.7, 4.7)
7F	245	244	99.6	(97.7, 100.0)	244	244	100.0	(98.5, 100.0)	-0.4	(-2.7, 1.6)
9V	245	240	98.0	(95.3, 99.3)	244	240	98.4	(95.9, 99.6)	-0.4	(-3.8, 2.8)
14	245	239	97.6	(94.7, 99.1)	244	240	98.4	(95.9, 99.6)	-0.8	(-4.3, 2.5)
18C	245	243	99.2	(97.1, 99.9)	244	239	98.0	(95.3, 99.3)	1.2	(-1.6, 4.5)
19A	245	244	99.6	(97.7, 100.0)	244	241	98.8	(96.4, 99.7)	0.8	(-1.6, 3.6)
19F	245	237	96.7	(93.7, 98.6)	244	237	97.1	(94.2, 98.8)	-0.4	(-4.4, 3.5)
23F	245	235	95.9	(92.6, 98.0)	244	234	95.9	(92.6, 98.0)	0.0	(-4.3, 4.4)

a. N = number of subjects with a valid and determinate IgG concentration to the given serotype.
b. n = Number of subjects with an antibody concentration ≥0.35 µg/mL for the given serotype.
c. Exact 2-sided confidence interval (Clopper and Pearson) based on the observed proportion of subjects.
d. Difference in proportions, 13vPnC MDV – 13vPnC SDS, expressed as a percentage.
e. Exact 2-sided confidence interval (based on Chan & Zhang) for the difference in proportions, 13vPnC MDV – 13vPnC SDS, expressed as a percentage.

Pneumococcal IgG Geometric Mean Concentrations

Pneumococcal IgG GMCs 1 month after Dose 3 of the infant series and the GMC ratios (GMRs) of the 13vPnC MDV group to the 13vPnC SDS group are presented for the evaluable immunogenicity population in Table 4. At 1 month after Dose 3 of the infant series, GMCs were similar in both vaccine groups for the majority of serotypes.

For the co-primary endpoint (IgG GMC), the non-inferiority criterion was met for all 13 serotypes in the 13vPnC MDV group compared with the 13vPnC SDS group 1 month after Dose 3 of the infant series (lower limit of the 97.5% CI of GMR was greater than 0.5).

Although the non-inferiority criterion for the co-primary endpoint was met for all 13 serotypes, in the 13vPnC MDV group compared with the 13vPnC SDS group, GMCs were statistically significantly higher (lower bound of the 97.5% CI >1.0) for serotype 18C (GMC ratio, 1.28; 97.5% CI, [1.09, 1.49]) and statistically significantly lower (upper limit of the 97.5% CI <1.0) for serotype 3 (GMC ratio, 0.79; 97.5% CI [0.71, 0.90]).

Table 4. Comparison of Pneumococcal IgG GMCs (µg/mL) 1 Month After Dose 3 – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	13vPnC MDV			13vPnC SDS				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(97.5% CI[e])
1	245	4.59	(4.11, 5.12)	244	4.45	(4.01, 4.93)	1.03	(0.87, 1.22)
3	245	1.38	(1.29, 1.49)	243	1.74	(1.62, 1.87)	0.79	(0.71, 0.90)
4	245	5.30	(4.84, 5.81)	244	5.28	(4.76, 5.85)	1.00	(0.86, 1.18)
5	245	2.00	(1.79, 2.22)	244	1.98	(1.79, 2.20)	1.01	(0.85, 1.19)
6A	243	2.25	(2.02, 2.50)	244	2.19	(1.96, 2.44)	1.03	(0.86, 1.22)
6B	245	3.42	(2.91, 4.02)	244	3.24	(2.77, 3.78)	1.06	(0.82, 1.36)
7F	245	3.92	(3.59, 4.27)	244	4.18	(3.83, 4.55)	0.94	(0.82, 1.08)
9V	245	2.83	(2.56, 3.13)	244	2.75	(2.49, 3.04)	1.03	(0.87, 1.21)
14	245	4.78	(4.06, 5.63)	244	4.96	(4.27, 5.77)	0.96	(0.75, 1.24)
18C	245	3.47	(3.17, 3.79)	244	2.72	(2.46, 3.00)	1.28	(1.09, 1.49)
19A	245	6.49	(5.70, 7.38)	244	6.44	(5.66, 7.32)	1.01	(0.82, 1.24)
19F	245	5.19	(4.59, 5.86)	244	5.00	(4.43, 5.63)	1.04	(0.85, 1.26)
23F	245	2.61	(2.30, 2.97)	244	2.17	(1.92, 2.46)	1.20	(0.98, 1.48)

a. n = Number of subjects with a valid and determinate antibody concentration for the specified serotype.

b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.

c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.

d. Ratio of GMCs, 13vPnC MDV to 13vPnC SDS, was calculated by back transforming the mean difference between the vaccine groups on the logarithmic scale.

e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC MDV – 13vPnC SDS).

Pneumococcal OPA Titer ≥ LLOQ

A comparison of a subset of subjects with pneumococcal OPA antibody titers ≥ LLOQ 1 month after Dose 3 of the infant series is presented for both vaccine groups in the evaluable immunogenicity population in Table 5.

The proportions of subjects achieving OPA antibody titers ≥ LLOQ 1 month after Dose 3 were ≥93.7% in both vaccine groups for the majority of serotypes, except for serotype 1 (71.7% in 13vPnC MDV group vs 79.4% in the 13vPnC SDS group), serotype 5 (83.1% vs 85.5%), serotype 9V (79.7% vs 75.0%), and serotype 14 (81.5% vs 89.4%). Although the study was not powered based on OPA endpoints and non-inferiority criterion was not pre-specified for the OPA endpoint, the lower limits of the 95% CI of the differences were greater than -10% except for serotypes 1, 5, and 14. There was a statistically significantly lower proportion of subjects with OPA titer ≥ LLOQ in the 13vPnC MDV group compared with the 13vPnC SDS group for serotype 14 (upper limit of 95% CI of difference <0); the upper limit of the 95% CI of difference was less than 0, hence the result was listed as -0.0 due to rounding.

Table 5. Comparison of Subjects Achieving a Pneumococcal OPA Antibody Titer ≥ LLOQ 1 Month After Dose 3 – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC MDV				13vPnC SDS					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
1	159	114	71.7	(64.0, 78.5)	160	127	79.4	(72.3, 85.4)	-7.7	(-17.2, 1.9)
3	160	158	98.8	(95.6, 99.8)	160	160	100.0	(97.7, 100.0)	-1.2	(-4.4, 1.1)
4	159	159	100.0	(97.7, 100.0)	159	159	100.0	(97.7, 100.0)	0.0	(-2.3, 2.3)
5	160	133	83.1	(76.4, 88.6)	159	136	85.5	(79.1, 90.6)	-2.4	(-10.6, 5.7)
6A	160	159	99.4	(96.6, 100.0)	160	159	99.4	(96.6, 100.0)	0.0	(-2.9, 2.8)
6B	156	151	96.8	(92.7, 99.0)	155	150	96.8	(92.6, 98.9)	0.0	(-4.5, 4.6)
7F	159	159	100.0	(97.7, 100.0)	160	160	100.0	(97.7, 100.0)	0.0	(-2.3, 2.3)
9V	158	126	79.7	(72.6, 85.7)	160	120	75.0	(67.6, 81.5)	4.7	(-4.5, 14.1)
14	157	128	81.5	(74.6, 87.3)	160	143	89.4	(83.5, 93.7)	-7.8	(-15.8, -0.0)
18C	159	158	99.4	(96.5, 100.0)	160	159	99.4	(96.6, 100.0)	-0.0	(-2.9, 2.9)
19A	160	153	95.6	(91.2, 98.2)	160	156	97.5	(93.7, 99.3)	-1.9	(-6.6, 2.4)
19F	158	148	93.7	(88.7, 96.9)	159	150	94.3	(89.5, 97.4)	-0.7	(-6.3, 4.9)
23F	159	153	96.2	(92.0, 98.6)	160	156	97.5	(93.7, 99.3)	-1.3	(-5.8, 3.0)

Abbreviation: LLOQ = lower limit of quantitation.
Note: OPA assays were performed on the blood sample taken 1 month after Dose 3 in a subset of randomly selected subjects from each group.
a. N = number of subjects with a valid and determinate OPA antibody titer to the given serotype.
b. n = Number of subjects with an antibody titer ≥ LLOQ for the given serotype.
c. Exact 2-sided confidence interval (Clopper and Pearson) based on the observed proportion of subjects.
d. Difference in proportions, 13vPnC MDV – 13vPnC SDS, expressed as a percentage.
e. Exact 2-sided confidence interval (based on Chan & Zhang) for the difference in proportions, 13vPnC MDV – 13vPnC SDS, expressed as a percentage.
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Pneumococcal OPA Geometric Mean Titers

A comparison of the pneumococcal OPA GMTs 1 month after Dose 3 of the infant series is presented for both vaccine groups of the evaluable immunogenicity population in Table 6.

OPA GMTs were similar in both vaccine groups for the majority of serotypes, with the exceptions of serotype 3 where the 13vPnC SDS was higher throughout the range of OPA titers and serotype 18C where the 13vPnC MDV titers were higher throughout the full range.

Although non-inferiority criterion was not pre-specified for the OPA GMT endpoint, all of the lower limits of the 95% CIs of OPA GMRs were greater than 0.5 except for serotypes 14, which was 0.48.

Table 6. Comparison of Pneumococcal OPA GMTs 1 Month After Dose 3 – Evaluable Immunogenicity Population

	Vaccine Group (as Randomized)							
	13vPnC MDV			13vPnC SDS				
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
1	159	48	(39.0, 58.0)	160	52	(43.2, 62.6)	0.9	(0.70, 1.20)
3	160	97	(87.3, 108.8)	160	122	(110.1, 135.7)	0.8	(0.69, 0.93)
4	159	1666	(1412.3, 1966.3)	159	1492	(1285.2, 1732.3)	1.1	(0.89, 1.39)
5	160	79	(67.7, 92.4)	159	80	(69.1, 92.6)	1.0	(0.80, 1.22)
6A	160	1690	(1460.5, 1955.9)	160	1968	(1698.5, 2279.3)	0.9	(0.70, 1.06)
6B	156	1990	(1611.7, 2456.9)	155	2014	(1639.1, 2475.4)	1.0	(0.74, 1.33)
7F	159	2891	(2565.4, 3258.5)	160	3450	(3014.7, 3947.9)	0.8	(0.70, 1.00)
9V	158	709	(600.5, 836.2)	160	706	(597.0, 835.3)	1.0	(0.79, 1.27)
14	157	567	(415.4, 773.5)	160	786	(607.8, 1015.3)	0.7	(0.48, 1.08)
18C	159	2792	(2387.5, 3264.8)	160	1605	(1352.0, 1904.4)	1.7	(1.38, 2.19)
19A	160	305	(256.2, 362.9)	160	329	(284.8, 379.8)	0.9	(0.74, 1.16)
19F	158	430	(357.6, 517.1)	159	470	(391.4, 565.3)	0.9	(0.71, 1.18)
23F	159	918	(729.0, 1156.4)	160	998	(810.6, 1229.6)	0.9	(0.67, 1.25)

Note: OPA assays were performed on the blood sample taken 1 month after Dose 3 in a subset of randomly selected subjects from each group.

a. n = Number of subjects with a valid and determinate antibody titer for the specified serotype.

b. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.

c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.

d. Ratio of GMTs, 13vPnC MDV to 13vPnC SDS, was calculated by back transforming the mean difference between the vaccine groups on the logarithmic scale.

e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC MDV – 13vPnC SDS).

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Assessor's comment: Overall, the response rates and GMTs and GMCs were similar in the two presentations, and the results do not raise new issues regarding the immunogenicity of Prevenar 13. The IgG concentrations and OPA titre were in agreement, i.e. the results for serotypes 3 and 18, which differed between groups, were in agreement in both assays. The relevance of these results are unknown, but considering the high response rates, they are not concerning.

Safety results

Local Reactions:

- The proportions of local reactions reported on Days 2 to 6 after each infant series dose were low (≤18.8% of subjects in either vaccine group) and comparable for the vaccine groups.
- Local reactions reported on Days 2 to 6 after each infant series dose were comprised entirely of tenderness, reported for similar proportions of subjects in both vaccine groups (≤18.8% of subjects in either vaccine group). The majority of reports of tenderness were mild in severity for both vaccine groups. No severe tenderness was reported for any subjects in either vaccine group.

- Mild or moderate redness and swelling were reported for a low proportion of subjects in the 13vPnC MDV group (≤0.8%) after any infant series dose, and no severe redness or swelling was reported. No redness and swelling was reported for subjects in the 13vPnC SDS group after any infant series dose.

- The mean duration of redness, swelling, and tenderness were ≤3 days for either vaccine group following each dose of the infant series.

- Local reactions were reported most frequently on Day 2 after each dose of the infant series for both vaccine groups.

Systemic Events:

- Systemic events were reported on Days 2 to 6 after any infant series dose for ≤46.0% of subjects. The proportions of subjects for whom any systemic event was reported on Days 2 to 6 after any infant series dose were similar in both vaccine groups.

- The proportions of subjects for whom any fever was reported on Days 2 to 6 after any infant series were similar between vaccine groups (≤3.6% of subjects in either vaccine group). No fever ≥40.0°C was reported for subjects in either vaccine group after any infant series dose.

- Use of antipyretic medication was reported on Days 2 to 6 after any infant series dose and was similar in both vaccine groups (≤23.2% of subjects in either vaccine group), despite the low frequency of documented fevers.

- Irritability was the most frequent systemic event reported on Days 2 to 6 after any infant series dose in both vaccine groups (≤41.4% of subjects in either vaccine group). After Dose 2, in the 13vPnC SDS group, there were 3 (1.2%) subjects for whom severe irritability was reported. After Dose 3, there was 1 (0.4%) subject in the 13vPnC MDV group and 5 (2.1%) subjects in the 13vPnC SDS group for whom severe irritability was reported.

- Other systemic events of decreased appetite and increased sleep were reported for a similar proportion of subjects in both vaccine groups (≤11.3% of subjects in both vaccine groups).

- For both vaccine groups, the mean duration (days) of systemic events and antipyretic medication use was ≤1.4 days for all systemic events reported on Days 2 to 6 after each dose of the infant series.

- Systemic events were reported most frequently on Day 2 after each dose of the infant series for both vaccine groups.

- All malaria test results for subjects with fever (temperature ≥38.0°C) after each dose of the infant series were negative.

Adverse Events:

- AEs were reported for a numerically similar proportion of subjects in both vaccine groups (49.2% of subjects in the 13vPnC MDV group and 50.8% of subjects in the 13vPnC SDS group) during the infant series.

- AEs were reported for a numerically similar proportion of subjects in both vaccine groups after Dose 1 of the infant series (24.0% of subjects in the 13vPnC MDV group and 22.0% of subjects in the 13vPnC SDS group), after Dose 2 of the infant series (18.1% and 16.1%, respectively), and after Dose 3 of the infant series (21.5% and 25.4%, respectively).

- The most frequently reported AEs during the infant series were those categorized as infections and infestations and skin and subcutaneous tissue disorders, reported for a numerically similar proportion of subjects in the 13vPnC MDV group (41.2% and 7.2%, respectively) and 13vPnC SDS group (43.6% and 11.2%, respectively). The most frequently reported individual AEs during the infant series were upper respiratory tract infection, viral diarrhea, and dermatitis, reported for a numerically similar proportion of subjects in the 13vPnC MDV group (23.2%, 7.6%, and 6.0%, respectively) and in the 13vPnC SDS group (20.0%, 12.0%, and 8.8%, respectively).

- The majority of AEs reported during the infant series were of mild severity in both vaccine groups.

- Pyrexia, that was assessed as related to the study vaccine was reported for 1 subject in the 13vPnC MDV group after Dose 3 of the infant series and for 2 subjects in the 13vPnC SDS group (1 subject each after Doses 1 and 3 of the infant series); pyrexia was the only AE considered to be related to the study vaccine and reported during the infant series.

- One (1) SAE of sudden infant death syndrome was reported for a subject in the 13vPnC MDV group on Day 20 after Dose 3 of the infant series; the SAE was assessed as not related to the study vaccine.

Assessor's comment: There were no differences in reactogenicity, local or systemic adverse reactions, or SAEs between the two groups. No new safety issue was detected in this study.

2.3.3. Discussion on clinical aspects

The current application concerns a clinical study with Prevenar 13, single dose syringe, compared to a multidose presentation including the preservative 2-phenoxyethanol. There were only very small differences in immune responses and reactogenicity between the two presentations, and no cocnerns regarding immunogenicity or safety of Prevenar 13 were raised.

3. Rapporteur's overall conclusion and recommendation

The application is considered fulfilled and no further regulatory action is required.

Overall conclusion

Recommendation

☒ Fulfilled:

No regulatory action required.

☐ **Not fulfilled:**

Additional clarifications requested

Not applicable.