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Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No1901/2006, as amended.

Prevenar 13

(Pneumococcal saccharide conjugated vaccine, adsorbed)

Procedure No. EMEA/H/C/001104

P46 037

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

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I. INTRODUCTION

On June 9, 2010, the MAH submitted completed paediatric studies for Prevenar 13, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Prevenar 13 and that there is no consequential regulatory action.

II. SCIENTIFIC DISCUSSION

Information on the pharmaceutical formulation used in the studies

The formulation used in the clinical studies is the currently approved formulation.

Clinical aspects

1. Introduction

The MAH submitted final reports for:

6096A1-012: A phase 3, randomized, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of a 13-valent pneumococcal conjugate vaccine in healthy infants given with routine pediatric vaccinations in Brazil

6096A1-3004; A phase 3, randomized, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of a 13-valent pneumococcal conjugate vaccine in healthy infants given with routine pediatric vaccinations in Taiwan

2. Clinical studies

6096A1-012: A phase 3, randomized, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of a 13-valent pneumococcal conjugate vaccine in healthy infants given with routine pediatric vaccinations in Brazil

- **Description**

Wyeth Lederle Vaccines S.A. states that study 6096A1-012 is part of the global clinical development program for the use of Prevenar 13 in infants and were conducted to support licensure in Brazil.

- **Methods**

  - ***Objective(s)***

The primary objectives of this study were as follows:

- To assess the pneumococcal immune responses induced by 13vPnC relative to the pneumococcal immune responses induced by 7vPnC when measured 1 month after the infant series.
- To assess the immune responses induced by diphtheria, tetanus, whole cell pertussis, and Haemophilus influenzae type b vaccine (DTP-Hib) given with 13vPnC relative to the immune responses induced by DTP-Hib given with 7vPnC when measured 1 month after the infant series.The following antigens in DTP-Hib were assessed: pertussis antigens (pertussis toxoid [PT], filamentous haemagglutinin [FHA], and pertactin [PRN]).

The secondary objectives of this study were as follows:

- To assess the pneumococcal immune responses induced by 13vPnC relative to the pneumococcal immune responses induced by 7vPnC when measured 1 month after the toddler dose.
- To assess the immune responses induced by DTP-Hib given with 13vPnC relative to the immune responses induced by DTP-Hib given with 7vPnC when measured 1 month after the toddler dose. The following antigens in DTP-Hib were assessed: pertussis antigens (PT, FHA, and PRN).

The safety objective of this study was as follows:

- To evaluate the acceptability of the safety profile of 13vPnC as measured by the incidence rates of local reactions, systemic events, and adverse events (AEs).

- ***Study design***

This was a phase 3, randomized, active-controlled, double-blind, parallel-group, multicenter trial to evaluate the safety, tolerability, and immunogenicity of 13vPnC in healthy infants and toddlers in Brazil. Subjects received either 13vPnC or 7vPnC (177 subjects randomly assigned to each group) at 2, 4, and 6 months of age (infant series) and at 12 months of age (toddler dose). The concomitant study vaccines were administered as follows: hepatitis B virus vaccine (HBV) at 1 and 6 months of age and diphtheria, tetanus, whole cell pertussis with Haemophilus influenzae type b (DTP-Hib) at 2, 4, 6, and 12 months of age. Oral polio vaccine (OPV) was also to be given at 2, 4, 6, and 12 months of age.

- ***Study population /Sample size***

Sample size estimation was based on the precision of the 2-sided 95% CI for the proportion of subjects achieving a serotype-specific pneumococcal IgG concentration ≥0.35 µg/mL and the proportion of subjects achieving a whole-cell pertussis antibody level ≥5 EU/mL in each vaccine group. Data from Wyeth studies 6096A1-003 and D118-P3 were used for the pneumococcal serotypes and the whole-cell pertussis antigens (PT, FHA, and PRN), respectively.

Assuming a dropout rate of at most 15%, 354 subjects (177 subjects per group) overall were to be enrolled to obtain 150 evaluable subjects per group in the study. This allowed estimation of the proportion of responders after the infant series third dose (primary objective) to within ±7.3% precision.

- ***Treatments***

Subjects were to receive either 13vPnC or 7vPnC at 2, 4, and 6 months of age (infant series) and at 12 months of age (toddler dose). The mandatory concomitant study vaccines were administered as follows: hepatitis B virus vaccine (HBV) at 1 month and 6 months of age, and DTP-Hib at 2, 4, 6, and 12 months of age. Initially, oral polio vaccine (OPV) was to be given at 2, 4, 6, and 12 months of age; however, this was changed so that subjects could receive OPV at any time during the study and it could count as the study visit dose if given within 28 days of the visit, because of an ongoing National Vaccination Campaign against Poliomyelitis in Brazil during the study period. Additional concomitant vaccines that could have been given at the discretion of the investigator according to the national recommended vaccination schedule included meningitis C vaccine (Meningitec); measles, mumps, and rubella vaccine (MMR); varicella vaccine; rotavirus vaccine; yellow fever vaccine; and influenza vaccine. A birth dose of bacillus Calmette-Guerin (BCG) was allowed.

- ***Outcomes/endpoints***

Pneumococcal Antibody Response

Blood samples were to be obtained at visit 5 (28 through 56 days after the third dose in the infant series) and at visit 7 (28 through 56 days after the toddler dose). Serum concentrations of anticapsular IgG for each of the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) were to be determined in all subjects for each blood sample and expressed as micrograms per milliliter (µg/mL). The assay employed 2 absorbents, a C polysaccharide containing cell wall extract plus serotype 22F capsular polysaccharide.

Assessor's comment: OPA responses were not assayed in this study, which is a limitation, and precludes a full assessment of the immune responses.

Concomitant Vaccine Antibody Response
Serum levels of IgG antibodies to PT, FHA, and PRN (69 kDa outer membrane protein) were to be measured using an anti-Bordetella pertussis enzyme-linked immunosorbent assay (ELISA) performed on blood samples collected 1 month after the infant series and 1 month after the toddler dose. Results were to be reported as ELISA units per milliliter (EU/mL).

Assessor's comment: Only the antibody responses to the pertussis component were evaluated in this study report. The same approach was used in some previously reported studies (see original MAA). It it therefore not possible to assess whether concomitant vaccination has an impact on the responses to the other antigens in this study.

Safety Assessment Methods:
Safety assessments were to be based on data from the daily monitoring and recording of local reactions at the injection site, systemic events, and use of antipyretic medication to treat and prevent symptoms by the parent(s)/legal guardian(s) in an e-diary for 4 days after each 13vPnC or 7vPnC vaccine administration (day 1 through day 4) and AE monitoring through visit 5 and from visit 6 to 7.

Local reactions (redness, swelling, and tenderness) on the left leg at the site of the pneumococcal conjugate injection were to be monitored daily for 4 days (day 1 through day 4) after each vaccine administration and this information was recorded in the e-diary by the parent(s)/legal guardian(s). The parent(s)/legal guardian(s) were to measure the actual size of redness or swelling with a caliper and record the measurement (1 to 14 or 14+ caliper units) in whole number increments in the e-diary. Each caliper unit represented 0.5 cm, and measurements were to be rounded up to the nearest whole number. If tenderness was present, whether or not it interfered with limb movement, it was to be recorded. The measurements for redness and swelling were to be categorized as absent (0 caliper units), mild (0.5 to 2.0 cm; 1 to 4 caliper units), moderate (2.5 to 7.0 cm; 5 to 14 caliper units), or severe (>7.0 cm; >14 caliper units) for analyses. If the measurement of redness or swelling was >7.0 cm (>14 caliper units), the subject was to be seen by study personnel for a medical assessment. Tenderness was to be recorded as none, present, or interfered with limb movement.

Systemic events (decreased appetite, irritability, increased sleep, and decreased sleep) were to be monitored daily and their presence or absence was recorded in the e-diary for 4 days after each vaccine administration (day 1 through day 4). Axillary temperature was to be collected daily at bedtime for 4 days, and at anytime during the 4 days if fever was suspected. If a fever (≥38.0°C [100.4 °F]) occurred, temperature was to be collected daily until the fever resolved (1 day of temperature <38.0 °C [100.4°F]). Temperature was to be measured and recorded to 1 decimal place and then categorized according to the following terms and scale: absent (<38.0°C [100.4°F]), mild (≥38.0°C [100.4°F] to <39.0°C [102.2°F]), moderate (≥39.0°C [102.2°F] to <40.0°C [104.0°F]), and severe (≥40.0°C [104.0°F]). An end date was to be captured for any reactions persisting at day 4.

In addition, the use of antipyretic medications to prevent or treat symptoms was to be recorded daily during the active safety observation periods (day 1 through day 4) after each vaccine administration. An end date was to be recorded for any antipyretic medication use persisting at day 4.

Signs and symptoms (AEs) were to be assessed and recorded during the physical examination and on clinical evaluation of the subject at the study visits. Clinic personnel were to observe the subject for at least 30 minutes after each vaccination for any significant, acute reactions. AEs were to be identified based on a review of any ancillary information reported on the e-diary, on clinical evaluation at the time of a study visit, or from information obtained by asking the parent(s)/legal guardian(s) a nonspecific question such as "How has your child been doing since your last visit?"
A subject's AEs were to be recorded from the signing of the ICF to visit 5 (1 month after infant series) and from visit 6 (toddler dose) to visit 7 (1 month after toddler dose). At visit 6 any newly diagnosed chronic medical conditions since visit 5 were to be recorded. All SAEs were to be recorded from the signing of the ICF to visit 7. During the clinical trial, the investigator had to follow up on all AEs, SAEs, and other reportable information until the events had subsided, returned to baseline, or in case of permanent impairment, until the condition stabilized.

- ***Statistical Methods***

The primary endpoint for each of the pneumococcal serotypes was the proportion of subjects achieving a serotype-specific IgG concentration ≥0.35 µg/mL measured 1 month after the infant series. This choice of endpoint was based upon a World Health Organization (WHO) guideline for the pneumococcal serotypes.25 The coprimary endpoint for each of the whole-cell pertussis antigens was the proportion of subjects achieving a predetermined antibody level measured 1 month after the infant series. The prespecified antibody levels for each whole-cell pertussis antigen were defined as PT, FHA, and PRN levels ≥5 EU/mL.

The secondary endpoint for each of the pneumococcal serotypes was the proportion of subjects achieving a serotype-specific IgG concentration ≥0.35 µg/mL measured 1 month after the toddler dose. The cosecondary endpoint for each of the whole-cell pertussis antigens was the proportion of subjects achieving PT, FHA, and PRN antibody levels of ≥5 EU/mL 1 month after the toddler dose.

All statistical analyses are descriptive and any comparisons between the 13vPnC and the 7vPnC groups are descriptive.

➢ **Results**

- Recruitment/ Number analysed

The number of subjects planned for this study was 354 (177 subjects in each vaccine group). A total of 356 subjects were enrolled, 2 of whom were screened but not randomly assigned. The subjects were randomly assigned in a 1:1 ratio prospectively to either the 13vPnC group (n=177) or the 7vPnC group (n=177) and 316 (89.3%) subjects completed the infant series. Of the 312 (88.1%) subjects vaccinated at the toddler dose, 309 (87.3%) subjects completed the study.

Thirty-eight (38, 10.7%) subjects were withdrawn from the study during the infant series: 20 (11.3%) subjects in the 13vPnC group and 18 (10.2%) subjects in the 7vPnC group. After the infant series (ie, in the period between the blood draw after visit 3 and visit 5), 4 (1.1%) subjects withdrew (1 subject in the 13vPnC group and 3 subjects in the 7vPnC group). Three (3, 0.8%) subjects in the 13vPnC group were withdrawn from the study during the toddler dose period.

Assessor's comment: The number of subjects withdrawn from the study is as can be expected from previous studies, or slightly higher. The reasons for withdrawal did not differ between the groups.

- Baseline data

Overall, 48.6% of the subjects were male and 51.4% were female, and the groups were similar with respect to race, ethnicity, age, and weight at enrolment. Across both vaccine groups, most subjects were white (84.8%) and all were Hispanic or Latino. In both vaccine groups, the mean age (±standard deviation [SD]) at enrolment was 1.2 (±0.2) months, with ages ranging from 1.0 months to 2.3 months. Mean weight (±SD) at enrolment was 4.2 (±0.6) kg in both the 13vPnC and 7vPnC groups.

- Efficacy results

Proportion of Subjects Achieving Pneumococcal IgG Concentration ≥0.35 µg/mL
Infant series

One (1) month after the infant series, 13vPnC elicited serum IgG antibody concentrations to the 7 common serotypes that were comparable with the responses elicited by 7vPnC (Table 9-3).
For the 7 common serotypes, the proportion of subjects with IgG concentrations ≥0.35 µg/mL was 94.2% or higher in the 13vPnC group and 93.0% or higher in the 7vPnC group.

13vPnC also elicited serum IgG antibody responses to the 6 additional serotypes not contained in 7vPnC. The percentage of 13vPnC recipients with IgG concentrations ≥0.35 µg/mL was 87.1% for serotype 3 and greater than 97% for the other 5 serotypes. The percentage of responders among 13vPnC recipients was significantly higher than the percentage of responders in the 7vPnC group for all serotypes except 19A.

In the 7vPnC group, the proportion of responders with IgG concentrations ≥0.35 µg/mL 1 month after the infant series ranged from 1.3% (serotype 7F) to 98.7% (serotype 19A) for the 6 additional serotypes. The response rates to serotypes 5, 6A, and 19A were higher compared with the percentages of responders to serotypes 1, 3, and 7F. The high responses to serotypes 19A and 6A (98.7% and 52.6%), may be due to cross-reactivity with the 19F and 6B serotypes, respectively.

The all-available pneumococcal infant immunogenicity population showed similar results (data not shown in this AR).

Table 9-3: Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After Dose 3 of the Infant Series – Evaluable Pneumococcal Infant Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC				7vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	156	156	100.0	(97.7, 100.0)	158	158	100.0	(97.7, 100.0)	0.0	(-2.4, 2.3)
6B	156	151	96.8	(92.7, 99.0)	158	151	95.6	(91.1, 98.2)	1.2	(-3.4, 6.1)
9V	156	154	98.7	(95.4, 99.8)	158	158	100.0	(97.7, 100.0)	-1.3	(-4.6, 1.1)
14	156	153	98.1	(94.5, 99.6)	158	154	97.5	(93.6, 99.3)	0.6	(-3.2, 4.7)
18C	156	152	97.4	(93.6, 99.3)	157	154	98.1	(94.5, 99.6)	-0.7	(-4.7, 3.2)
19F	156	147	94.2	(89.3, 97.3)	158	156	98.7	(95.5, 99.8)	-4.5	(-9.5, -0.4)
23F	156	151	96.8	(92.7, 99.0)	157	146	93.0	(87.8, 96.5)	3.8	(-1.2, 9.3)
Additional										
1	156	155	99.4	(96.5, 100.0)	158	4	2.5	(0.7, 6.4)	96.8	(92.7, 99.0)
3	155	135	87.1	(80.8, 91.9)	158	7	4.4	(1.8, 8.9)	82.7	(75.5, 88.3)
5	156	154	98.7	(95.4, 99.8)	152	58	38.2	(30.4, 46.4)	60.6	(52.2, 68.4)
6A	156	152	97.4	(93.6, 99.3)	156	82	52.6	(44.4, 60.6)	44.9	(36.3, 53.2)
7F	156	156	100.0	(97.7, 100.0)	155	2	1.3	(0.2, 4.6)	98.7	(95.4, 99.8)
19A	156	155	99.4	(96.5, 100.0)	156	154	98.7	(95.4, 99.8)	0.6	(-2.3, 4.0)

a. N = number of subjects with a determinate IgG antibody 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 based on the observed proportion of subjects.
d. Difference in proportions, 13vPnC – 7vPnC reference, expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, 13vPnC – 7vPnC reference, expressed as a percentage.

Assessor's comments: The frequencies of subjects achieving a pneumococcal IgG concentration ≥0.35 µg/ml is not significantly different from what has been seen in other studies. The responses to serotype 6B are generally higher than what has been seen in several other studies from other locations previously, and the response to serotype 3 is lower than what was seen in at least some previous studies (006). A more relevant comparison between groups for the 6 additional serotypes in the 13-valent vaccine would have been to use the lowest response rate seen for the 7 common serotypes in the Pnc7 group as a comparator.

Toddler Dose

After the toddler dose, 13vPnC elicited serum IgG antibody concentrations to the 7 common serotypes that were comparable with the responses elicited by 7vPnC (Table 9-4). The proportion of responders with IgG concentrations ≥0.35 µg/mL were 97.4% or higher in the 13vPnC group and 98.7% or higher in the 7vPnC group.

For the 6 additional serotypes not contained in 7vPnC, the percentage of 13vPnC recipients with IgG concentrations ≥0.35 µg/mL was **92.1%** for serotype 3 and 100.0% for the other 5 serotypes.

The percentage of responders among 13vPnC recipients was significantly higher than the percentage of responders among 7vPnC recipients for all serotypes except serotype 19A.

In the 7vPnC group, the proportion of responders with IgG concentrations ≥0.35 µg/mL 1 month after the toddler dose ranged from 2.7% (serotype 1) to 100.0% (serotype 19A) for the 6 additional serotypes. The response rates to serotypes 5, 6A, and 19A were higher compared with the percentages of responders to serotypes 1, 3, and 7F. The high responses to serotypes 19A and 6A (100.0% and 92.1%), may be due to cross-reactivity with the 19F and 6B serotypes, respectively.

The all-available pneumococcal toddler immunogenicity population showed similar results (data not shown in this AR).

Table 9-4: Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After the Toddler Dose – Evaluable Pneumoccoccal Toddler Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC				7vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	152	152	100.0	(97.6, 100.0)	152	152	100.0	(97.6, 100.0)	0.0	(-2.5, 2.5)
6B	151	147	97.4	(93.4, 99.3)	152	150	98.7	(95.3, 99.8)	-1.3	(-5.5, 2.3)
9V	152	152	100.0	(97.6, 100.0)	152	152	100.0	(97.6, 100.0)	0.0	(-2.5, 2.5)
14	151	151	100.0	(97.6, 100.0)	152	151	99.3	(96.4, 100.0)	0.7	(-1.9, 3.6)
18C	152	151	99.3	(96.4, 100.0)	152	152	100.0	(97.6, 100.0)	-0.7	(-3.6, 1.8)
19F	152	151	99.3	(96.4, 100.0)	152	150	98.7	(95.3, 99.8)	0.7	(-2.4, 4.1)
23F	152	150	98.7	(95.3, 99.8)	152	151	99.3	(96.4, 100.0)	-0.7	(-4.1, 2.4)
Additional										
1	152	152	100.0	(97.6, 100.0)	149	4	2.7	(0.7, 6.7)	97.3	(93.3, 99.3)
3	151	139	92.1	(86.5, 95.8)	147	11	7.5	(3.8, 13.0)	84.6	(77.4, 90.0)
5	152	152	100.0	(97.6, 100.0)	140	101	72.1	(63.9, 79.4)	27.9	(20.6, 36.1)
6A	152	152	100.0	(97.6, 100.0)	151	139	92.1	(86.5, 95.8)	7.9	(4.2, 13.5)
7F	152	152	100.0	(97.6, 100.0)	144	6	4.2	(1.5, 8.8)	95.8	(91.2, 98.5)
19A	152	152	100.0	(97.6, 100.0)	152	152	100.0	(97.6, 100.0)	0.0	(-2.5, 2.5)

a. N = number of subjects with a determinate IgG antibody 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 based on the observed proportion of subjects.
d. Difference in proportions, 13vPnC – 7vPnC reference, expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, 13vPnC – 7vPnC reference, expressed as a percentage.

Assessor's comment: The responses following the toddler dose are well within the range that has been seen in previous studies.

Pneumococcal IgG Geometric Mean Concentrations
Infant Series

For the 7 common serotypes, serotype-specific IgG GMCs were comparable with those in the 7vPnC group; ranging from 1.47 µg/mL for serotype 9V to 6.32 µg/mL for serotype 14 in the 13vPnC group, and from 1.69 µg/mL for serotype 9V to 6.86 µg/mL for serotype 14 in the 7vPnC group (Table 9-5).
For all 6 of the additional serotypes, the IgG GMCs for 13vPnC recipients were higher than the GMCs for 7vPnC recipients (the lower limit of the 95% CI was >1.0). In the 13vPnC group, serotype-specific IgG GMCs ranged from 0.77 µg/mL for serotype 3 to 4.30 µg/mL for serotype 7F. In the 7vPnC group, serotype-specific IgG GMCs ranged from 0.02 µg/mL for serotype 1 to 1.83 µg/mL for serotype 19A. The all-available pneumococcal infant immunogenicity population showed similar results.

Table 9-5: Comparison of Pneumococcal IgG GMCs (µg/mL) After Dose 3 of the Infant Series – Evaluable Pneumococcal Infant Immunogenicity Population

	Vaccine Group (as Randomized)							
	13vPnC			7vPnC				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	156	2.13	(1.91, 2.39)	158	2.84	(2.57, 3.14)	0.75	(0.65, 0.87)
6B	156	4.73	(3.98, 5.62)	158	3.71	(3.12, 4.41)	1.27	(1.00, 1.63)
9V	156	1.47	(1.31, 1.63)	158	1.69	(1.52, 1.88)	0.87	(0.74, 1.01)
14	156	6.32	(5.39, 7.42)	158	6.86	(5.78, 8.14)	0.92	(0.73, 1.16)
18C	156	1.96	(1.72, 2.23)	157	2.17	(1.93, 2.44)	0.90	(0.76, 1.08)
19F	156	2.30	(1.97, 2.68)	158	3.12	(2.74, 3.55)	0.74	(0.60, 0.90)
23F	156	1.91	(1.63, 2.22)	157	1.94	(1.64, 2.31)	0.98	(0.78, 1.23)
Additional								
1	156	2.39	(2.10, 2.72)	158	0.02	(0.02, 0.03)	97.83	(79.70, 120.09)
3	155	0.77	(0.69, 0.86)	158	0.05	(0.04, 0.06)	15.31	(12.23, 19.16)
5	156	2.09	(1.85, 2.37)	152	0.27	(0.23, 0.31)	7.80	(6.40, 9.50)
6A	156	3.52	(3.06, 4.04)	156	0.39	(0.32, 0.46)	9.10	(7.29, 11.35)
7F	156	4.30	(3.84, 4.82)	155	0.03	(0.02, 0.03)	157.39	(128.34, 193.03)
19A	156	3.63	(3.22, 4.10)	156	1.83	(1.61, 2.09)	1.98	(1.66, 2.36)

a. n = Number of subjects with a 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 to 7vPnC reference.
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 – 7vPnC reference).

Assessor's comments: For the 7 common serotypes the GMCs were generally slightly lower in the 13vPnC group than in the 7vPnC group, which is on accordance with previously reported studies. The levels are well within the previously reported GMC from other studies.

Toddler Dose

For the 7 common serotypes after the toddler dose, IgG GMCs in the 13vPnC group were comparable with those in the 7vPnC group with the exception of serotype 19F, which was significantly higher for 13vPnC recipients (lower limit of the 95% CI was >1.0) after the toddler dose (Table 9-6). Serotype-specific IgG GMCs ranged from 3.07 µg/mL for serotype 9V to 13.04 µg/mL for serotype 6B in the 13vPnC group, and from 2.76 µg/mL for serotype 9V to 11.68 µg/mL for serotype 6B in the 7vPnC group.

For all 6 of the additional serotypes, the IgG GMCs in 13vPnC recipients were higher than the GMCs for 7vPnC recipients (the lower limit of the 95% CI was >1.0). In the 13vPnC group, serotype-specific IgG GMCs ranged from 0.85 µg/mL for serotype 3 to 8.96 µg/mL for serotype 6A. In the 7vPnC group, serotype-specific IgG GMCs ranged from 0.03 µg/mL for serotype 1 to 3.59 µg/mL for serotype 19A. The all-available pneumococcal toddler immunogenicity population showed similar results.

Table 9-6: Comparison of Pneumococcal IgG GMCs (µg/mL) After the Toddler Dose – Evaluable Pneumococcal Toddler Immunogenicity Population

	Vaccine Group (as Randomized)							
	13vPnC			7vPnC				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	152	3.67	(3.19, 4.23)	152	4.09	(3.57, 4.69)	0.90	(0.74, 1.09)
6B	151	13.04	(11.03, 15.42)	152	11.68	(9.85, 13.86)	1.12	(0.88, 1.42)
9V	152	3.07	(2.67, 3.53)	152	2.76	(2.45, 3.12)	1.11	(0.93, 1.34)
14	151	8.66	(7.56, 9.93)	152	8.30	(7.07, 9.74)	1.04	(0.85, 1.29)
18C	152	3.20	(2.75, 3.71)	152	3.69	(3.21, 4.25)	0.87	(0.71, 1.06)
19F	152	5.97	(5.09, 7.01)	152	4.02	(3.45, 4.68)	1.49	(1.19, 1.85)
23F	152	5.10	(4.32, 6.02)	152	5.99	(5.15, 6.96)	0.85	(0.68, 1.07)
Additional								
1	152	3.72	(3.23, 4.29)	149	0.03	(0.02, 0.03)	133.80	(107.34, 166.78)
3	151	0.85	(0.75, 0.96)	147	0.07	(0.06, 0.08)	12.43	(9.77, 15.82)
5	152	4.30	(3.76, 4.91)	140	0.58	(0.49, 0.69)	7.39	(5.98, 9.13)
6A	152	8.96	(7.80, 10.28)	151	1.84	(1.52, 2.24)	4.85	(3.84, 6.14)
7F	152	6.81	(5.98, 7.76)	144	0.03	(0.02, 0.04)	223.03	(175.51, 283.43)
19A	152	8.91	(7.92, 10.03)	152	3.59	(3.13, 4.11)	2.49	(2.08, 2.97)

a. n = Number of subjects with a 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 to 7vPnC reference.
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 – 7vPnC reference).

Assessor's comment: The GMCs are generally in line with what has been reported following the toddler dose previously.

Concomitant Vaccine Immunogenicity

In this study, 13vPnC or 7vPnC was administered concomitantly with DTP-Hib and the responses to 3 pertussis antigens, pertussis toxoid (PT), filamentous hemagglutinin (FHA) and pertactin (PRN) were compared in the 2 groups. The percentage of responders (≥5 EU/mL) varied across the 3 antigens, but was not different in 13vPnC and 7vPnC recipients. The **percentage of responders to PT was low** (13vPnC **35.9%, 50.7%;** 7vPnC 32.3%, 49.3%, respectively) in both groups after the infant series and toddler dose. The percentage of responders to FHA was high (13vPnC 70.1%, 91.4%; 7vPnC 71.5%, 88.8%, respectively) in both groups after the infant series and toddler dose. The percentage of responders to PRN was also high (13vPnC 93.5%, 99.3%; 7vPnC 96.2%, 98.7%, respectively) in both groups after the infant series and toddler dose. A technical report assessing the immune responses to the DTP-Hib vaccine used in this study, showed that the proportion of infants with levels of anti-pertussis antibodies indicative of seroprotection (≥15 UEL/mL) was >98%. There are no published data (including the package insert for the Brazilian combined DTP-Hib vaccine) on the responses to specific antigens (PT, FHA, PRN), to which the responses seen in the current study can be compared. The GMCs for the pertussis antigens also show similar results for the 13vPnC and 7vPnC groups. These data support a conclusion that 13vPnC can be given as part of the routine immunization schedule without impacting pertussis responses.

Assessor's comment: The immune responses to the PT component were unexpectedly low in this study, but it is unclear what the clinical relevance of this is. In one other study using whole cell pertussis vaccine the responses to PT were considerably higher (see study 011, assessed in the original MAA, and FUM 008 currently under assessment). The low responses to pertussis causes some concern, but considering that this phenomenon has not been seen in other studies no further action is required. Several studies using acellular pertussis vaccines have evaluated the responses to concomitantly administered pertussis vaccines, but they do not confirm the results of this study.

- ***Safety results***

Local Reactions

During the 4-day reactogenicity period after each vaccine administration, the numbers and percentages of subjects reporting local reactions were comparable between the 13vPnC and 7vPnC groups and there were no significant differences between the groups for individual reactions. At least 1 local reaction was reported for 53.7% to 61.4% of subjects in the 13vPnC group and for 51.5% to 63.5% of subjects in the 7vPnC group after the 3 infant series doses, and for 68.8% and 54.7% of subjects in the 13vPnC and 7vPnC groups, respectively, after the toddler dose. In both vaccine groups, most local reactions were mild or moderate in severity. The most frequent local reaction was local tenderness. Significant local tenderness was reported by 14% or fewer in either vaccine group after the infant series and 18.3% or fewer after the toddler dose; however, the duration of any tenderness was 2.4 days or less in the 13vPnC and 7vPnC groups.

No severe swelling or redness at the injection site was reported. Generally, the mean duration for any local reaction after any dose was 1 to 2 days with most reactions reported on the first 2 days after study vaccine administration and declining thereafter.

Systemic Events

The numbers and percentages of subjects reporting systemic events were comparable between the 13vPnC and 7vPnC groups and few differences were noted between groups for individual events. Few subjects reported fever during the 4-day reactogenicity period after each vaccine administration and most cases of fever were mild in severity (38.0°C to 39.0°C). Severe fever (>40°C) was reported in 1 subject in each group after dose 3 of the infant series and was reported in 1 subject in the 13vPnC group after the toddler dose. Irritability was the most frequently reported systemic event after each dose. Overall, most systemic events, as well as antipyretic medication use, were reported on the first 2 days after study vaccine administration and the mean durations of individual events did not exceed 2.9 days across groups.

Spontaneously Reported Adverse Events

The percentages of subjects reporting AEs were similar in the 13vPnC and 7vPnC groups and few differences were noted between the groups. For the 13vPnC and 7vPnC groups, respectively, at least 1 AE was reported in 85.9% and 86.4% of subjects during the infant series; 11.0% and 7.4% of subjects after the infant series; and 44.5% and 41.0% of subjects after the toddler dose. Most AEs reported were consistent with illnesses considered common in this age group and were characterized as mild in severity. AEs categorized as infections and infestations were reported most frequently in both vaccine groups at all doses. During the infant series, 1 subject in the 7vPnC group had a life-threatening AE of intussusception, which resolved and was not considered related to study vaccine. No other life-threatening AEs were reported.

Most SAEs reported were consistent with illnesses considered common in this age group and were most frequently categorized as infections and infestations. No significant differences between vaccine groups were noted for any individual SAEs. All SAEs, except for 2 that occurred during the infant series (HHEs), were considered unrelated to study vaccine administration and all resolved without sequelae.

One (1) subject died during the study of sudden infant death syndrome (SIDS) after receiving an HBV dose at visit 1 during the infant series; this subject did not receive pneumococcal conjugate vaccine. This event was assessed as not related to vaccine administration. There were no other subject deaths during the study.

Six (6) subjects were withdrawn from the study because of AEs. Five (5) subjects (2 in the 13vPnC group and 3 in the 7vPnC group) were withdrawn from the study during the infant series because of AEs: 4 subjects for the SAE HHE and 1 subject for the SAE grand mal convulsion. The HHE rate was similar to the rates reported after vaccination with DTP-Hib alone. One (1) subject in the 7vPnC group was withdrawn from the study during the period after the infant series because of the SAE congenital hydrocephalus. No subjects were withdrawn from the study after the toddler dose.

Assessor's comment: The safety results did not reveal any unexpected safety signal. The frequency of local and systemic adverse events was similar to what has been reported previously. It should be noted that an interim report for study 6096A1-012 (CSR-78828) was submitted to the EMA on 5 May 2010 as part of the Type II variation procedure EMEA/H/C/1104/II/016. The purpose of this Type II variation was to move the "hypotonic-hyporesponsive episode" (HHE) undesirable effect from the

Prevenar clinical trial ADR section to the Prevenar 13 clinical trial ADR section of the SmPC and in the PL. This change was based on the trial findings reported after the infant series. The MAH committed on 18 May 2010 (as part of the responses to the validation issues) to submit the full CSR describing the trial findings from both the infant series and toddler dose in the present Article 46 submission. No further regulatory action is considered necessary.

6096A1-3004: A phase 3, randomized, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of a 13- valent pneumococcal conjugate vaccine in healthy infants given with routine pediatric vaccinations in Taiwan

- **Description**

Wyeth Lederle Vaccines S.A. states that study 6096A1-3004 is part of the global clinical development program for the use of Prevenar 13 in infants and were conducted to support licensure in Taiwan.

- **Methods**

- ***Objective(s)***

The primary objective of the study was to describe the pneumococcal immune responses induced by 13vPnC relative to the pneumococcal immune responses induced by 7vPnC when measured 1 month after the infant series. The secondary objective of the study was to describe the pneumococcal immune responses induced by 13vPnC relative to the immune responses induced by 7vPnC when measured 1 month after the toddler dose. The safety objective of the study was to evaluate the acceptability of the safety profile of 13vPnC as measured by the incidence rates of local reactions, systemic events, and adverse events (AEs).

- ***Study design***

This was a parallel-group, randomized, active-controlled, double-blind, multicenter trial to describe the immunogenicity, safety, and tolerability of 13vPnC compared with 7vPnC in healthy infants, when given with routine pediatric vaccinations in Taiwan.

- ***Study population /Sample size***

Approximately 168 subjects (84 subjects per group) were to be enrolled in this study in order to achieve 75 evaluable subjects per group at 2 sites in Taiwan.

Sample size estimation was based on the proportion of responders in the 13vPnC dose group. Data from Wyeth study 6096A1-003 were used for the proportion of responders for pneumococcal serotypes. The study was powered to allow estimation of the proportion of responders to within ±7.3% precision for each vaccine group. Assuming a drop out rate of at most 10%, 168 subjects overall should be enrolled to ensure 150 subjects are evaluable.

- ***Treatments***

Subjects were to be randomly assigned in a 1:1 ratio to receive either 13vPnC or 7vPnC administered at 2, 4, and 6 months of age (infant series) and 15 months of age (toddler dose). Routine pediatric combination vaccines containing diphtheria, tetanus, and acellular pertussis (DTaP); inactivated poliovirus (IPV); Haemophilus influenzae type b (Hib); and hepatitis B virus (HBV) were to be given; DTaP-IPV-Hib was to be administered at 2 and 4 months of age (infant series); DTaP-IPV-Hib-HBV was to be administered at 6 months of age.

- ***Outcomes/endpoints***

Immunogenicity assessment methods: Blood samples (approximately 5 mL) were collected 27 to 56 days after dose 3 of the infant series, and 27 to 56 days after the toddler dose. All samples were analyzed using ELISA to determine serum concentrations of anticapsular polysaccharide IgG for each of the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F).

Assessor's comment: OPA responses were not assayed in this study, which is a limitation, and precludes a full assessment of the immune responses.

Safety assessment methods: Safety measurements included evaluation of local reactions, systemic events (including fever and use of antipyretic medications), and adverse events. For days 1 to 4 after each vaccination, the parent(s)/guardian(s) were to record local reactions and systemic events daily in an e-diary. For any local reaction or systemic event that persisted on day 4 an end date was to be recorded.

Local Reactions: Local reactions included redness, swelling, and tenderness at the injection site and were recorded for **4 days** after each vaccination. Tenderness was recorded as none, present, or interfered with limb movement. For redness and swelling, the parent/legal guardian measured the size of the local reaction at its largest diameter with a caliper and recorded the measurement in caliper units (1 to 14, or 14+). One (1) caliper unit represents 0.5 cm. In case a calliper measurement was between 2 values, the higher value was to be reported. If the measurement of redness or swelling was greater than 14 caliper units (greater than 7.0 cm), the subject was to be seen by study personnel. The measurements for redness and swelling were categorized as mild (0.5 to 2.0 cm), moderate (2.5 to 7.0 cm), or severe (greater than 7.0 cm) for analysis.
Systemic Events: Tympanic temperature was collected daily at bedtime for 4 days and at any time during days 1 through 4 if fever was suspected. Fever was defined as tympanic temperature of greater than or equal to 38.0°C (100.4°F). In the event of a fever, temperature was collected daily until the fever had resolved (1 day of temperature less than 38.0°C). For analysis, the severity of fever was categorized as follows: absent <38.0°C; mild ≥38.0°C to ≤39.0°C; moderate >39.0°C to ≤40.0°C; and severe >40.0°C. The use of antipyretic medications to prevent or treat symptoms was also recorded daily for 4 days. Other systemic events recorded in the e-diary as present or absent included decreased appetite, irritability, increased sleep, and decreased sleep.

Adverse Events: After each vaccination, clinic personnel observed the subject for at least 30 minutes for any significant, acute reactions. Any AEs noted in this observation period were recorded in the CRF. In addition, AEs were identified based on clinical evaluation at the time of a study visit, or from information obtained by asking the parents/legal guardians. Signs and symptoms were recorded using standard medical terminology. Both AEs and SAEs had to be recorded on both subject's source documents and CRFs.

- ***Statistical Methods***

Immunogenicity: The primary immunological comparisons were the pneumococcal immune responses in subjects receiving 13vPnC relative to the immune responses in subjects receiving 7vPnC. All statistical analyses were descriptive. For the immunogenicity analyses, 2 analysis populations were defined: evaluable infant immunogenicity population and all-available infant immunogenicity population.

The primary endpoint for each pneumococcal serotype was the proportion of subjects achieving serotype-specific IgG concentrations ≥0.35 µg/mL (ie, the proportion of responders) measured 1 month after dose 3 of the infant series. Exact, unconditional, 2-sided, 95% confidence intervals (CIs) on the proportion were calculated. For each of the pneumococcal serotypes, exact, unconditional, 2-sided, 95% CIs on the difference in proportions (13vPnC – 7vPnC) were calculated. In addition for each of the 6 additional serotypes, exact, unconditional, 2-sided, 95% CIs on the difference in proportions were calculated using the serotype with the lowest proportion among the 7 common serotypes in the 7vPnC group as the reference group (13vPnC – 7vPnC reference).

The pneumococcal serotype IgG concentrations were logarithmically transformed for analysis. Within each vaccine group and for each antibody concentration separately, geometric means of the antibody concentrations from each blood draw were calculated. Two (2)-sided, 95% CIs were constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using the Student t distribution. In addition, for each of the serotypes, the ratios of the geometric mean concentrations ([GMCs] 13vPnC/7vPnC) with their 2-sided, 95% CIs were calculated. For the 6 additional serotypes, an additional comparison was made using the serotype with the lowest GMC among the 7 common serotypes in the 7vPnC group as the reference value (13vPnC/7vPnC reference).

The empirical reverse cumulative distribution curves (RCDCs) were presented graphically by vaccine group for each of the serotype-specific pneumococcal concentrations.

Safety: The incidence of local reactions, systemic events, and AEs were summarized separately for each dose of pneumococcal vaccine (dose 1, dose 2, dose 3, and the toddler dose). The proportions of subjects with local reactions and systemic events reported on any day within the 4-day period after

each vaccination were summarized for each type of event. Local reactions were also summarized according to severity (mild, moderate, severe); and summary statistics for the duration (in days) of both local and systemic reactions were reported.

For summarization, AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA). AE summaries show, for each MedDRA preferred term, the number and percentage of subjects experiencing at least 1 event and the number of events. SAEs were summarized for the infant series rather than for each vaccination separately. Additional summaries by AE severity and by relationship to test article were also produced.

➢ Results

- ***Recruitment/ Number analysed***

Approximately 168 subjects (84 subjects per group) were to be enrolled in this study in order to achieve 75 evaluable subjects per group at 2 sites in Taiwan. A total of 169 subjects were screened, and 168 subjects were enrolled. One (1) subject whose parents/legal guardians consented to participate was screened only and was not randomized. Four (4) subjects (2.4%) were withdrawn from the study during the infant series, 1 subject was randomized but not vaccinated, thus only 167 subjects (99.4%) received dose 1; after receiving dose 1, 3 subjects were withdrawn at the request of the parents/legal guardians, thus 164 subjects (97.6%) who received both dose 2 and dose 3 completed the infant series, 80 (95.2%) in the 13vPnC group and 84 (100.0%) in the 7vPnC group.

No subjects were withdrawn after the infant series. Thus, 164 subjects received the toddler dose of 13vPnC (n=80) or 7vPnC (n=84). These subjects constituted the safety population for the toddler dose, and all completed the toddler dose blood draw. Of the 84 subjects randomized to receive 13vPnC, 80 were included in the all-available toddler immunogenicity population and 79 were included in the evaluable toddler immunogenicity population. In the 7vPnC group, all 84 subjects randomized to receive 7vPnC were included in the all-available and evaluable toddler immunogenicity populations. In the 13vPnC group, 4 subjects were excluded from the all-available toddler immunogenicity populations because they had no post–toddler assay result for any pneumococcal serotype (these 4 subjects were withdrawn during the infant series at the request of the parent[s]/legal guardian[s]); 1 additional subject was also excluded from the evaluable toddler immunogenicity population because the subject was >486 days old on the day of the toddler dose.

- ***Baseline data***

The 2 vaccine groups were similar with respect to sex, race, ethnicity, age at enrolment, and weight at enrolment. The proportion of male subjects was slightly higher in the 13vPnC group (52.4%) than in the 7vPnC group (44.0%). All subjects (100.0%) were Asian and of non-Hispanic and non-Latino ethnicity.
The mean age (±standard deviation [SD]) at enrolment was 2.2 (±0.3) months and the mean weight at enrolment was 5.5 (±0.8) kg for all subjects in both groups.

- Efficacy results

Proportion of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL
Infant series
For the evaluable infant immunogenicity population, for the 7 common serotypes the proportions of responders after dose 3 of the infant series were comparable and ranged from 95.0% to 100% in the 13vPnC group and was overall 100% in the 7vPnC group (Table 9-3). For the 6 additional serotypes unique to 13vPnC the proportion of responders in the 13vPnC group ranged from 97.5% to 100.0%; in the 7vPnC group responder rates for serotypes 1, 3, and 7F were 2.4%, for serotype 5 was 61.5%, for serotype 6A was 77.1%, and for serotype 19A was 100.0%.
For the comparison of 13vPnC relative to 7vPnC, the difference in the proportion of responders, between the 2 vaccine groups was calculated and presented in Table 9-3. For the 7 common serotypes the difference in the proportion of responders, ranged from -5.0 for serotype 23F to 0.0 for serotypes 6B, 14, and 18C. For the 6 additional serotypes the difference ranged from 0.0 for serotype 19A to 97.6 for serotype 7F.
For the 6 additional serotypes, when the serotype with the lowest proportion among the 7 common serotypes in the 7vPnC group as the reference value is used for comparison the difference in

proportions of responders between the 2 vaccine groups for the 6 additional serotypes ranged from -2.5 for serotype 3 to 0.0 for serotypes 6A, 7F, and 19A.

Table 9-3: Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After Dose 3 of the Infant Series – Evaluable Infant Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC				7vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	80	79	98.8	(93.2, 100.0)	83	83	100.0	(95.7, 100.0)	-1.2	(-6.8, 3.3)
6B	80	80	100.0	(95.5, 100.0)	83	83	100.0	(95.7, 100.0)	0.0	(-4.6, 4.3)
9V	80	79	98.8	(93.2, 100.0)	83	83	100.0	(95.7, 100.0)	-1.2	(-6.8, 3.3)
14	80	80	100.0	(95.5, 100.0)	83	83	100.0	(95.7, 100.0)	0.0	(-4.6, 4.3)
18C	80	80	100.0	(95.5, 100.0)	83	83	100.0	(95.7, 100.0)	0.0	(-4.6, 4.3)
19F	80	79	98.8	(93.2, 100.0)	83	83	100.0	(95.7, 100.0)	-1.2	(-6.8, 3.3)
23F	80	76	95.0	(87.7, 98.6)	83	83	100.0	(95.7, 100.0)	-5.0	(-12.3, -0.3)
Additional										
1	80	79	98.8	(93.2, 100.0)	83	2	2.4	(0.3, 8.4)	96.3	(89.4, 99.2)
3	80	78	97.5	(91.3, 99.7)	83	2	2.4	(0.3, 8.4)	95.1	(87.7, 98.6)
5	80	79	98.8	(93.2, 100.0)	78	48	61.5	(49.8, 72.3)	37.2	(26.2, 48.9)
6A	80	80	100.0	(95.5, 100.0)	83	64	77.1	(66.6, 85.6)	22.9	(14.4, 33.4)
7F	80	80	100.0	(95.5, 100.0)	83	2	2.4	(0.3, 8.4)	97.6	(91.6, 99.7)
19A	80	80	100.0	(95.5, 100.0)	82	82	100.0	(95.6, 100.0)	0.0	(-4.6, 4.5)

a. N = number of subjects with a 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 based on the observed proportion of subjects.
d. Difference in proportions, 13vPnC–7vPnC reference, expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, 13vPnC–7vPnC reference, expressed as a percentage.

Assessor's comments: The frequencies of subjects achieving a pneumococcal IgG concentration ≥0.35 µg/ml is not significantly different from what has been seen in other studies. The responses to serotype 6B are generally higher than what has been seen in several other studies from other locations previously.

Toddler dose

For the 7 common serotypes, the 2 vaccine groups had similar proportions of subjects achieving IgG concentrations ≥0.35 µg/mL after the toddler dose. The proportions of responders to the 7 common serotypes in the evaluable toddler immunogenicity population ranged from 98.7% to 100% in the 13vPnC group and were 100% for all serotypes in the 7vPnC group (Table 9-2). The difference in the proportion of responders (13vPnC – 7vPnC) was -1.3 for serotypes 4, 9V, and 19F and 0.0 for serotypes 6B, 14, 18C, and 23F For the 6 additional serotypes unique to 13vPnC, the proportion of responders in the 13vPnC group ranged from 96.2% to 100.0%; in the 7vPnC group, responder rates for serotypes 1, 3, and 7F ranged from 5.0% to 13.8%, for serotype 5 it was 90.4%, for serotype 6A it was 100.0%, and for serotype 19A it was 98.8%. The difference in the proportion of responders ranged from 82.5% to 95.0% for serotypes 1, 3, and 7F and from 0% to 9.6% for serotypes 5, 6A, and 19A (Table 9-2). For each of the 6 additional serotypes, the difference in the proportion of responders between the 2 vaccine groups was also calculated using the serotype with the lowest proportion of responders among the 7 common serotypes in the 7vPnC group as the reference value. Thus calculated, the difference in the proportion of responders was 0.0 for 5 of the 6 additional serotypes; for serotype 3, the difference in the proportion of responders was -3.8.

Table 9-2: Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After the Toddler Dose - Evaluable Toddler Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC				7vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	79	78	98.7	(93.1, 100.0)	84	84	100.0	(95.7, 100.0)	-1.3	(-6.9, 3.1)
6B	79	79	100.0	(95.4, 100.0)	84	84	100.0	(95.7, 100.0)	0.0	(-4.6, 4.4)
9V	79	78	98.7	(93.1, 100.0)	84	84	100.0	(95.7, 100.0)	-1.3	(-6.9, 3.1)
14	79	79	100.0	(95.4, 100.0)	84	84	100.0	(95.7, 100.0)	0.0	(-4.6, 4.4)
18C	79	79	100.0	(95.4, 100.0)	84	84	100.0	(95.7, 100.0)	0.0	(-4.6, 4.4)
19F	79	78	98.7	(93.1, 100.0)	84	84	100.0	(95.7, 100.0)	-1.3	(-6.9, 3.1)
23F	79	79	100.0	(95.4, 100.0)	84	84	100.0	(95.7, 100.0)	0.0	(-4.6, 4.4)
Additional										
1	79	79	100.0	(95.4, 100.0)	80	4	5.0	(1.4, 12.3)	95.0	(87.7, 98.6)
3	79	76	96.2	(89.3, 99.2)	80	11	13.8	(7.1, 23.3)	82.5	(72.0, 90.1)
5	79	79	100.0	(95.4, 100.0)	83	75	90.4	(81.9, 95.7)	9.6	(3.8, 18.1)
6A	79	79	100.0	(95.4, 100.0)	84	84	100.0	(95.7, 100.0)	0.0	(-4.6, 4.4)
7F	79	79	100.0	(95.4, 100.0)	80	5	6.3	(2.1, 14.0)	93.8	(86.0, 97.9)
19A	79	79	100.0	(95.4, 100.0)	84	83	98.8	(93.5, 100.0)	1.2	(-3.4, 6.5)

Abbreviations: CI = confidence interval; IgG = immunoglobulin G.

a. N = number of subjects with a determinate IgG antibody 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 CI based on the observed proportion of subjects.
d. Difference in proportions, 13vPnC–7vPnC reference, expressed as a percentage.
e. Exact 2-sided CI for the difference in proportions, 13vPnC–7vPnC reference, expressed as a percentage.

Assessor's comment: The responses following the toddler dose are well within the range that has been seen in previous studies.

Pneumococcal IgG Geometric Mean Concentrations
Infant series
In the evaluable infant immunogenicity population, IgG GMCs for the 7 common serotypes were generally lower in the 13vPnC group and ranged from 1.93 (serotype 23F) to 9.76 µg/mL (serotype 14), compared with 2.92 (serotype 9V) to 11.59 µg/mL (serotype 14) in the 7vPnC group; for the 6 additional pneumococcal serotypes IgG GMCs were higher in the 13vPnC group and ranged from **1.20 (serotype 3**) to 4.57 µg/mL (serotype 6A), compared with 0.02 (serotype 1) to 2.46 µg/mL (serotype 19A) in the 7vPnC group (Table 9-6).

For the comparison of 13vPnC relative to 7vPnC, the GMC ratio (13vPnC/7vPnC) was calculated for each serotype and summarized by vaccine group (Table 9-6). For the 7 common serotypes the ratio ranged from 0.59 for serotype 23F to 0.91 for serotype 6B. For the 6 additional serotypes the ratio ranged from 1.50 for serotype 19A to 202.58 for serotype 1.

Table 9-6: Comparison of Pneumococcal IgG GMCs (µg/mL) After Dose 3 of the Infant Series – Evaluable Infant Immunogenicity Population

	Vaccine Group (as Randomized)							
	13vPnC			7vPnC				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	80	2.89	(2.45, 3.42)	83	4.64	(4.00, 5.37)	0.62	(0.50, 0.78)
6B	80	4.37	(3.58, 5.33)	83	4.82	(4.09, 5.67)	0.91	(0.70, 1.17)
9V	80	1.97	(1.70, 2.27)	83	2.92	(2.55, 3.34)	0.67	(0.55, 0.82)
14	80	9.76	(8.34, 11.43)	83	11.59	(9.79, 13.71)	0.84	(0.67, 1.06)
18C	80	2.39	(2.04, 2.82)	83	3.07	(2.64, 3.56)	0.78	(0.63, 0.97)
19F	80	3.60	(3.00, 4.32)	83	4.77	(4.17, 5.47)	0.75	(0.60, 0.94)
23F	80	1.93	(1.56, 2.37)	83	3.25	(2.78, 3.80)	0.59	(0.46, 0.77)
Additional								
1	80	4.14	(3.45, 4.96)	83	0.02	(0.02, 0.02)	202.58	(157.04, 261.32)
3	80	1.20	(1.00, 1.45)	83	0.05	(0.04, 0.06)	24.11	(18.46, 31.49)
5	80	2.47	(2.09, 2.92)	78	0.43	(0.35, 0.53)	5.69	(4.37, 7.41)
6A	80	4.57	(3.92, 5.34)	83	0.79	(0.63, 0.99)	5.82	(4.42, 7.67)
7F	80	3.67	(3.14, 4.29)	83	0.04	(0.03, 0.05)	96.10	(75.60, 122.17)
19A	80	3.69	(3.20, 4.24)	82	2.46	(2.13, 2.84)	1.50	(1.23, 1.83)

a. n = Number of subjects with a determinate IgG concentration to the given 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–7vPnC reference.
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–7vPnC reference).

Assessor's comments: For the 7 common serotypes the GMCs were generally slightly lower in the 13vPnC group than in the 7vPnC group, which is on accordance with previously reported studies. The levels are well within the previously reported GMC from other studies.

Toddler dose
For the 7 common serotypes, GMCs ranged from 3.18 µg/mL for serotype 9V to 13.62 µg/mL for serotype 6B in the 13vPnC group and from 3.88 µg/mL for serotype 9V to 13.28 µg/mL for serotype 6B in the 7vPnC group. For the 6 additional serotypes, the GMCs were higher in the 13vPnC group. GMCs ranged from 1.29 µg/mL for serotype 3 to 11.55 µg/mL for serotype 6A in the 13vPnC group and from 0.03 µg/mL for serotype 1 to 3.79 µg/mL for serotype 6A in the 7vPnC group (Table 9-4).

For the comparison of 13vPnC relative to 7vPnC, the GMC ratios were calculated for each serotype (Table 9-4). For the 7 common serotypes, the GMC ratios ranged from 0.64 for serotype 4 to 1.09 for serotype 19F. For the 6 additional serotypes, the GMC ratios ranged from 3.05 for serotype 6A to 303.73 for serotype 1.

For the 6 additional serotypes, the GMC ratios were also calculated using the serotype with the lowest GMC among the 7 common serotypes in the 7vPnC group as the reference value (in this study, serotype 9V had the lowest GMC, 3.88). Thus calculated, the GMC ratio for the 6 additional serotypes ranged from 0.33 for serotype 3 to 2.98 for serotype 6A.

Table 9-4: Comparison of Pneumococcal IgG GMCs (µg/mL) After the Toddler Dose - Evaluable Toddler Immunogenicity Population

	Vaccine Group (as Randomized)							
	13vPnC			7vPnC				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	79	4.06	(3.34, 4.93)	84	6.34	(5.26, 7.65)	0.64	(0.49, 0.84)
6B	79	13.62	(11.08, 16.73)	84	13.28	(10.87, 16.21)	1.03	(0.77, 1.36)
9V	79	3.18	(2.66, 3.80)	84	3.88	(3.27, 4.60)	0.82	(0.64, 1.05)
14	79	8.17	(6.53, 10.22)	84	12.04	(9.90, 14.63)	0.68	(0.51, 0.91)
18C	79	3.67	(3.00, 4.49)	84	4.87	(4.01, 5.90)	0.75	(0.57, 0.99)
19F	79	8.07	(6.58, 9.90)	84	7.41	(6.16, 8.92)	1.09	(0.83, 1.43)
23F	79	5.51	(4.46, 6.81)	84	7.97	(6.55, 9.68)	0.69	(0.52, 0.92)
Additional								
1	79	7.62	(6.30, 9.21)	80	0.03	(0.02, 0.03)	303.73	(213.63, 431.83)
3	79	1.29	(1.09, 1.53)	80	0.12	(0.09, 0.16)	10.65	(7.77, 14.62)
5	79	4.57	(3.87, 5.39)	83	0.95	(0.80, 1.13)	4.79	(3.78, 6.08)
6A	79	11.55	(9.66, 13.81)	84	3.79	(3.01, 4.76)	3.05	(2.28, 4.08)
7F	79	5.91	(4.95, 7.06)	80	0.06	(0.04, 0.07)	105.00	(75.60, 145.84)
19A	79	8.82	(7.45, 10.43)	84	1.98	(1.69, 2.32)	4.45	(3.54, 5.60)

Abbreviations: CI = confidence interval; GMC = geometric mean concentration; IgG = immunoglobulin G.

a. n = Number of subjects with a determinate IgG antibody concentration to the given serotype.
b. GMCs were calculated using all subjects with available data for the specified blood draw.
c. 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 to 7vPnC reference.
e. 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–7vPnC reference).

Assessor's comment: The GMCs are generally in line with what has been reported following the toddler dose previously.

- ***Safety results***

Local Reactions

The percentages of subjects reporting local reactions were comparable between the 13vPnC and 7vPnC groups after the infant series and the toddler dose. At least 1 local reaction was reported for 33.3% to 51.3% of subjects in the 13vPnC group and for 30.4% to 51.9% of subjects in the 7vPnC group after the 3 infant series doses, and for 25.8% and 30.7% of subjects in the 13vPnC and 7vPnC groups, respectively, after the toddler dose. In both vaccine groups, most local reactions were mild or moderate in severity and occurred on days 1 and 2. Significant local tenderness was reported by 9.3% or fewer subjects in either vaccine group after dose 1 and by 2.9% or fewer subjects in either vaccine group after dose 2 and 3 in the infant series. No subject in either vaccine group reported severe swelling or severe redness at the injection site after any dose in the infant series. After the toddler dose, no significant local tenderness and no severe swelling or severe redness at the injection site were reported for any subject in either vaccine group. There were few significant differences between the 2 vaccine groups in the incidence of any local reactions after the infant series, and none after the toddler dose.

Systemic Events

The percentage of subjects reporting systemic events was generally similar in the 2 vaccine groups after each dose. The overall percentage of subjects reporting 1 or more systemic events within 4 days of vaccination ranged from 76.4% to 97.6% in the 13vPnC group and from 75.0% to 91.7% in the 7vPnC group, across the 3 doses in the infant series. After the toddler dose, 1 or more systemic events were reported by 54.2% and 61.0% of subjects in the 13vPnC and 7vPnC groups, respectively. There were no statistically significant differences between the 2 vaccine groups in the incidence of any systemic events. The most commonly reported systemic events were mild fever, irritability, and decreased appetite. Most reports of fever were mild in severity. Only 1 subject (1.6%) in the 7vPnC

group reported severe fever (>40°C), after receiving dose 3. With few exceptions, most systemic events were reported on the first 2 days after each vaccination. For the 13vPnC and 7vPnC groups, respectively, mean durations of individual systemic events did not exceed 3.3 and 2.5 days after the infant series, or 2.8 days and 3.5 days after the toddler dose.

Spontaneously Reported Adverse Events
The percentages of subjects reporting AEs were similar in the 13vPnC and 7vPnC groups and few differences were noted between the groups. For the 13vPnC and 7vPnC groups, respectively, at least 1 AE was reported in 72.3% and 79.8% of subjects during the infant series; 25.3% and 25.0% of subjects after the infant series; and 26.3% and 19.0% of subjects after the toddler dose. Most of the AEs were illnesses that could be expected in infants and toddlers. The most frequent categories of AEs were infections and infestations and skin and subcutaneous tissue disorders. The individual AEs with the highest incidences were upper respiratory tract infections, eczema, and contact dermatitis. There was only 1 possibly related AE of alopecia after dose 1 in the study.

The SAEs reported were consistent with illnesses considered common in infants and toddlers and were most frequently categorized as infections and infestations. None were considered related to the study vaccine. No deaths or life-threatening events were reported in this study. No subject was withdrawn from the study because of an AE.

Assessor's comment: No new safety signals were detected in this study, and the pattern of adverse events was similar to what has been seen in previous studies. No further regulatory action is required based on safety data from this study.

3. Discussion on clinical aspects
The two studies presented in this application are part of the global clinical development program for the use of Prevenar 13 in infants and were conducted to support licensure in Brazil and in Taiwan, respectively. The vaccination schedule used was the same as in previously submitted studies. The immunogenicity and safety results of both studies are well in line with what has been previously reported in other studies. The only unexpected results were the low PT responses in study 012, but considering the number of studies which do not confirm these results, and the fact that the results were very similar in the two study groups, no further regulatory action is required based on these results.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The MAH's conclusions of the study are endorsed. The results of this clinical study are well in line with previously reported results from other clinical studies. Therefore, the submitted data does not necessitate any changes to the current SPC, and no type II variation will be needed.

- **Recommendation**

X Fulfilled –

No further action required

☐ **Not fulfilled:**

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable.