EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 February 2015
EMA/135529/2015
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 036

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

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I. INTRODUCTION

On, March 1, 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 study(ies)

13vPnC contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to nontoxic diphtheria toxin cross-reactive material 197 (CRM_{197}). The vaccine is formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B per 0.5-mL dose. The final formulation contains 5 mM succinate buffer, 0.02% polysorbate 80, with 0.125 mg of aluminium as aluminium phosphate per 0.5-mL dose.

Clinical aspects

1. Introduction
Wyeth has developed Prevenar 13, a 13-valent pneumococcal conjugate vaccine (13vPnC), as a successor to the currently registered vaccine, Prevenar, for use in infants and young children to prevent pneumococcal disease (invasive pneumococcal disease [IPD], nonbacteremic pneumonia, and acute otitis media [AOM]) caused by the 13 pneumococcal serotypes contained in the vaccine. Prevenar is a 7-valent pneumococcal conjugate vaccine (7vPnC) that contains serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. In addition to these serotypes, 13vPnC contains serotypes 1, 3, 5, 6A, 7F, and 19A.

The MAH submitted final reports for:

Study 6096A1-3003: A Phase 3, Open-Label Trial evaluating the Safety, Tolerability, and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants in Japan. Final infant and toddler report.

Study 6096A1-3008: A Phase 3, Randomized, Active-Controlled, Doubleblind Trial Evaluating the Safety, Tolerability, and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given With Routine Pediatric Vaccinations in Canada
Final infant and toddler report.

Studies 6096A1-3003 and 6096A1-3008 are part of the global clinical development program for the use of Prevenar 13 in infants and were conducted to support licensure in Japan and in Canada, respectively.

2. Clinical studies

Study 6096A1-3003: A Phase 3, Open-Label Trial evaluating the Safety, Tolerability, and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants in Japan. Final infant and toddler report.

Description

- **Methods**
  - Objective(s)

The primary objective of this study was to assess the immune response to the 13 pneumococcal conjugates (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) induced by 13vPnC when measured 1 month after the infant series.

The safety objective 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).

Secondary objectives were as follows:

- To assess the immune response to the 13 pneumococcal conjugates (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) induced by 13vPnC when measured 1 month after the toddler dose.
- To evaluate the comparability/superiority of immunogenicity data after the infant series and after the toddler dose between this study in Japanese infants (6096A1-3003-JA) and the pivotal licensure study in the United States (6096A1-004).

- Study design

This was an open-label, single-group, multicenter trial to evaluate the safety, tolerability, and immunogenicity of 13vPnC administered SC to Japanese infants. No concomitant vaccines were administered.

- Study population /Sample size

Approximately 165 subjects were to participate in this study at 20 to 30 sites to achieve a total of 140 evaluable subjects.

- Treatments

All subjects were to be vaccinated with open-label 13vPnC in a schedule that included a 3-dose infant series and a toddler (booster) dose. The protocol stated that it was preferable for infants to be vaccinated at 2, 4, and 6 months of age. However, the first vaccination (dose 1) could be given at any time between 2 and 6 months of age, with dose 2 given at least 28 days after dose 1, dose 3 given at least 28 days after dose 2, and with the infant series being completed before 12 months of age. The toddler dose could be administered at any time between 12 and 15 months of age, but at least 60 days after dose 3.

- Outcomes/endpoints

Blood samples (5 mL) were to be obtained from all subjects at 4 timepoints: before dose 1, one month (28 to 42 days) after dose 3, before the toddler dose, and one month (28 to 42 days) after the toddler dose. For all subjects and for each of the 4 blood samples, serotype-specific immunoglobulin G (IgG) concentrations were to be determined for each of the 13 pneumococcal serotypes.

Parent(s)/legal guardian(s) were asked to monitor and record in an electronic diary (e-diary) the subject's local reactions and systemic events (including the use of antipyretic medication to treat and prevent symptoms) for 7 days after each vaccination. AEs were to be collected and recorded on the CRF based on ancillary information recorded by the parents/legal guardians in a paper diary, clinical evaluation during a study visit, and verbal questioning of the parent/legal guardian about the child's health since the last visit. AEs were collected from the signing of the ICF to visit 4 (the visit for the postinfant series blood draw) and from visit 5 (toddler dose) to visit 6. At visit 5 any newly diagnosed chronic medical conditions or serious adverse events (SAEs) since visit 4 were to be recorded. All SAEs were recorded from the signing of the ICF to visit 6.

- 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 endpoints was based on the World Health Organization (WHO) guideline for the pneumococcal serotypes.

The secondary endpoints for each of the pneumococcal serotypes were the proportion of subjects achieving a serotype-specific IgG concentration ≥0.35 µg/mL after the toddler dose, and the serotype-specific geometric mean IgG concentrations measured 1 month after the infant series, before the toddler dose, and 1 month after the toddler dose.

The comparison of interest was to evaluate the comparability of immunogenicity data 1 month after the infant series and 1 month after the toddler dose between this study in Japanese infants (6096A1-3003) and the pivotal licensure study in the United States (6096A1-004).

Unless specified otherwise, the following analyses were performed for each of the 13 pneumococcal serotypes, using data for both time points (infant series and toddler dose) and for both the evaluable immunogenicity populations and the all-available immunogenicity populations:

- *Proportion of Subjects Achieving Specified Concentrations of IgG*

These analyses were performed for the protocol-specified level of ≥0.35 µg/mL and also for the additional level of ≥0.15 µg/mL, which was specified in the SAP.
Values for the proportion of subjects achieving antibody concentrations ≥0.35 µg/mL in this study (3003) were compared with reference values from the pivotal US licensure study (004). For each of the pneumococcal serotypes, exact, unconditional, 2-sided 95% CIs on the difference in proportions (study 3003 – study 004) were computed using the procedure of Chan and Zhang, and using the standardized test statistic and gamma = 0.000001.

- *Geometric Mean Antibody Concentrations*

The geometric mean concentration (GMC) of serotype-specific IgG was calculated for each of the 13 pneumococcal serotypes at 4 timepoints: before and after the infant series, and before and after the toddler dose. Each concentration was logarithmically transformed for analysis. 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.

Values for IgG GMCs from this study (3003) were compared with values from the pivotal US study (004). For each of the 13 serotypes, the ratio of the GMCs (geometric mean ratio, GMR) was calculated, and the 95% CI was computed using the Student t distribution for the mean difference of the measures on the log scale (the GMC from study 3003 relative to the reference value from study 004).

- *Geometric Mean Fold Rise in Antibody Concentrations*

The geometric mean fold rise (GMFR) in the concentration of serotype-specific IgG was calculated for each of the 13 pneumococcal serotypes using data from the determinations made before the toddler dose and after the toddler dose. The GMFRs with 95% CIs were computed using the logarithmically transformed assay results and the Student t distribution.

In addition, the GMFRs from this study were compared with those from study 004. The ratio of the GMFRs and the corresponding 2-sided 95% CIs were calculated. The CIs were computed using the Student t distribution for the mean difference of the measures on the logarithmic scale (the value from study 3003 relative to the value from study 004). The mean difference of the log-transformed results is equivalent to the mean of the ratio of the logarithmic scale: log (x/y) = (log x) – (log y).

- *Reverse Cumulative Distribution Curves*

Results for IgG concentrations are presented graphically using reverse cumulative distribution curves (RCDCs). Only data for the evaluable immunogenicity populations are presented in RCDCs. Separate RCDCs were prepared for each of the 13 pneumococcal serotypes, for both the postinfant series and posttoddler dose determinations. To provide for comparison of data between studies, RCDCs for both study 3003 and study 004 are displayed on the same graph.

- *Safety analyses*

The safety endpoints were AEs, local reactions, and systemic events, including fever and the use of antipyretic medications to treat and prevent symptoms. Fever was defined as axillary temperature ≥37.5°C.

The incidences of local reactions, systemic events, and AEs were summarized separately for each dose of study vaccine (dose 1, dose 2, dose 3, and the toddler dose). AEs were also summarized for any time during the infant series (dose 1, 2, or 3).

The proportions of subjects with local reactions and systemic events reported on any day within the 7-day period after each vaccination were summarized for each type of event. These data were also summarized for just the first 4 days after vaccination, in order to provide data for comparison with data from others studies in which e-diary data were collected for only 4 days after each vaccination.

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

Summary tabulations of AEs were produced separately for solicited (e-diary) AEs and for unsolicited AEs, and additional tabulations are provided for all AEs combined (both solicited and unsolicited). 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 and the toddler dose, rather than for each vaccination separately. Additional summaries by AE severity and by relationship to study vaccine were also produced.

- **Results**

- Recruitment/ Number analysed

Approximately 165 subjects were to participate in this study, per protocol. A total of 193 subjects were screened and enrolled, and written informed consent was provided for all subjects. All 193 subjects received dose 1, and 190 (98.4%) received both dose 2 and dose 3. Five subjects (2.6%) were withdrawn from the study during the infant series, while 188 (97.4%) completed the infant series.
Three subjects (1.6%) were withdrawn from the study after completing the infant series but before receiving the toddler dose. A total of 185 subjects (95.9%) were vaccinated at the toddler dose, and all but 1 of these subjects completed the toddler dose.

- Demographics and other baseline characteristics

All subjects were Japanese, and 51.8% were male. The mean age at enrollment was 3.7 months, and the mean weight at enrollment was 6.7 kg. Demographic characteristics for the 176 subjects in the evaluable infant immunogenicity population in study 3003 were similar to those for all enrolled subjects. For these subjects, the mean age at dose 1 was 3.7 months, mean age at dose 2 was 5.1 months, and the mean age at dose 3 was 6.7 months. For the 178 subjects in the evaluable toddler immunogenicity population, the mean age at the toddler dose was 12.6 months. In comparison, in study 004, the mean age was 2.1 months at dose 1, 4.1 months at dose 2, and 6.1 months at dose 3.

- Immunogenicity results

Infant dose
Proportion of Subjects Achieving Prespecified Antibody Levels
In study 3003, the proportion of subjects achieving pneumococcal antibody concentrations ≥0.35 µg/mL 1 month after the infant series was 97.2% or higher for all 13 pneumococcal serotypes (Table 9-3). In study 004, the proportion of responders was 87.3% or higher for all serotypes except serotype 3, for which the proportion of responders was 63.5%. The proportion of responders was higher in study 3003 than in study 004 for all serotypes except serotype 19F (for which the proportion was 97.2% in study 3003 and 98.0% in study 004), and the difference between the studies was 11.0% or less for all serotypes except serotype 3 (difference of 36.5%). (Table 9-3). Results for the all-available infant immunogenicity population were similar to those observed for the evaluable infant population.

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/Study									
	13vPnC 6096A1-3003-JA				13vPnC 6096A1-004					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	176	176	100.0	(97.9, 100.0)	252	238	94.4	(90.9, 96.9)	5.6	(3.0, 9.2)
6B	176	173	98.3	(95.1, 99.6)	252	220	87.3	(82.5, 91.1)	11.0	(6.2, 15.9)
9V	176	176	100.0	(97.9, 100.0)	252	228	90.5	(86.2, 93.8)	9.5	(6.2, 13.8)
14	176	176	100.0	(97.9, 100.0)	251	245	97.6	(94.9, 99.1)	2.4	(0.2, 5.2)
18C	176	176	100.0	(97.9, 100.0)	252	244	96.8	(93.8, 98.6)	3.2	(1.0, 6.2)
19F	176	171	97.2	(93.5, 99.1)	252	247	98.0	(95.4, 99.4)	-0.9	(-4.6, 2.2)
23F	175	171	97.7	(94.3, 99.4)	252	228	90.5	(86.2, 93.8)	7.2	(2.6, 11.9)
Additional										
1	176	176	100.0	(97.9, 100.0)	252	241	95.6	(92.3, 97.8)	4.4	(2.0, 7.7)
3	176	176	100.0	(97.9, 100.0)	249	158	63.5	(57.1, 69.4)	36.5	(30.6, 42.9)
5	176	176	100.0	(97.9, 100.0)	252	226	89.7	(85.2, 93.1)	10.3	(6.9, 14.8)
6A	176	176	100.0	(97.9, 100.0)	252	242	96.0	(92.8, 98.1)	4.0	(1.6, 7.2)
7F	176	176	100.0	(97.9, 100.0)	252	248	98.4	(96.0, 99.6)	1.6	(-0.5, 4.0)
19A	176	176	100.0	(97.9, 100.0)	251	247	98.4	(96.0, 99.6)	1.6	(-0.5, 4.1)

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, 3003JA study – 004 study, expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, 3003JA study – 004 study, expressed as a percentage.

Proportion of Subjects Achieving an Additional Prespecified Antibody Level
In analyses of data for the additional antibody level of ≥0.15 µg/mL, the proportion of responders 1 month after the infant series in study 3003 was 100% for all serotypes except for serotype 19F (98.9%) and serotype 23F (98.3%); and in study 004 the proportion of responders was 92.4% or higher for all serotypes. The difference between the studies was greatest for serotype 3 (difference of 7.6%) and serotype 6B (difference of 6.0%).

Reverse Cumulative Distribution Curves
RCDCs showing the distribution of IgG responses for each of the 13 serotypes after the infant series were provided in the clinical study report. For all 13 serotypes, the RCDCs were higher along most of the curve for study 3003 as compared with study 004.

Pneumococcal IgG Geometric Mean Concentrations
In study 3003, GMCs for the 13 serotypes 1 month after the infant series ranged from 2.57µg/mL for serotype 23F to 6.97 µg/mL for serotype 19A, with the exception of serotype 14, for which the concentration was 14.69 µg/mL, more than twice that for any other serotype (Table 9-4). IgG concentrations were lower in study 004 for all 13 serotypes, ranging from 0.49 µg/mL for serotype 3 to 2.57 µg/mL for serotype 7F, with serotype 14 again being an outlier, with a serum concentration of 4.74 µg/mL. GMRs comparing data for study 3003 versus study 004 ranged from 1.72 for serotype 6A to 5.88 for serotype 3. Antibody GMCs for the 13 serotypes before the infant series ranged from a low of 0.03 µg/mL for serotype 4 to a high of 0.35 µg/mL for serotype 19A.

Table 9-4: Comparisons of Pneumococcal IgG GMCs (µg/mL) After Dose 3 of the Infant Series - Evaluable Infant Immunogenicity Population

	Vaccine Group / Study							
	13vPnC 6096A1-3003-JA			13vPnC 6096A1-004				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	176	6.76	(6.02, 7.59)	252	1.31	(1.19, 1.45)	5.16	(4.43, 6.00)
6B	176	4.77	(4.07, 5.59)	252	2.10	(1.77, 2.49)	2.27	(1.78, 2.90)
9V	176	3.39	(3.03, 3.78)	252	0.98	(0.89, 1.08)	3.45	(2.97, 4.02)
14	176	14.69	(13.26, 16.26)	251	4.74	(4.18, 5.39)	3.10	(2.60, 3.68)
18C	176	3.68	(3.27, 4.14)	252	1.37	(1.24, 1.52)	2.68	(2.29, 3.13)
19F	176	5.71	(4.90, 6.65)	252	1.85	(1.69, 2.04)	3.08	(2.60, 3.65)
23F	175	2.57	(2.21, 3.00)	252	1.33	(1.17, 1.51)	1.93	(1.58, 2.36)
Additional								
1	176	5.11	(4.48, 5.82)	252	2.03	(1.78, 2.32)	2.52	(2.08, 3.05)
3	176	2.87	(2.55, 3.24)	249	0.49	(0.43, 0.55)	5.88	(4.93, 7.01)
5	176	3.85	(3.42, 4.33)	252	1.33	(1.18, 1.50)	2.89	(2.43, 3.44)
6A	176	3.77	(3.35, 4.25)	252	2.19	(1.93, 2.48)	1.72	(1.44, 2.06)
7F	176	5.78	(5.19, 6.45)	252	2.57	(2.28, 2.89)	2.25	(1.91, 2.66)
19A	176	6.97	(6.25, 7.77)	251	2.07	(1.87, 2.30)	3.36	(2.88, 3.92)

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; 3003-JA study to 004 study.
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 (3003JA study – 004 study reference).

Toddler Dose

Proportion of Subjects Achieving Prespecified Antibody Levels

In study 3003, the proportion of subjects achieving antibody concentrations ≥0.35 µg/mL 1 month after the toddler dose was 98.9% or greater for all 13 serotypes. In study 004, the proportion of responders was 98.7% or greater for all serotypes except serotype 3, for which the proportion was 90.5% (Table 9-5). Data for the all-available infant immunogenicity population were similar (data were submitted but not shown in this AR).

Table 9-5: Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After the Toddler Dose - Evaluable Toddler Immunogenicity Population

	Vaccine Group/Study									
	13vPnC 6096A1-3003-JA				13vPnC 6096A1-004					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	178	178	100.0	(97.9, 100.0)	235	233	99.1	(97.0, 99.9)	0.9	(-1.2, 3.1)
6B	177	177	100.0	(97.9, 100.0)	234	233	99.6	(97.6, 100.0)	0.4	(-1.6, 2.4)
9V	178	178	100.0	(97.9, 100.0)	234	232	99.1	(96.9, 99.9)	0.9	(-1.2, 3.1)
14	178	178	100.0	(97.9, 100.0)	235	232	98.7	(96.3, 99.7)	1.3	(-0.8, 3.8)
18C	178	178	100.0	(97.9, 100.0)	236	233	98.7	(96.3, 99.7)	1.3	(-0.8, 3.7)
19F	178	176	98.9	(96.0, 99.9)	235	235	100.0	(98.4, 100.0)	-1.1	(-4.0, 0.6)
23F	178	176	98.9	(96.0, 99.9)	234	233	99.6	(97.6, 100.0)	-0.7	(-3.6, 1.4)
Additional										
1	178	178	100.0	(97.9, 100.0)	235	235	100.0	(98.4, 100.0)	0.0	(-2.1, 1.7)
3	178	177	99.4	(96.9, 100.0)	232	210	90.5	(86.0, 94.0)	8.9	(5.0, 13.5)
5	178	178	100.0	(97.9, 100.0)	235	234	99.6	(97.7, 100.0)	0.4	(-1.6, 2.4)
6A	178	178	100.0	(97.9, 100.0)	235	235	100.0	(98.4, 100.0)	0.0	(-2.1, 1.7)
7F	178	178	100.0	(97.9, 100.0)	235	234	99.6	(97.7, 100.0)	0.4	(-1.6, 2.4)
19A	178	178	100.0	(97.9, 100.0)	236	236	100.0	(98.4, 100.0)	0.0	(-2.1, 1.6)

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, 3003JA study – 004 study, expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, 3003JA study – 004 study, expressed as a percentage.

Reverse Cumulative Distribution Curves

RCDCs for the posttoddler dose time point were provided in the clinical study report. For all 13 serotypes, the RCDCs were higher along most of the curve for study 3003 as compared with study 004.

Pneumococcal IgG Geometric Mean Concentrations

Before the Toddler Dose

In study 3003, before the toddler dose, GMCs for the 13 pneumococcal serotypes ranged from 0.73 µg/mL for serotype 3 to 5.25 µg/mL for serotype 14 (Table 9-6). GMCs were lower in study 004 for all 13 serotypes, ranging from 0.15 µg/mL for serotype 3 to 1.89 µg/mL for serotype 14. GMRs ranged from 2.37 for serotype 23F to 4.84 for serotype 3.

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

	Vaccine Group / Study							
	13vPnC 6096A1-3003-JA			13vPnC 6096A1-004				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	178	1.68	(1.48, 1.90)	229	0.35	(0.31, 0.39)	4.76	(4.02, 5.63)
6B	178	2.53	(2.23, 2.86)	229	0.78	(0.69, 0.89)	3.23	(2.68, 3.88)
9V	178	1.09	(0.97, 1.22)	227	0.39	(0.35, 0.43)	2.81	(2.42, 3.27)
14	178	5.25	(4.62, 5.97)	228	1.89	(1.64, 2.17)	2.78	(2.29, 3.38)
18C	178	0.92	(0.81, 1.05)	229	0.34	(0.30, 0.37)	2.74	(2.33, 3.23)
19F	178	2.28	(1.95, 2.67)	229	0.73	(0.65, 0.82)	3.13	(2.59, 3.79)
23F	176	0.90	(0.77, 1.05)	229	0.38	(0.33, 0.44)	2.37	(1.92, 2.93)
Additional								
1	178	1.54	(1.34, 1.77)	229	0.64	(0.57, 0.72)	2.41	(2.00, 2.89)
3	178	0.73	(0.64, 0.83)	224	0.15	(0.13, 0.17)	4.84	(3.95, 5.93)
5	178	2.11	(1.88, 2.37)	228	0.77	(0.69, 0.86)	2.74	(2.32, 3.23)
6A	178	2.21	(1.96, 2.49)	228	0.83	(0.75, 0.92)	2.67	(2.29, 3.12)
7F	178	2.27	(2.02, 2.55)	228	0.83	(0.75, 0.93)	2.72	(2.31, 3.20)
19A	178	3.16	(2.76, 3.62)	229	0.92	(0.81, 1.05)	3.43	(2.83, 4.15)

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; 3003-JA study to 004 study.
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 (3003JA study – 004 study reference).

After the Toddler dose

In study 3003, 1 month after the toddler dose, GMCs ranged from 2.06 µg/mL for serotype 3 to 16.33 µg/mL for serotype 14 (Table 9-7). For all serotypes, GMCs 1 month after the toddler dose were higher than GMCs observed before the toddler dose, demonstrating the booster effect of the toddler dose. Furthermore, GMCs were higher after the toddler dose than after the infant series for all serotypes except serotype 3. In study 004, GMCs 1 month after the toddler dose ranged from 0.94 µg/mL for serotype 3 to 11.53 µg/mL for serotype 6B. For all serotypes, IgG concentrations were higher in study 3003 than in study 004, with GMRs (study 3003 relative to study 004) ranging from 1.27 to 2.60 (Table 9-7).

Table 9-7: Comparisons of Pneumococcal IgG GMCs (µg/mL) After the Toddler Dose - Evaluable Toddler Immunogenicity Population

	Vaccine Group / Study							
	13vPnC 6096A1-3003-JA			13vPnC 6096A1-004				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	178	9.70	(8.43, 11.17)	235	3.73	(3.28, 4.24)	2.60	(2.15, 3.15)
6B	177	14.61	(12.52, 17.05)	234	11.53	(9.99, 13.30)	1.27	(1.03, 1.57)
9V	178	4.49	(4.00, 5.06)	234	2.62	(2.34, 2.94)	1.71	(1.45, 2.02)
14	178	16.33	(14.49, 18.41)	235	9.11	(7.95, 10.45)	1.79	(1.49, 2.16)
18C	178	6.09	(5.34, 6.95)	236	3.20	(2.82, 3.64)	1.90	(1.58, 2.29)
19F	178	12.20	(10.37, 14.35)	235	6.60	(5.85, 7.44)	1.85	(1.52, 2.25)
23F	178	6.55	(5.53, 7.75)	234	5.07	(4.41, 5.83)	1.29	(1.04, 1.60)
Additional								
1	178	9.85	(8.62, 11.27)	235	5.06	(4.43, 5.80)	1.95	(1.60, 2.36)
3	178	2.06	(1.83, 2.32)	232	0.94	(0.83, 1.05)	2.21	(1.86, 2.61)
5	178	7.31	(6.52, 8.20)	235	3.72	(3.31, 4.18)	1.97	(1.67, 2.32)
6A	178	11.03	(9.69, 12.55)	235	8.20	(7.30, 9.20)	1.35	(1.13, 1.60)
7F	178	8.31	(7.39, 9.35)	235	5.67	(5.01, 6.42)	1.47	(1.23, 1.74)
19A	178	15.97	(14.07, 18.13)	236	8.55	(7.64, 9.56)	1.87	(1.58, 2.21)

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; 3003-JA study to 004 study.
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 (3003JA study – 004 study reference).

Assessor's comment: The GMCs for serotype 3 were lower after the toddler doser than after the infant dose in study 6096A1-3003. However, the titres had decreased between the third infant dose and before the toddler dose, which indicates that there was indeed a response to the toddler dose. The slightly lower response therefore does not seem to be the result of immune hyporesponsiveness, but it may be that the immunological memory induced by serotype 3 is different from that induced by the other serotypes. These results are consistent with what has been seen previously in other studies for serotype 3.

Geometric Mean Fold Rises

The GMFRs in serum IgG concentrations from before the toddler dose to 1 month after the toddler dose are summarized in Table 9-9 for both studies. In study 3003, GMFRs ranged from 2.83 to 7.48, while in study 004, GMFRs ranged from 4.85 to 15.12. For all serotypes, the GMFRs were higher in study 004 than in study 3003, with GMFR ratios (study 3003/study 004) ranging from 0.38 to 0.79 (Table 9-9). The relatively low GMFRs in study 3003 reflect the high GMCs observed before the toddler dose in that study.

Table 9-9: Comparisons of Pneumococcal IgG GMFRs for the Toddler Dose - Evaluable Toddler Immunogenicity Population

	Vaccine Group/ Study					
	13vPnC 6096A1-3003-JA		13vPnC 6096A1-004			
Serotype	n[a]	GMFR[b]	n[a]	GMFR[b]	Ratio[c]	(95% CI[d])
7vPnC						
4	178	5.79	226	10.71	0.54	(0.45, 0.65)
6B	177	5.72	225	15.12	0.38	(0.32, 0.45)
9V	178	4.13	223	6.85	0.60	(0.52, 0.70)
14	178	3.11	225	4.92	0.63	(0.52, 0.76)
18C	178	6.60	227	9.67	0.68	(0.58, 0.81)
19F	178	5.34	226	9.21	0.58	(0.48, 0.71)
23F	176	7.48	226	13.83	0.54	(0.45, 0.65)
Additional						
1	178	6.41	226	8.15	0.79	(0.65, 0.95)
3	178	2.83	220	6.37	0.44	(0.37, 0.54)
5	178	3.46	225	4.85	0.71	(0.61, 0.83)
6A	178	4.99	225	10.23	0.49	(0.41, 0.58)
7F	178	3.66	225	6.92	0.53	(0.45, 0.62)
19A	178	5.05	227	9.32	0.54	(0.45, 0.66)

a. n = Number of subjects with a determinate IgG antibody concentration to the given serotype.
b. Geometric mean fold rises (GMFRs) were calculated using all subjects with available data from both the pretoddler dose and posttoddler dose blood draws.
c. Ratio of GMFRs; 3003-JA study to 004 study
d. 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 (3003-JA study – 004 study).

- Safety results

Local Reactions

In comparing the data for local reactions, it should be noted that while 13vPnC was administered SC in study 3003, study vaccine was administered IM in study 004.

Infant Series

The number and percentage of subjects with local reactions reported within 7 days after each dose in the infant series are presented in Table 10-3 through Table 10-5. For comparison, data for the 13vPnC group in study 004 are also shown.

In study 004, the incidence of tenderness after each dose was higher than in study 3003, both for any tenderness (between 72% and 79%) and for significant tenderness (between 8% and 14%). In contrast, the incidence of induration after each dose was higher in study 3003 (between 47% and 54%) than in study 004 (between 27% and 38%), as was the incidence of erythema (between 67% and 75% in study 3003 and between 35% and 49% in study 004). In both studies, most reports of induration and erythema were mild. Local reactions of moderate intensity were reported more frequently in study 3003 than in study 004, both for induration (between 14% and 30% versus between 5% and 7%, respectively) and for erythema (between 24% and 44% versus between 1% and 6%, respectively). There were no reports of severe induration or erythema in study 004, while in study 3003, severe induration and severe erythema were each reported for 2 subjects after dose 2 (1.3%) and for 1 subject after dose 3 (0.7%). In study 004, there was a trend toward higher incidences of

tenderness, induration, and erythema with each subsequent dose, while in study 3003, no pattern of increasing or decreasing incidence across doses was apparent.

Table 10-3: Subjects Reporting Local Reactions Within 7 Days - Dose 1 Infant Series

	Vaccine Group (as Administered) /Study					
	13vPnC 6096A1-3003-JA			13vPnC 6096A1-004		
Local Reaction	**N[a]**	**n[b]**	**%**	**N[a]**	**n[b]**	**%**
Tenderness						
Any	165	22	13.3	264	192	72.7
Significant[c]	160	1	0.6	182	25	13.7
Induration						
Any	176	83	47.2	201	55	27.4
Mild[d]	174	80	46.0	199	46	23.1
Moderate[d]	167	24	14.4	176	12	6.8
Severe[d]	160	0	0.0	173	0	0.0
Erythema						
Any	186	138	74.2	202	72	35.6
Mild[d]	183	125	68.3	200	69	34.5
Moderate[d]	170	42	24.7	177	8	4.5
Severe[a]	160	0	0.0	173	0	0.0
Any of the above	186	139	74.7	270	206	76.3

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Significant = present and interfered with limb movement.
d. Mild, 0.5-2.0 cm; moderate, 2.5-7.0 cm; and severe, >7.0 cm.

Table 10-4: Subjects Reporting Local Reactions Within 7 Days - Dose 2 Infant Series

	Vaccine Group (as Administered) /Study					
	13vPnC 6096A1-3003-JA			13vPnC 6096A1-004		
Local Reaction	**N[a]**	**n[b]**	**%**	**N[a]**	**n[b]**	**%**
Tenderness						
Any	156	31	19.9	200	154	77.0
Significant[c]	152	0	0.0	123	13	10.6
Induration						
Any	173	93	53.8	141	44	31.2
Mild[d]	171	84	49.1	141	42	29.8
Moderate[d]	164	47	28.7	118	6	5.1
Severe[d]	153	2	1.3	116	0	0.0
Erythema						
Any	180	134	74.4	155	70	45.2
Mild[d]	179	116	64.8	155	69	44.5
Moderate[d]	168	73	43.5	117	2	1.7
Severe[d]	153	2	1.3	116	0	0.0
Any of the above	180	136	75.6	212	177	83.5

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Significant = present and interfered with limb movement.
d. Mild, 0.5-2.0 cm; moderate, 2.5-7.0 cm; and severe, >7.0 cm.

Table 10-5: Subjects Reporting Local Reactions Within 7 Days - Dose 3 Infant Series

	Vaccine Group (as Administered) /Study					
	13vPnC 6096A1-3003-JA			13vPnC 6096A1-004		
Local Reaction	**N[a]**	**n[b]**	**%**	**N[a]**	**n[b]**	**%**
Tenderness						
Any	147	21	14.3	178	140	78.7
Significant[c]	143	0	0.0	91	8	8.8
Induration						
Any	165	89	53.9	116	44	37.9
Mild[d]	163	82	50.3	113	40	35.4
Moderate[d]	150	44	29.3	91	6	6.6
Severe[d]	143	1	0.7	87	0	0.0
Erythema						
Any	171	116	67.8	131	64	48.9
Mild[d]	162	90	55.6	128	61	47.7
Moderate[d]	157	61	38.9	91	5	5.5
Severe[d]	143	1	0.7	87	0	0.0
Any of the above	174	123	70.7	189	156	82.5

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Significant = present and interfered with limb movement.
d. Mild, 0.5-2.0 cm; moderate, 2.5-7.0 cm; and severe, >7.0 cm.

Toddler Dose

The number and percentage of subjects with local reactions within 7 days after the toddler dose are presented in Table 10-6. In study 3003, the incidence of each type of reaction after the toddler dose was similar to the incidence that had been observed during the infant series, whereas in study 004, the incidences were somewhat higher after the toddler dose than during the infant series. Similar to what was seen during the infant series, the incidence of tenderness after the toddler dose was markedly higher in study 004 (81.2%) than in study 3003 (18.2%), while the incidences of induration and erythema were higher in study 3003 (57.1% and 68.1%, respectively) than in study 004 (44.0% and 54.4%). There were no reports of significant tenderness after the toddler dose in study 3003, while 10 subjects (15.4%) experienced significant tenderness in study 004. In both studies, most reports of induration and erythema were mild. There were no reports of severe induration or erythema after the toddler dose in study 004, while in study 3003, severe induration was reported in 3 subjects (2.3%) and severe erythema was reported in 2 subjects (1.5%).

Table 10-6: Subjects Reporting Local Reactions Within 7 Days - Toddler Dose

	Vaccine Group (as Administered) /Study					
	13vPnC 6096A1-3003-JA			13vPnC 6096A1-004		
Local Reaction	N[a]	n[b]	%	N[a]	n[b]	%
Tenderness						
Any	143	26	18.2	149	121	81.2
Significant[c]	132	0	0.0	65	10	15.4
Induration						
Any	163	93	57.1	91	40	44.0
Mild[d]	154	68	44.2	90	39	43.3
Moderate[d]	151	55	36.4	68	10	14.7
Severe[d]	132	3	2.3	59	0	0.0
Erythema						
Any	166	113	68.1	103	56	54.4
Mild[d]	156	84	53.8	102	55	53.9
Moderate[d]	155	63	40.6	62	5	8.1
Severe[d]	132	2	1.5	59	0	0.0
Any of the above	170	122	71.8	160	133	83.1

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Significant = present and interfered with limb movement.
d. Mild, 0.5-2.0 cm; moderate, 2.5-7.0 cm; and severe, >7.0 cm.

Systemic Events
Infant Series
The number and percentage of subjects reporting systemic events, including the use of antipyretic medications, within 7 days after each dose in the infant series are presented in Table 10-7 through Table 10-9. In study 3003, fever was defined as an axillary temperature ≥37.5°C, while in study 004, fever was defined as a core (rectal) temperature ≥38.0°C. In the following tables, the incidence of fever after each dose in the infant series is summarized for study 3003 only, using the protocol-defined criterion (any temperature ≥37.5°C). In addition, data from study 3003 are compared with those from study 004 using the criterion from study 004 for mild fever (≥38°C but ≤39°C). The protocols for both studies defined moderate fever as a temperature >39°C but ≤40°C and severe fever as a temperature >40°C.

Table 10-7: Subjects Reporting Systemic Events and Antipyretic Medication Use Within 7 Days - Dose 1 Infant Series

	Vaccine Group (as Administered) / Study					
	13vPnC 6096A1-3003-JA			13vPnC 6096A1-004		
Systemic Event	N[a]	n[b]	%	N[a]	n[b]	%
Any fever (≥37.5°C)	170	56	32.9	-	-	-
Fever ≥38°C but ≤39°C (mild)	163	11	6.7	196	47	24.0
Fever >39°C but ≤40°C (moderate)	161	2	1.2	177	5	2.8
Fever >40°C (severe)	160	0	0.0	174	0	0.0
Decreased appetite	163	19	11.7	228	125	54.8
Irritability	170	52	30.6	289	259	89.6
Increased sleep	175	71	40.6	268	213	79.5
Decreased sleep	169	36	21.3	221	101	45.7
Hives (urticaria)	160	2	1.3	178	3	1.7
Use of medication to treat symptoms	160	3	1.9	257	202	78.6
Use of medication to prevent symptoms	160	1	0.6	272	204	75.0
Any systemic event[c]	181	107	59.1	317	307	96.8

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Includes fever ≥38°C, decreased appetite, irritability, increased sleep, decreased sleep, and hives (urticaria).

Table 10-8: Subjects Reporting Systemic Events and Antipyretic Medication Use Within 7 Days - Dose 2 Infant Series

	Vaccine Group (as Administered) / Study					
	13vPnC 6096A1-3003-JA			13vPnC 6096A1-004		
Systemic Event	N[a]	n[b]	%	N[a]	n[b]	%
Any fever (≥37.5°C)	163	54	33.1	-	-	-
Fever ≥38°C but ≤39°C (mild)	156	19	12.2	146	63	43.2
Fever >39°C but ≤40°C (moderate)	153	4	2.6	118	3	2.5
Fever >40°C (severe)	152	1	0.7	116	0	0.0
Decreased appetite	158	26	16.5	177	106	59.9
Irritability	166	60	36.1	236	212	89.8
Increased sleep	160	47	29.4	203	161	79.3
Decreased sleep	160	37	23.1	169	83	49.1
Hives (urticaria)	152	2	1.3	118	3	2.5
Use of medication to treat symptoms	153	10	6.5	221	182	82.4
Use of medication to prevent symptoms	153	5	3.3	233	202	86.7
Any systemic event[c]	175	105	60.0	260	246	94.6

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Includes fever ≥38°C, decreased appetite, irritability, increased sleep, decreased sleep, and hives (urticaria).

Table 10-9: Subjects Reporting Systemic Events and Antipyretic Medication Use Within 7 Days - Dose 3 Infant Series

	Vaccine Group (as Administered) / Study					
	13vPnC 6096A1-3003-JA			13vPnC 6096A1-004		
Systemic Event	N[a]	n[b]	%	N[a]	n[b]	%
Any fever (≥37.5°C)	154	62	40.3	-	-	-
Fever ≥38°C but ≤39°C (mild)	146	15	10.3	123	49	39.8
Fever >39°C but ≤40°C (moderate)	143	4	2.8	94	8	8.5
Fever >40°C (severe)	143	0	0.0	87	0	0.0
Decreased appetite	144	14	9.7	147	87	59.2
Irritability	149	35	23.5	216	191	88.4
Increased sleep	153	34	22.2	164	117	71.3
Decreased sleep	145	23	15.9	154	93	60.4
Hives (urticaria)	143	1	0.7	89	4	4.5
Use of medication to treat symptoms	145	8	5.5	203	167	82.3
Use of medication to prevent symptoms	144	3	2.1	202	164	81.2
Any systemic event[c]	158	69	43.7	244	228	93.4

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Includes fever ≥38°C, decreased appetite, irritability, increased sleep, decreased sleep, and hives (urticaria).

Comparisons of data between the studies show that the incidence of mild fever (defined as a temperature ≥38°C but ≤39°C) was substantially higher in study 004 (ranging from 24.0% to 43.2% across doses) than in study 3003 (ranging from 6.7% to 12.2%). In contrast, the incidences of moderate fever (>39°C but ≤40°C) were similar in the 2 studies, between 1.2% and 2.8% after each dose, except after dose 3 in study 004, where the incidence of moderate fever was 8.5% (8 subjects). Severe fever (>40°C) was reported for only 1 subject, after dose 2 in study 3003.

The frequency of antipyretic medication use within 7 days after each dose in the infant series was much higher in study 004 than in study 3003. Antipyretic medications were used to treat symptoms in ≤6.5% of subjects after each dose in study 3003, compared with between 78.6% and 82.4% of subjects in study 004. Similarly, antipyretic medications were used to prevent symptoms in ≤3.3% of subjects after each dose in study 3003, compared with between 75.0% and 86.7% of subjects in study 004.

Other systemic events were consistently reported more frequently in study 004 than in study 3003:

- Decreased appetite was reported for ≤16.5% of subjects in study 3003 but for ≥54.8% of subjects in study 004.
- Irritability was reported for ≤36.1% of subjects in study 3003 but for ≥88.4% of subjects in study 004.
- Increased sleep was reported for ≤40.6% of subjects in study 3003 but for ≥71.3% of subjects in study 004.
- Decreased sleep was reported for ≤23.1% of subjects in study 3003 but for ≥45.7% of subjects in study 004.

The mean duration of systemic events after each dose of the infant series was between 1.8 and 3.1 days for all events except hives, for which the duration ranged from 1.0 day for 1 subject after dose 3 to 4.0 days for 1 subject after dose 2.

Toddler Dose

The number and percentage of subjects reporting systemic events within 7 days after the toddler dose are presented in Table 10-10. In study 3003, the incidence of fever ≥37.5ºC was higher after the toddler dose (50.7%) than after any dose in the infant series (maximum of 40.3%), as was the incidence of mild fever (≥38ºC but ≤39°C) (20.4%, compared with a maximum of 12.2% during the

infant series). For all other types of systemic events in study 3003, there was no clear trend toward higher or lower incidence after the toddler dose as compared with the infant doses. Similar to what was observed during the infant series, the incidence of each type of systemic event after the toddler dose was consistently higher in study 004 than in study 3003.

Table 10-10: Subjects Reporting Systemic Events and Antipyretic Medication Use Within 7 Days - Toddler Dose

	Vaccine Group (as Administered) / Study					
	13vPnC 6096A1-3003-JA			13vPnC 6096A1-004		
Systemic Event	N[a]	n[b]	%	N[a]	n[b]	%
Any fever (≥37.5°C)	150	76	50.7	-	-	-
Fever ≥38°C but ≤39°C (mild)	137	28	20.4	99	53	53.5
Fever >39°C but ≤40°C (moderate)	133	7	5.3	61	4	6.6
Fever >40°C (severe)	132	0	0.0	60	1	1.7
Decreased appetite	138	25	18.1	116	76	65.5
Irritability	140	37	26.4	199	183	92.0
Increased sleep	139	34	24.5	115	81	70.4
Decreased sleep	138	17	12.3	113	66	58.4
Hives (urticaria)	132	0	0.0	62	3	4.8
Use of medication to treat symptoms	135	11	8.1	162	136	84.0
Use of medication to prevent symptoms	134	4	3.0	164	145	88.4
Any systemic event[c]	152	79	52.0	213	202	94.8

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Includes fever ≥38°C, decreased appetite, irritability, increased sleep, decreased sleep, and hives (urticaria).

Spontaneously reported Adverse Events

During the infant series, spontaneously reported AEs were reported for approximately 92% of subjects in study 3003 and 83% of subjects in study 004. In general, the types of AEs reported in both studies were consistent with the types of childhood illnesses and conditions commonly occurring in this age group. In study 3003, the types of AEs reported most frequently during the infant series were infections (most often respiratory tract infection, nasopharyngitis, exanthema subitum, and bronchitis); skin disorders (mostly diaper dermatitis and eczema); general disorders and administration site conditions (mostly injection site erythema and injection site induration); gastrointestinal disorders (mostly diarrhea); and respiratory, thoracic, and mediastinal disorders (mostly rhinorrhea, asthma, and upper respiratory tract inflammation). Similar events were reported after the toddler dose. The types and frequencies of spontaneously reported AEs reported in study 004 were similar to those observed in study 3003.

In study 3003, a total of 30 SAEs were reported for 22 subjects (11.4%): 9 subjects (4.7%) during the infant series, 14 subjects (7.3%) after the infant series, and 1 subject (0.5%) after the toddler dose. Most were infections and infestations that required hospitalization. None of the SAEs were considered related to study vaccine by the investigator. There were no deaths during the study.
Three (3) subjects were withdrawn from study 3003 because of AEs: 2 because of febrile convulsions (considered not related to study vaccine) and 1 because of injection site swelling (considered related to study vaccine).

Assessor's comment: The local reactions induration and erythema were reported more frequently in study 3003 than in study 004, while tenderness had a higher incidence in study 004 than in 3003. The same pattern was seen after the infant and toddler doses. The systemic reactions also differed between the two studies.

MAH overall conclusions for study 6096A1-3003-JA
In conclusion, 13vPnC administered SC as a 3-dose infant series followed by a booster dose at 12 to 15 months of age was immunogenic, safe, and well tolerated in Japanese infants. For all 13 serotypes, serum IgG concentrations were higher in Japanese infants (study 3003) than in infants in the United States (study 004), with GMRs (3003 relative to 004) for the 13 serotypes ranging from 1.72 to 5.88 after the infant series. The incidence of local reactions differed markedly between subjects vaccinated SC in study 3003 and subjects vaccinated IM in study 004. After each dose, the incidence of tenderness was consistently lower in study 3003 than in study 004, while the incidences of both erythema and induration were consistently higher in study 3003 than in study 004. In addition, the incidence of mild fever (defined as a temperature ≥38°C but ≤39°C) was higher in study 004 than in study 3003. The adverse event profile of 13vPnC in Japanese infants was comparable to that observed in US infants.

Assessor's comment: The conclusions of the MAH are partly endorsed for this study. The adverse events profile are not considered comparable between the two studies, as there are several differences in incidences of local and systemic adverse events between the two studies. Whether they are due to the route of administration, other concomitant vaccines or other reasons is not clear.
The reasons for the higher immune responses in the Japanese study were discussed in the clinical study report. There are several possible reasons for these results, e.g. the SC route,the age at vaccination,the lack of concomitant vaccinations or among others. Considering the many differences between the studies it is difficult to conclude on the reason for the differing safety and immunogenicity results.

Study 6096A1-3008: A Phase 3, Randomized, Active-Controlled, Doubleblind Trial Evaluating the Safety, Tolerability, and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given With Routine Pediatric Vaccinations in Canada

- **Description**

- **Methods**

  - Objective(s)

The primary objectives of this study were as follows:

- To demonstrate that the immune response induced by NeisVac-C given with 13vPnC is non-inferior to the immune response induced by NeisVac-C given with 7vPnC, when measured 1 month after the 2-dose NeisVac-C infant series. The immune response to the meningococcal C antigen in NeisVac-C was assessed using a serum bactericidal assay (SBA).

To demonstrate that the immune responses induced by Pentacel given with 13vPnC are non-inferior to the immune responses induced by Pentacel given with 7vPnC, when measured 1 month after the 3-dose infant series. The immune responses to the following antigens in Pentacel were assessed: Hib and pertussis antigens (pertussis toxoid [PT], filamentous hemagglutinin [FHA], pertactin [PRN], and fimbrial agglutinogens [FIM]). Immune responses to diphtheria, tetanus, and poliovirus antigens were not assessed in this study.

The 13vPnC immunogenicity objectives were as follows:

- To assess the immune response to 13vPnC 1 month after a 3-dose infant series, as measured by serum immunoglobulin G (IgG) levels.
- To assess the immune response to 13vPnC 1 month after the toddler dose, as measured by serum IgG levels.

The secondary objectives of this **study** were as follows:

- To assess the immune response induced by NeisVac-C given with 13vPnC relative to the immune response induced by NeisVac-C given with 7vPnC, when measured 1 month after the toddler dose. Immune response to the meningococcal C antigen in NeisVac-C was assessed using an SBA.
- To assess the immune response induced by Pentacel given with 13vPnC relative to the immune response induced by Pentacel given with 7vPnC at an alternative cutoff level, when measured 1 month after the infant series. Immune response to the Hib antigen in Pentacel was assessed.

The safety objective of this study was as follows:

- To evaluate the acceptability of the safety profile of the 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 evaluate the immunogenicity, safety, and tolerability of 13vPnC compared with 7vPnC in healthy infants.

- Study population /Sample size

Approximately 570 subjects (285 subjects per group) were to be enrolled in this study in order to achieve 241 evaluable subjects per group at approximately 12 sites. Subjects were to be randomly assigned (in a 1:1 ratio prospectively) to receive 13vPnC plus routine pediatric vaccines or 7vPnC plus routine pediatric vaccines.

- Treatments

Each subject was to receive 1 dose (0.5 mL) of either 13vPnC or 7vPnC together with at least 1 concomitant dose of a routine pediatric vaccine at each of the 4 vaccination visits. Standard vaccination practices were observed, and appropriate resuscitative equipment was available in the event of an anaphylactic reaction. 13vPnC and 7vPnC were to be administered by intramuscular injection into the anterolateral thigh muscle of the left leg at 2, 4, and 6 months (infant series) and 12 months of age (toddler dose).
The following routine pediatric vaccines were given: Pentacel using a 2-, 4-, and 6-month infant series; NeisVac-C using a 2- and 6-month infant series followed by a toddler dose at 12 months of age; and measles, mumps, and rubella (MMR) and varicella vaccines at 12 months of age.

- Outcomes/endpoints

Blood samples were to be obtained 1 month after the third 7vPnC or 13vPnC dose of the infant series (visit 4, at approximately 7 months of age) and 1 month after the toddler dose (visit 6, at approximately 13 months of age). Samples obtained after the infant series and toddler dose were to be tested for IgG antibodies against the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) present in 13vPnC in subjects receiving 13vPnC. Antibody responses to NeisVac-C and to selected antigens in Pentacel (Hib and pertussis antigens PT, FHA, PRN, and FIM) were to be measured in blood samples collected from all subjects 1 month after the infant series. Antibody responses to NeisVac-C were to be measured in blood samples collected from all subjects 1 month after the toddler dose.

Antibody responses to the NeisVac-C antigens were to be measured in blood samples collected from all subjects 1 month after the 2-dose NeisVac-C infant series (visit 4, at approximately 7 months of age). In addition, antibody responses to the pertussis antigens (PT, FHA, PRN, and FIM) in Pentacel were to be measured in blood samples collected from all subjects 1 month after the third dose (visit 4, at approximately 7 months of age).

Parents/legal guardians were asked to monitor and record in an e-diary the subject's local reactions, systemic events, and use of antipyretic medication to treat and prevent symptoms for 4 days after each vaccination. Other signs and symptoms were to be recorded on the e-diary as well from visit 1 through visit 4, and from visit 5 to visit 6; the e-diary was collected at visit 4, returned to the parent(s)/legal guardian(s) at visit 5, and collected for the final time at visit 6.

AEs were to be collected and recorded on the CRF based on ancillary information on the e-diary, clinical evaluation during a study visit, and verbal questioning of the parent about the child's health since the last visit. AEs were to be collected from the signing of the informed consent to visit 4 and from visit 5 to visit 6. All SAEs were to be recorded from the signing of the informed consent to 6 months after the last study vaccination. At visit 5, any newly diagnosed chronic medical conditions since visit 4 were to be recorded.

A telephone contact was to be made 6 months after the last study vaccination to record any newly diagnosed chronic medical conditions, hospitalizations, SAEs, and other reportable information that occurred since the last study visit.

- Statistical Methods

For the pneumococcal IgG concentrations, the proportion of subjects achieving an antibody concentration ≥0.35 µg/mL was computed for each blood sample obtained from subjects in the 13vPnC group.
Within each vaccine group and for each concomitant antigen separately, the proportion of subjects achieving at least a prespecified antibody concentration was computed. For all concomitant vaccine antigens, non-inferiority was declared if the lower limit of the 2-sided, 95% CI for the difference in proportions was greater than −0.10.

➢ Results

- Recruitment/ Number analysed

The number of subjects planned for this study was 570, with 285 in each vaccine group. Actual enrollment in the study was 603 subjects, who were randomly assigned in a 1:1 ratio prospectively to either the 13vPnC group (n=300) or the 7vPnC group (n=303). In addition, 5 subjects were screened but not randomly assigned; consent had been obtained from the parent(s)/legal guardian(s) of 4 of these 5 subjects.
All 603 randomly assigned subjects (100%) received dose 1, 593 subjects (98.3%) received dose 2, and 587 subjects (97.3%) received dose 3. Overall, 96.8% (96.0% to 97.7% by group) completed the infant series. A total of 584 subjects (96.8%) completed the infant series, with a similar percentage of subjects in each group completing the series: 293 (97.7%) in the 13vPnC group and 291 (96.0%) in the 7vPnC group.

Demographic and Other Baseline Characteristics
The 2 vaccine groups were well balanced with respect to sex, race, ethnicity, age at enrollment, and weight at enrollment. The proportion of male subjects was slightly higher in the 13vPnC group (52.3%) than in the 7vPnC group (49.8%). Most subjects were white (81.7%) and non-Hispanic and non-Latino (95.9%). The mean age (±standard deviation [SD]) at enrollment was 2.1 (±0.3) months and the mean weight at enrollment was 5.4 (±0.8) kg.

- Immunogenicity results

Immune Response to Pneumococcal Antigens
Proportion of Subjects Achieving Prespecified Antibody Levels
For the evaluable pneumococcal infant immunogenicity population, the proportions of responders after dose 3 of the infant series were all greater than 90.0% for each serotype common to both 13vPnC and 7vPnC (Table 9-5). The proportion of responders was greater than 95.0% for each of the 6 additional serotypes unique to 13vPnC, except serotype 3 (79.6%) and serotype 5 (87.0%).

Table 9-5: Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL for the 13vPnC Group After Dose 3 of Infant Series - Evaluable Pneumococcal Infant Immunogenicity Population

	Vaccine Group (as Randomized) 13vPnC			
Serotype	N[a]	n[b]	%	(95% CI[c])
7vPnC				
4	277	269	97.1	(94.4, 98.7)
6B	276	257	93.1	(89.5, 95.8)
9V	277	264	95.3	(92.1, 97.5)
14	275	270	98.2	(95.8, 99.4)
18C	277	267	96.4	(93.5, 98.3)
19F	273	269	98.5	(96.3, 99.6)
23F	275	248	90.2	(86.0, 93.4)
Additional				
1	277	265	95.7	(92.6, 97.7)
3	275	219	79.6	(74.4, 84.2)
5	276	240	87.0	(82.4, 90.7)
6A	276	266	96.4	(93.4, 98.2)
7F	276	272	98.6	(96.3, 99.6)
19A	272	266	97.8	(95.3, 99.2)

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 a given serotype.
c. Exact 2-sided confidence interval based upon the observed proportion of subjects.

Pneumococcal IgG Geometric Mean Concentrations

GMCs of each serotype were measured 1 month after the infant series, and were calculated for each serotype of the 13vPnC vaccine group. In the evaluable infant immunogenicity population, IgG GMCs were 1.00 µg/mL or greater for all pneumococcal serotypes except serotype 3 (0.63 µg/mL) and serotype 5 (0.90 µg/mL) (Table 9-6).

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

	Vaccine Group (as Randomized) 13vPnC		
Serotype	n[a]	GMC[b]	(95% CI[c])
7vPnC			
4	277	1.46	(1.33, 1.60)
6B	276	2.16	(1.87, 2.49)
9V	277	1.12	(1.03, 1.22)
14	275	5.43	(4.86, 6.06)
18C	277	1.37	(1.23, 1.52)
19F	273	2.18	(1.99, 2.39)
23F	275	1.15	(1.03, 1.30)
Additional			
1	277	1.82	(1.63, 2.04)
3	275	0.63	(0.58, 0.70)
5	276	0.90	(0.81, 0.99)
6A	276	1.92	(1.73, 2.12)
7F	276	2.26	(2.09, 2.45)
19A	272	2.00	(1.82, 2.19)

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.

Concomitant Vaccine Immunogenicity

The immune response induced by NeisVac-C given with 13vPnC was shown to be non-inferior to the immune response induced by NeisVac-C given with 7vPnC following the infant series and toddler dose. After the infant series, the proportion of responders was 96.8% for the 13vPnC group and 99.3% for the 7vPnC group. This non-inferiority conclusion was supported by the geometric mean titers (GMTs) for meningococcal C serum bactericidal assay (SBA) antibodies, which were approximately 361 for the 13vPnC group and 303 for the 7vPnC group. The ratio of GMTs (13vPnC to 7vPnC) was 1.19, and the lower limit of the 95% confidence interval (CI) of the ratio was 0.96, meeting the non-inferiority criterion. After the toddler dose, the proportion of responders was 100.0% for both the 13vPnC and 7vPnC groups. This non-inferiority conclusion was supported by the GMTs for meningococcal C SBA antibodies, which were approximately 1380 for the 13vPnC group and 1084 for the 7vPnC group. The ratio of GMTs (13vPnC to 7vPnC) was 1.27, and the lower limit of the 95% CI of the ratio was 1.08, meeting the non-inferiority criterion.

The immune responses induced by Pentacel given with 13vPnC were shown to be non-inferior to the immune responses induced by Pentacel given with 7vPnC after the infant series. The immune responses were very similar in the 2 vaccine groups for the specific antigens assessed (pertussis and Hib). All comparisons of the proportions of subjects achieving prespecified antibody levels for concomitant vaccine antigens met the non-inferiority criterion for the 4 pertussis antigens (pertussis toxoid [PT], filamentous hemagglutinin [FHA], pertactin [PRN], and fimbrial agglutinogens [FIM]) and Hib. When Hib was assessed at the higher antibody level (≥1.0 µg/mL), the responses were also shown to be non-inferior. Similarly, when the pertussis antigen responses were assessed at the higher antibody concentration for FHA and the concentrations achieved by 95% of the 7vPnC group, non-inferiority criteria were also met.

GMTs and GMCs in the 2 groups were comparable for all antigens and were formally non-inferior using the 2-fold criterion for each of these antigens. The results for the infant series are summarised in Table 9-3, the results of the toddler dose are not presented in this AR.

Table 9-3: Comparison of Subjects Achieving a Prespecified Level for Concomitant Vaccine Antigens After the Infant Series - Evaluable Concomitant Immunogenicity Population With FIM Specified Level of 2.2 EU/mL

		Vaccine Group (as Randomized)									
		13vPnC				7vPnC					
Concomitant Vaccine Antigen	Comparison Level	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
Hib (PRP)	≥0.15 µg/mL	272	266	97.8	(95.3, 99.2)	266	265	99.6	(97.9, 100.0)	-1.8	(-4.4, 0.1)
	≥1.0 µg/mL	272	222	81.6	(76.5, 86.0)	266	225	84.6	(79.7, 88.7)	-3.0	(-9.4, 3.4)
Meningococcal C	≥1:8	284	275	96.8	(94.1, 98.5)	278	276	99.3	(97.4, 99.9)	-2.4	(-5.3, -0.1)
Pertussis											
PT	≥5 EU/mL	282	281	99.6	(98.0, 100.0)	277	276	99.6	(98.0, 100.0)	0.0	(-1.6, 1.7)
PT[f]	≥12.00 EU/mL	282	278	98.6	(96.4, 99.6)	277	266	96.0	(93.0, 98.0)	2.6	(-0.2, 5.7)
FHA	≥5 EU/mL	283	283	100.0	(98.7, 100.0)	278	278	100.0	(98.7, 100.0)	0.0	(-1.3, 1.3)
FHA	≥7.82 EU/mL	283	283	100.0	(98.7, 100.0)	278	278	100.0	(98.7, 100.0)	0.0	(-1.3, 1.3)
FHA[f]	≥20.00 EU/mL	283	281	99.3	(97.5, 99.9)	278	266	95.7	(92.6, 97.7)	3.6	(1.1, 6.8)
PRN	≥5 EU/mL	283	277	97.9	(95.4, 99.2)	277	268	96.8	(93.9, 98.5)	1.1	(-1.7, 4.2)
PRN[f]	≥7.00 EU/mL	283	274	96.8	(94.0, 98.5)	277	266	96.0	(93.0, 98.0)	0.8	(-2.5, 4.2)
FIM	≥2.2 EU/mL	282	269	95.4	(92.2, 97.5)	275	268	97.5	(94.8, 99.0)	-2.1	(-5.5, 1.2)
FIM[f]	≥4.00 EU/mL	282	264	93.6	(90.1, 96.2)	275	262	95.3	(92.1, 97.5)	-1.7	(-5.7, 2.3)

a. N = number of subjects with a determinate postinfant series antibody concentration/titer to the given concomitant antigen.
b. n = Number of subjects with an antibody concentration/titer ≥ prespecified level for the given concomitant antigen.
c. Exact 2-sided confidence interval based upon the observed proportion of subjects.
d. Difference in proportions, 13vPnC – 7vPnC, expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, 13vPnC – 7vPnC, expressed as a percentage.
f. Comparison level = the level achieved by 95% of the subjects in the 7vPnC group.

- Safety results

Prompted Adverse Events

Local Reactions

The majority of local reactions were mild in severity after any dose. The incidence and severity of local reactions at the pneumococcal vaccine injection site were similar for the 13vPnC and 7vPnC groups. With the exception of significant tenderness (p=0.034) after dose 3 (3.8% and 0.8% in the 13vPnC and 7vPnC groups, respectively), there were no statistically significant differences between the 2 vaccine groups in the incidence of local reactions within 4 days of vaccination after any dose. Significant tenderness was reported by fewer than 4.5% of subjects in either vaccine group following any dose in the infant series and by 2.5% or fewer subjects in either vaccine group following the toddler dose. No subjects reported severe induration or severe erythema at the injection site after any dose.

Systemic Events

The incidence of each type of systemic event was generally similar for the 13vPnC and 7vPnC groups after each dose. There were no statistically significant differences between vaccine groups in the incidence of any type of prompted systemic event following any dose, except for irritability, which had a higher incidence in the 13vPnC group (68.8%) than in the 7vPnC group (58.5%; p=0.023) after the toddler dose.

Most occurrences of fever were mild and did not exceed 13.3% in the 13vPnC group and 12.2% in the 7vPnC group following any dose. The incidence of moderate fever did not exceed 2.0% and 1.4% among 13vPnC and 7vPnC recipients, respectively, after any dose. Severe fever (>40°C) was reported in 1 subject (0.5%) in the 7vPnC group.

Spontaneously Reported Adverse Events

During the infant series, spontaneously reported AEs were reported for 76.3% of 13vPnC recipients and 75.9% of 7vPnC recipients. Most of the AEs were the types of conditions and symptoms expected in infants in this age group. The types of AEs reported most frequently during the infant series were infections (most often nasopharyngitis, upper respiratory tract infection, and bronchiolitis); gastrointestinal disorders (mostly diarrhea, vomiting, teething, and constipation); general disorders and administration site conditions (mostly pyrexia, irritability, and injection site erythema); respiratory, thoracic, and mediastinal disorders (mostly nasal congestion, cough, and rhinorrhea); and skin disorders (mostly eczema, rash, and diaper dermatitis). Similar events were reported after the toddler dose.

AEs that were assessed by the investigator as related to study vaccine were general disorders and administration site conditions (injection site erythema and irritability), gastrointestinal disorders

(diarrhea and vomiting), and infections and infestations (nasopharyngitis and upper respiratory tract infection).
A total of 35 SAEs were reported for 25 subjects who received 13vPnC and 20 SAEs for 17 subjects who received 7vPnC. During the infant series, SAEs occurred in 5 subjects (8 events) vaccinated with 13vPnC and in 5 subjects (7 events) vaccinated with 7vPnC. After the infant series, 11 subjects reported 17 SAEs and 7 subjects reported 7 SAEs in the 13vPnC and 7vPnC groups, respectively. Two (2) SAEs in 2 subjects were reported in each of the 13vPnC and 7vPnC groups during the toddler dose. During the 6-month follow-up period, SAEs were reported for 7 subjects (8 SAEs) in the 13vPnC group and 3 subjects (4 SAEs) in the 7vPnC group. Most were infections and infestations that required hospitalization and were not considered related to study vaccine. One (1) subject reported a related SAE of severe pyrexia after receiving the 13vPnC toddler dose. There were no deaths during the study.

Five (5) subjects in the 7vPnC group withdrew from the study after dose 3 because of AEs (urticaria, febrile neutropenia, convulsion, febrile convulsion, and movement disorder).

Conclusions of the MAH:
13vPnC may be given safely in a 3-dose infant series, administered at 2, 4, and 6 months of age with concomitant NeisVac-C and Pentacel. The immunogenicity of the meningococcal group C, Hib, and pertussis components of these vaccines was not adversely affected by concomitant administration of 13vPnC. The 13vPnC was immunogenic with substantial responses seen to all 13 serotypes after the infant series. The safety analysis of infant series data showed that most local reactions and systemic events were mild, and no clinically important differences between vaccine groups were noted for the prompted symptoms or unsolicited AEs. Although not formally tested, no increase in local or systemic AEs was seen in this study from dose 1 to dose 2 to dose 3. For most events, the proportion of reported AEs actually tended to decrease with subsequent doses. These results indicate that the safety profile of 13vPnC is similar to that of 7vPnC, the standard of care for infants and young children.
13vPnC administered with concomitant vaccines in this study in Canadian children demonstrated a comparable safety profile to 7vPnC and good immunogenicity for all pneumococcal and concomitant vaccine antigens studied.

3. Discussion on clinical aspects

MAH overall conclusions:
Subcutaneous administration of 13vPnC in study 3003 elicited strong IgG responses to all 13 pneumococcal conjugate serotypes after the infant series and toddler dose. When compared with study 004, the antibody responses were generally higher in study 3003. The higher immune responses in study 3003 may be due to ethnic differences in response to pneumococcal conjugate vaccination. Studies with Prevenar given subcutaneously in Japan and intramuscularly in other Asian populations have also shown a high immune response. Pneumococcal immunogenicity results from study 3008 with IM administration of 13vPnC also indicate a strong IgG response to all 13 serotypes following the infant series and toddler dose in the 13vPnC group.
Concomitant vaccine immunogenicity data from study 3008 show that the responses elicited by NeisVac-C given with 13vPnC are non-inferior to those elicited by NeisVac-C given with 7vPnC using a 2- and 6-month infant series followed by a toddler dose at 12 months of age. The immune responses to pertussis and Hib antigens induced by Pentacel given with 13vPnC were also shown to be non-inferior to the immune responses induced by Pentacel given with 7vPnC after the 2-, 4-, and 6-month infant series.
Overall, safety and tolerability in study 3003 was acceptable. The incidence of local reactions differed markedly between subjects vaccinated SC in study 3003 and subjects vaccinated IM in study 004. The difference in local reactions is likely due to the different route of administration. The incidence of systemic events was either similar to or lower in study 3003 compared with study 004.
Safety data from study 3008 demonstrate similar rates of local reactions and systemic events among 13vPnC and 7vPnC recipients. The rates and nature of SAEs and other AEs associated with 13vPnC were similar to those associated with 7vPnC. The safety profile of 13vPnC was shown to be comparable with that of 7vPnC and the frequency of adverse drug reactions (ADRs) has not changed compared with the frequency reported in the MAA.

The data presented in this Article 46 submission package do not alter the benefit-risk assessment of 13vPnC; therefore, no further regulatory action is required at this time with respect to the marketing authorization for Prevenar 13.

Assessor's comment: The conclusions of the MAH are generally endorsed, except that the safety results of the Japanese study and the US study are not considered comparable. The Japanese study provides data on SC administration of Prevenar 13, which has not been used previously in other clinical studies. This information can be useful for prescribers when vaccinating children with thrombocytopaenia or any coagulation disorder that would contraindicate intramuscular injection. Therefore, we do not agree that no further regulatory action is required, and the MAH should submit a variation to include a statement on subcutaneous administration.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Immunogenicity: The conclusions of the MAH are generally endorsed. The Immunogenicity results from the two submitted studies are in agreement with previously submitted studies.
Safety: The conclusions of the MAH are generally endorsed. The safety results from the two submitted studies are in agreement with previously submitted studies.
However, we do not agree with the MAH that no further regulatory action is needed. The Japanese study provides data on SC administration of Prevenar 13, which has not been used previously in other clinical studies. This information can be useful for prescribers when vaccinating children with thrombocytopaenia or any coagulation disorder that would contraindicate intramuscular injection. Therfore the MAH should submit a variation to include a statement on subcutaneous administration.

Update 2010-05-11
One comment from a MS was received not supporting the demand for a type II variation. The Rapporteur does not agree with the MS comment. Since information is available from SC vaccination of children this could be valuable for the prescriber. However, the Rapporteur does agree that it is not possible to state that the immune responses are in any way superior to IM vaccination, considering that the data are not entirely comparable due to the many differences between the studies. The Rapporteur suggests a statement in the SPC that the vaccine has been given SC without safety or immunogenicity concerns.

- **Overall conclusion**
- **Recommendation**

X Fulfilled –

Type II variation to be requested from the MAH by October 1, 2010.

☐ **Not fulfilled:**

IV. ADDITIONAL CLARIFICATIONS REQUESTED

None.