EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 February 2015
EMA/126275/2015
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 042

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

I. INTRODUCTION

On June 23, 2011 the MAH submitted a completed paediatric study 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 study does not influence the benefit risk for Prevenar 13 and that there is no consequential regulatory action.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the study(ies)

The formulation used in the studies was the same as the currently approved formulation.

II.2 Clinical aspects

1. Introduction

The MAH submitted a final report for:

6096A-3016; FINAL REPORT: PILOT: Characterization of the Prevnar Infant Long-Term Immune Response Versus a Prevnar-Naive Cohort

2. Clinical study

6096A-3016; FINAL REPORT: PILOT: Characterization of the Prevnar Infant Long-Term Immune Response Versus a Prevnar-Naive Cohort

- **Description**

Study 6096A1-3016 is part of the global clinical development program for the use of Prevenar 13 in infants and children. Study 6096A1-3016 was conducted in United States in subjects who were originally enrolled in the pivotal phase 3 safety, immunogenicity, and efficacy study for 7vPnC (protocol D118-P8). Subjects in the study 6096A1-3016 were 11 to 14 years of age at the time of vaccination. This study was designed to characterize the "late" immune response to an additional dose of pneumococcal conjugate vaccine (PnC) more than 10 years after primary vaccination with 7vPnC in infancy versus a 7vPnC-naïve cohort.

- **Methods**

  - Objectives

The primary objective of the study was to characterize the "late" immune response to an additional dose of pneumococcal conjugate vaccine more than 10 years after primary vaccination with 7-valent pneumococcal conjugate vaccine (7vPnC) in infancy versus a 7vPnCnaïve cohort.

The exploratory objective of the study was to evaluate kinetics of secondary immune responses in order to measure serotype-specific anti-pneumococcal immunoglobulin G (IgG) and opsonophagocytic assay (OPA) titer.

The safety objective was to evaluate the safety profile of 13-valent pneumococcal conjugate vaccine (13vPnC) as measured by the rate of serious adverse events (SAEs), adverse events (AEs), and solicited local reactions and systemic events in the 2 groups.

  - Study design

This was a single-center open-label, nonrandomized study in which all children received a single dose of 13vPnC.

- Study population /Sample size

Children were recruited based on their prior participation in a pneumococcal conjugate versus meningococcal C conjugate (MnCC) clinical study conducted at Northern California Kaiser Permanente (NCKP) in California, United States, between 1995 and 1998 (protocol D118-P8). More than 38,000 subjects were enrolled in the original study and were randomized to receive a primary series of the Wyeth investigational 7vPnC (now licensed and marketed in the United States as Prevnar) or MnCC (now licensed and marketed outside the United States as Meningitec) at 2, 4, 6, and 12 to 15 months of age. Subjects from both vaccine groups were recruited in the current study to return to receive a single dose of 13vPnC at visit 1.

A sufficient number of subjects (approximately 75) was to be enrolled within 6 months to ensure at least 50 evaluable subjects (25 per group):

- 25 fully vaccinated per-protocol subjects (4 doses of vaccine given at 2, 4, 6, and 12 to 15 months of age) originally enrolled in the 7vPnC group of the study, and
- 25 fully vaccinated per-protocol subjects originally enrolled in the control group of the study (who received MnCC) who did not receive 7vPnC after the close of the study.

- Treatments

All subjects received a single dose of Prevenar 13.

- Outcomes/endpoints

Blood samples (approximately 30 mL total, 10 mL each at visits 1, 4, and 5) were collected from every subject prior to vaccination, on day 7 to 10, and on day 28 to 42 after vaccination.
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 determined in all subjects for each blood sample using a standardized ELISA and expressed as µg/mL.

Serotype specific opsonophagocytic activity was determined using a modified microcolony opsonophagocytic assay (mcOPA) and expressed as a titer.

The co-primary endpoints specified in the protocol were the proportion of subjects achieving a serotype-specific IgG concentration ≥0.35 µg/mL by ELISA and the proportion of subjects achieving a titer ≥1:8 by OPA for each of the pneumococcal serotypes at visit 5 (28 to 42 days after vaccine administration). These endpoints were selected based on the World Health Organization (WHO) guideline for evaluation of pneumococcal serotypes.
However, based on the use of the microcolony OPA (mcOPA) assay instead of the planned dribble OPA (dOAP) assay, an OPA responder was defined as a subject with an OPA titer ≥lower limit of quantitation (LLOQ). Analyses using an OPA ≥1:8 were also reported. In addition, the proportion of subjects achieving a serotype-specific IgG concentration ≥1.0 µg/mL by ELISA was calculated.

- Statistical Methods

For each serotype, exact, unconditional, 2-sided 95% confidence intervals (CIs) on the proportions of subjects achieving IgG concentration ≥0.35 µg/mL, OPA titers ≥1:8, IgG concentration ≥1.0 µg/mL and OPA titers ≥LLOQ were calculated. To assess treatment differences, exact, unconditional, 2-sided, 95% CIs on the difference in proportions (7vPnC/13vPnC – MnCC/13vPnC) were calculated.
Within each vaccine group and for each antibody concentration or titer, geometric mean concentrations/titers (GMCs/GMTs) were calculated. Each concentration/titer was logarithmically transformed for analysis. Two (2)-sided, 95% CIs were constructed by back transformation of the CI for the mean of the logarithmically transformed assay results computed using the Student t distribution. The geometric mean fold rises (GMFRs) in antibody concentration/titers (postvaccination/prevaccination) were summarized by geometric means and 95% CIs, also computed using the logarithmically transformed assay results. To assess differences between the 2 vaccine groups, 2-sided, 95% CIs for the ratio [(7vPnC/13vPnC)/(MnCC/13vPnC)] of the GMCs and the GMTs were constructed. In addition, the ratio of the GMFRs and 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 (7vPnC/13vPnC relative to MnCC/13vPnC).

Reverse cumulative distribution curves (RCDCs) were presented graphically by vaccination group for each serotype-specific pneumococcal IgG concentration and OPA titer before and after vaccination.
The kinetics of the immune response were described by graphical representations of summary values over time for the immunogenicity endpoints.
The safety variables were AEs, local reactions, systemic events including fever, and vital signs. Fever was defined as an oral temperature ≥38.0°C (100.4°F). The proportion of subjects with local reactions and systemic events reported on any day within the 4-day period after vaccination was summarized for each type of event. Use of antipyretic medication was reported with systemic events, but these were analyzed separately.

AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) and the incidence of each type of event (MedDRA preferred term) was summarized.

Comparisons between the vaccine groups were performed using a 2-sided Fisher's exact test. All summaries show the number and percentage of subjects with at least 1 event and the number of events. Additional summaries by AE severity or by vaccine relationship were also produced.

- **Results**

- Recruitment/ Number analysed

Of the 75 enrolled subjects, 74 (98.7%) subjects were included in the all-available immunogenicity population and 73 (97.3%) subjects were included in both the evaluable immunogenicity population and the evaluable kinetic population.
One (1) subject (1.3%) in the MnCC/13vPnC group did not receive the 13vPnC vaccination and was excluded from the all-available immunogenicity population because no assay results for any pneumococcal serotypes were available. Two (2) subjects (2.7%) were excluded from both the evaluable immunogenicity population and the evaluable kinetic population: 1 subject was not in the all-available immunogenicity population (above mentioned subject), and 1 subject received prohibited concomitant vaccines.

- Efficacy results

Proportion of Subjects Achieving IgG Concentrations ≥0.35 µg/mL
The proportions of subjects in the evaluable immunogenicity population achieving a pneumococcal IgG concentration ≥0.35 µg/mL before vaccination with 13vPnC (visit 1) were generally similar for the assessed serotypes between the 2 groups and greater than or equal to 62.9% with the exception of serotype 4 (≥28.0%).
For the 7 serotypes present in 7vPnC, the proportion of subjects achieving IgG concentrations ≥0.35 µg/mL at visit 5 (28 to 42 days after 13vPnC) was 100% for each serotype in both vaccine groups of the evaluable immunogenicity population, except for serotype 14 (97.1%) in the MnCC/13vPnC group (Table 9-3).
For the 6 additional serotypes in 13vPnC but not in 7vPnC the proportion of responders in both groups was 100% except for serotype 3 (94.7% and 97.0% in the 7vPnC/13vPnC and MnCC/13vPnC groups, respectively; Table 9-3).
Results for the all-available immunogenicity population were overall similar to those observed for the evaluable immunogenicity population.

Table 9-3: Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After Vaccination (Visit 5) – Evaluable Immunogenicity Population

	Vaccine Group									
	7vPnC/13vPnC				MnCC/13vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	38	38	100.0	(90.7, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-9.5, 10.0)
6B	38	38	100.0	(90.7, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-9.5, 10.0)
9V	38	38	100.0	(90.7, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-9.5, 10.0)
14	38	38	100.0	(90.7, 100.0)	35	34	97.1	(85.1, 99.9)	2.9	(-6.9, 14.9)
18C	38	38	100.0	(90.7, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-9.5, 10.0)
19F	38	38	100.0	(90.7, 100.0)	34	34	100.0	(89.7, 100.0)	0.0	(-9.4, 10.3)
23F	38	38	100.0	(90.7, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-9.5, 10.0)
Additional										
1	38	38	100.0	(90.7, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-9.5, 10.0)
3	38	36	94.7	(82.3, 99.4)	33	32	97.0	(84.2, 99.9)	-2.2	(-15.7, 10.9)
5	38	38	100.0	(90.7, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-9.5, 10.0)
6A	38	38	100.0	(90.7, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-9.5, 10.0)
7F	38	38	100.0	(90.7, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-9.5, 10.0)
19A	38	38	100.0	(90.7, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-9.5, 10.0)

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, [(7vPnC/13vPnC) – (MnCC/13vPnC)], expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, [(7vPnC/13vPnC) – (MnCC/13vPnC)], expressed as a percentage.

Proportion of Subjects Achieving OPA Titers ≥LLOQ

The proportions of subjects in the evaluable immunogenicity population achieving pneumococcal OPA titers ≥LLOQ before vaccination with 13vPnC (visit 1) were generally similar for the 2 groups. For the 7 serotypes present in 7vPnC, the proportion of subjects achieving OPA titers ≥LLOQ ranged from 21.4% (serotype 23F) to 90.6% (serotype 6B). For the 6 additional serotypes included in 13vPnC but not in 7vPnC, the proportion of responders ranged from 2.8% (serotype 5) to 72.7% (serotype 19A).

For the 7 serotypes present in 7vPnC, the proportion of subjects in the evaluable immunogenicity population achieving OPA titers ≥LLOQ at visit 5 (28 to 42 days after vaccination) was 100% for each serotype in both vaccine groups except for serotype 19F (Table 9-4).

For the 6 additional serotypes in 13vPnC but not in 7vPnC, 100% of subjects in both groups achieved OPA titers ≥LLOQ for each serotype, with the exception of serotype 1, serotype 5 and serotype 19A.

Results for the all-available immunogenicity population were overall similar to those observed for the evaluable immunogenicity population.

Table 9-4: Comparison of Subjects Achieving a Pneumococcal OPA Antibody Titer ≥ LLOQ After Vaccination (Visit 5) – Evaluable Immunogenicity Population

	Vaccine Group									
	7vPnC/13vPnC				MnCC/13vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	36	36	100.0	(90.3, 100.0)	32	32	100.0	(89.1, 100.0)	0.0	(-10.2, 10.9)
6B	37	37	100.0	(90.5, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-10.0, 10.1)
9V	38	38	100.0	(90.7, 100.0)	34	34	100.0	(89.7, 100.0)	0.0	(-9.4, 10.3)
14	38	38	100.0	(90.7, 100.0)	34	34	100.0	(89.7, 100.0)	0.0	(-9.4, 10.3)
18C	38	38	100.0	(90.7, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-9.5, 10.0)
19F	38	37	97.4	(86.2, 99.9)	34	34	100.0	(89.7, 100.0)	-2.6	(-13.9, 8.0)
23F	37	37	100.0	(90.5, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-10.0, 10.1)
Additional										
1	38	38	100.0	(90.7, 100.0)	34	33	97.1	(84.7, 99.9)	2.9	(-6.7, 15.3)
3	38	38	100.0	(90.7, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-9.5, 10.0)
5	38	34	89.5	(75.2, 97.1)	35	31	88.6	(73.3, 96.8)	0.9	(-15.0, 17.6)
6A	38	38	100.0	(90.7, 100.0)	34	34	100.0	(89.7, 100.0)	0.0	(-9.4, 10.3)
7F	37	37	100.0	(90.5, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-10.0, 10.1)
19A	38	37	97.4	(86.2, 99.9)	35	35	100.0	(90.0, 100.0)	-2.6	(-13.9, 7.6)

a. N = number of subjects with a determinate OPA antibody titer to the given serotype.
b. n = Number of subjects with an antibody titer ≥ LLOQ for the given serotype.
c. Exact 2-sided confidence interval based on the observed proportion of subjects.
d. Difference in proportions, [(7vPnC/13vPnC) – (MnCC/13vPnC)], expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, [(7vPnC/13vPnC) – (MnCC/13vPnC)], expressed as a percentage.

IgG Concentrations ≥1.0 µg/mL

The proportions of subjects in the evaluable immunogenicity population achieving pneumococcal IgG concentrations ≥1.0 µg/mL before vaccination with 13vPnC (visit 1) were generally similar between the 2 groups and greater than or equal to 31.6% with the exception of serotype 4 (≥16.0%).

For the 7 serotypes present in 7vPnC, the proportion of subjects achieving IgG concentrations ≥1.0 µg/mL at visit 5 (28 to 42 days after 13vPnC) was 100% for each serotype in both vaccine groups of the evaluable immunogenicity population, except for serotype 9V, serotype 14 and serotype 18C; (Table 9-5).

For the 6 additional serotypes in 13vPnC but not in 7vPnC the proportion of responders in both groups was 100% for each serotype except for serotype 1, serotype 3 (81.6% and 66.7% in the 7vPnC/13vPnC and MnCC/13vPnC groups, respectively), serotype 5 and serotype 7F (Table 9-5). None of the differences between the 2 groups were considered clinically relevant.

Results for the all-available immunogenicity population were overall similar to those observed for the evaluable immunogenicity population.

Table 9-5: Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥1.0 µg/mL After Vaccination (Visit 5) – Evaluable Immunogenicity Population

	Vaccine Group									
	7vPnC/13vPnC				MnCC/13vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	38	38	100.0	(90.7, 100.0)	35	30	85.7	(69.7, 95.2)	14.3	(3.2, 30.3)
6B	38	38	100.0	(90.7, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-9.5, 10.0)
9V	38	38	100.0	(90.7, 100.0)	35	34	97.1	(85.1, 99.9)	2.9	(-6.9, 14.9)
14	38	37	97.4	(86.2, 99.9)	35	32	91.4	(76.9, 98.2)	5.9	(-6.6, 20.3)
18C	38	37	97.4	(86.2, 99.9)	35	34	97.1	(85.1, 99.9)	0.2	(-11.6, 12.5)
19F	38	38	100.0	(90.7, 100.0)	34	34	100.0	(89.7, 100.0)	0.0	(-9.4, 10.3)
23F	38	38	100.0	(90.7, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-9.5, 10.0)
Additional										
1	38	38	100.0	(90.7, 100.0)	35	33	94.3	(80.8, 99.3)	5.7	(-4.2, 19.2)
3	38	31	81.6	(65.7, 92.3)	33	22	66.7	(48.2, 82.0)	14.9	(-6.0, 35.8)
5	38	36	94.7	(82.3, 99.4)	35	33	94.3	(80.8, 99.3)	0.5	(-12.8, 14.6)
6A	38	38	100.0	(90.7, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-9.5, 10.0)
7F	38	38	100.0	(90.7, 100.0)	35	33	94.3	(80.8, 99.3)	5.7	(-4.2, 19.2)
19A	38	38	100.0	(90.7, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-9.5, 10.0)

a. N = number of subjects with a determinate IgG antibody concentration to the given serotype.
b. n = Number of subjects with an antibody concentration ≥1.0 µg/mL for the given serotype.
c. Exact 2-sided confidence interval based on the observed proportion of subjects.
d. Difference in proportions, [(7vPnC/13vPnC) – (MnCC/13vPnC)], expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, [(7vPnC/13vPnC) – (MnCC/13vPnC)], expressed as a percentage.

IgG Geometric Mean Concentrations

Before vaccination with 13vPnC (visit 1), IgG GMCs in the evaluable immunogenicity population for all 13 serotypes were generally similar for the 2 vaccine groups (Table 9-7).

For the 7 serotypes present in 7vPnC, IgG GMCs at visit 5 in the 7vPnC/13vPnC group ranged from 5.72 µg/mL (serotype 18C) to 66.72 µg/mL (serotype 6B; Table 9-6). In the MnCC/13vPnC group, GMCs ranged from 2.92 µg/mL (serotype 4) to 22.62 µg/mL (serotype 6B). The GMC ratios (7vPnC/13vPnC to MnCC/13vPnC) ranged from 0.63 (serotype 18C) to 2.95 (serotype 6B) and were >1.0 for 4 of the 7 serotypes; the lower limit of the 95% CI was >1.0 for serotypes 4, 6B, 9V and 14.

For the 6 additional serotypes in 13vPnC but not in 7vPnC, the GMCs were generally similar between the 2 vaccine groups. In the 7vPnC/13vPnC group, GMCs ranged from 2.13 µg/mL (serotype 3) to 29.11 µg/mL (serotype 6A). In the MnCC/13vPnC group, GMCs ranged from 1.71 µg/mL (serotype 3) to 20.17 µg/mL (for serotype 19A). The GMC ratios (7vPnC/13vPnC to MnCC/13vPnC) ranged from 0.90 (serotype 5) to 1.81 (serotype 6A); the 95% CIs included 1.0 for all serotypes except for serotype 7F where the lower limit was >1.0.

Table 9-7 presents the pneumococcal IgG GMFRs from predose to visit 5 (28 through 42 days after 13vPnC) for the evaluable immunogenicity population. For all serotypes, the GMCs increased from predose to Visit 5.

Results for the all-available immunogenicity population were overall similar to those observed for the evaluable immunogenicity population.

Table 9-6: Comparison of Pneumococcal IgG GMCs (µg/mL) After Vaccination (Visit 5) – Evaluable Immunogenicity Population

	Vaccine Group							
	7vPnC/13vPnC			MnCC/13vPnC				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	38	5.73	(4.21, 7.81)	35	2.92	(2.22, 3.83)	1.97	(1.31, 2.95)
6B	38	66.72	(50.19, 88.70)	35	22.62	(14.56, 35.16)	2.95	(1.78, 4.90)
9V	38	8.72	(6.68, 11.40)	35	4.70	(3.49, 6.33)	1.85	(1.25, 2.75)
14	38	41.45	(27.72, 61.97)	35	18.50	(10.10, 33.90)	2.24	(1.11, 4.53)
18C	38	5.72	(4.18, 7.82)	35	9.04	(5.98, 13.68)	0.63	(0.38, 1.05)
19F	38	14.17	(9.54, 21.07)	34	15.80	(10.00, 24.96)	0.90	(0.50, 1.62)
23F	38	17.20	(12.44, 23.77)	35	20.80	(13.07, 33.08)	0.83	(0.48, 1.43)
Additional								
1	38	9.55	(6.46, 14.13)	35	5.63	(3.67, 8.64)	1.70	(0.96, 3.00)
3	38	2.13	(1.58, 2.87)	33	1.71	(1.20, 2.44)	1.25	(0.79, 1.96)
5	38	6.80	(4.75, 9.74)	35	7.52	(5.12, 11.04)	0.90	(0.54, 1.52)
6A	38	29.11	(19.04, 44.50)	35	16.08	(10.18, 25.40)	1.81	(0.98, 3.34)
7F	38	9.92	(7.03, 14.01)	35	5.75	(3.98, 8.33)	1.72	(1.05, 2.83)
19A	38	21.29	(14.90, 30.43)	35	20.17	(15.28, 26.63)	1.06	(0.67, 1.66)

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; (7vPnC/13vPnC) to (MnCC/13vPnC).
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 [(7vPnC/13vPnC) – (MnCC/13vPnC)].

Table 9-7: Pneumococcal IgG GMCs (µg/mL) and Fold Rises for Vaccination (Visit 5) – Evaluable Immunogenicity Population

		Sampling Time[a]								
		Prevaccination (Visit 1)			Postvaccination (Visit 5)			Fold Rise		
Serotype	Vaccine Group	n[b]	GMC[c]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])	n[b]	GMFR[e]	(95% CI[d])
7vPnC										
4	7vPnC/13vPnC	31	0.20	(0.12, 0.33)	31	5.96	(4.10, 8.65)	31	29.47	(17.61, 49.33)
	MnCC/13vPnC	25	0.15	(0.07, 0.29)	25	2.86	(2.00, 4.07)	25	19.68	(9.99, 38.77)
6B	7vPnC/13vPnC	38	5.89	(4.61, 7.51)	38	66.72	(50.19, 88.70)	38	11.34	(8.49, 15.13)
	MnCC/13vPnC	35	3.97	(2.78, 5.67)	35	22.62	(14.56, 35.16)	35	5.70	(3.90, 8.33)
9V	7vPnC/13vPnC	37	1.54	(1.19, 2.00)	37	8.62	(6.55, 11.34)	37	5.58	(4.06, 7.67)
	MnCC/13vPnC	35	1.69	(1.20, 2.38)	35	4.70	(3.49, 6.33)	35	2.78	(2.16, 3.57)
14	7vPnC/13vPnC	38	0.58	(0.39, 0.86)	38	41.45	(27.72, 61.97)	38	71.09	(40.74, 124.08)
	MnCC/13vPnC	35	0.79	(0.43, 1.43)	35	18.50	(10.10, 33.90)	35	23.46	(13.17, 41.79)
18C	7vPnC/13vPnC	37	0.75	(0.48, 1.18)	37	5.93	(4.34, 8.11)	37	7.91	(4.92, 12.73)
	MnCC/13vPnC	33	0.72	(0.46, 1.13)	33	9.79	(6.43, 14.90)	33	13.68	(8.94, 20.92)
19F	7vPnC/13vPnC	36	2.94	(2.08, 4.15)	36	13.41	(8.89, 20.23)	36	4.56	(2.87, 7.26)
	MnCC/13vPnC	32	2.01	(1.32, 3.05)	32	18.02	(11.56, 28.08)	32	8.98	(6.21, 12.97)
23F	7vPnC/13vPnC	38	2.51	(1.92, 3.27)	38	17.20	(12.44, 23.77)	38	6.85	(4.51, 10.42)
	MnCC/13vPnC	35	2.31	(1.70, 3.14)	35	20.80	(13.07, 33.08)	35	9.00	(5.91, 13.72)
Additional										
1	7vPnC/13vPnC	30	1.04	(0.71, 1.54)	30	11.59	(7.34, 18.30)	30	11.10	(6.98, 17.64)
	MnCC/13vPnC	32	0.70	(0.43, 1.15)	32	5.30	(3.40, 8.26)	32	7.58	(5.36, 10.72)
3	7vPnC/13vPnC	36	1.30	(0.83, 2.04)	36	2.19	(1.60, 2.99)	36	1.68	(1.37, 2.07)
	MnCC/13vPnC	31	1.16	(0.73, 1.86)	31	1.81	(1.25, 2.62)	31	1.56	(1.30, 1.86)
5	7vPnC/13vPnC	38	3.24	(2.45, 4.27)	38	6.80	(4.75, 9.74)	38	2.10	(1.52, 2.90)

	MnCC/13vPnC	34	3.83	(2.77, 5.31)	34	7.39	(4.98, 10.96)	34	1.93	(1.43, 2.60)
6A	7vPnC/13vPnC	38	3.78	(2.85, 5.03)	38	29.11	(19.04, 44.50)	38	7.70	(4.77, 12.42)
	MnCC/13vPnC	34	3.82	(2.79, 5.23)	34	17.05	(10.82, 26.87)	34	4.46	(3.09, 6.45)
7F	7vPnC/13vPnC	38	1.38	(0.93, 2.05)	38	9.92	(7.03, 14.01)	38	7.20	(4.95, 10.48)
	MnCC/13vPnC	34	1.12	(0.73, 1.72)	34	5.94	(4.08, 8.65)	34	5.32	(3.65, 7.75)
19A	7vPnC/13vPnC	38	7.05	(5.52, 8.99)	38	21.29	(14.90, 30.43)	38	3.02	(2.23, 4.10)
	MnCC/13vPnC	35	6.18	(4.57, 8.35)	35	20.17	(15.28, 26.63)	35	3.27	(2.49, 4.28)

a. Prespecified timing for blood sample.
b. n = Number of subjects with valid and determinate assay results for the specified serotype at both the prevaccination and postvaccination blood draws.
c. Geometric mean concentrations (GMCs) were calculated using all subjects with available data at both the prevaccination and postvaccination blood draws.
d. Confidence intervals (CIs) are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations, or the mean fold rise.
e. Geometric mean fold rises (GMFRs) were calculated (postvaccination/prevaccination) using all subjects with available data from both the prevaccination and postvaccination blood draws.

OPA Geometric Mean Titers

Before vaccination with 13vPnC (visit 1), OPA GMTs in the evaluable immunogenicity population for all 13 serotypes were, with some exceptions, generally similar between the 2 vaccine groups (Table 9-11). For the 7 serotypes present in 7vPnC, the GMT ratios (7vPnC/13vPnC to MnCC/13vPnC) ranged from 0.3 (serotype 9V) to 7.4 (serotype 23F).

For the 6 additional serotypes in 13vPnC but not in 7vPnC the GMT ratios ranged from 0.7 (serotypes 6A and 7F) to 1.9 (serotype 19A).

For the 7 serotypes present in 7vPnC, OPA GMTs at visit 5 were also generally similar in the 2 vaccine groups (Table 9-10). The GMT ratios (7vPnC/13vPnC to MnCC/13vPnC) ranged from 0.6 (serotypes 19F and 23F) to 1.1 (serotype 6B). The upper limit of 95% CI was <1.0 for serotype 23F; all other 95% CIs for the ratios included 1.0.

For the 6 additional serotypes in 13vPnC but not in 7vPnC, the GMTs were also generally similar for the 2 vaccine groups. The GMT ratios (7vPnC/13vPnC to MnCC/13vPnC) ranged from 0.9 (serotypes 5, 6A and 19A) to 1.3 (serotype 1); the 95% CIs for the ratios included 1.0 for all serotypes.

Results for the all-available immunogenicity population were overall similar to those observed for the evaluable immunogenicity population.

Table 9-10: Comparison of Pneumococcal OPA GMTs After Vaccination (Visit 5) – Evaluable Immunogenicity Population

	Vaccine Group							
	7vPnC/13vPnC			MnCC/13vPnC				
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	36	4626	(3322.5, 6441.2)	32	6065	(4590.9, 8012.5)	0.8	(0.50, 1.17)
6B	37	11451	(8290.4, 15817.9)	35	10380	(7515.2, 14336.9)	1.1	(0.70, 1.73)
9V	38	6346	(5152.2, 7817.5)	34	7555	(5916.7, 9646.8)	0.8	(0.61, 1.15)
14	38	5898	(4481.0, 7762.1)	34	7031	(5195.6, 9515.5)	0.8	(0.56, 1.25)
18C	38	5090	(3428.4, 7557.7)	35	6005	(4389.3, 8214.6)	0.8	(0.51, 1.40)
19F	38	1623	(995.2, 2647.9)	34	2696	(1831.0, 3968.5)	0.6	(0.32, 1.12)
23F	37	2752	(2074.6, 3651.3)	35	4841	(3574.5, 6555.1)	0.6	(0.38, 0.85)
Additional								
1	38	449	(312.8, 643.2)	34	347	(228.3, 527.4)	1.3	(0.75, 2.22)
3	38	113	(89.2, 143.5)	35	99	(77.0, 126.3)	1.1	(0.82, 1.61)
5	38	296	(158.8, 549.9)	35	336	(175.4, 642.2)	0.9	(0.36, 2.13)
6A	38	9458	(6674.2, 13404.0)	34	10842	(7904.9, 14870.9)	0.9	(0.55, 1.39)
7F	37	6740	(4933.2, 9207.7)	35	6050	(4515.0, 8106.7)	1.1	(0.73, 1.70)
19A	38	2120	(1308.0, 3435.3)	35	2340	(1667.0, 3285.4)	0.9	(0.50, 1.63)

a. n = Number of subjects with a determinate antibody titer for the specified serotype.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
d. Ratio of GMTs; (7vPnC/13vPnC) to (MnCC/13vPnC).
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 [(7vPnC/13vPnC) – (MnCC/13vPnC)].

Table 9-11 presents a summary of the pneumococcal OPA GMFRs from predose to visit 5 (28 through 42 days after 13vPnC) for the evaluable immunogenicity population. For all serotypes, the GMTs increased from predose to Visit 5.

Table 9-11: Pneumococcal OPA GMTs and Fold Rises for Vaccination (Visit 5) – Evaluable Immunogenicity Population

		Sampling Time[a]								
		Prevaccination (Visit 1)			Postvaccination (Visit 5)			Fold Rise		
Serotype	Vaccine Group	n[b]	GMT[c]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])	n[b]	GMFR[e]	(95% CI[d])
7vPnC										
4	7vPnC/13vPnC	21	22	(6.3, 80.7)	21	4535	(2836.5, 7251.3)	21	201.8	(55.11, 739.05)
	MnCC/13vPnC	13	28	(4.5, 174.3)	13	4704	(2958.0, 7481.1)	13	168.8	(20.22, 1409.76)
6B	7vPnC/13vPnC	31	1024	(488.4, 2148.4)	31	11939	(8748.1, 16293.9)	31	11.7	(5.20, 26.10)
	MnCC/13vPnC	27	288	(74.8, 1106.9)	27	11607	(7762.6, 17354.1)	27	40.3	(10.97, 148.44)
9V	7vPnC/13vPnC	27	43	(13.4, 137.3)	27	6709	(5097.5, 8829.4)	27	156.4	(48.72, 501.86)
	MnCC/13vPnC	30	120	(37.9, 382.8)	30	7457	(5702.3, 9751.9)	30	61.9	(18.83, 203.72)
14	7vPnC/13vPnC	32	159	(63.7, 396.0)	32	5946	(4361.1, 8107.6)	32	37.4	(13.71, 102.31)
	MnCC/13vPnC	29	262	(98.1, 700.5)	29	7006	(4997.7, 9822.1)	29	26.7	(9.67, 73.84)
18C	7vPnC/13vPnC	37	54	(19.5, 149.5)	37	5067	(3375.1, 7607.2)	37	93.9	(30.99, 284.31)
	MnCC/13vPnC	33	25	(8.4, 75.7)	33	5736	(4141.4, 7943.8)	33	226.9	(79.81, 645.29)
19F	7vPnC/13vPnC	38	33	(15.1, 73.3)	38	1623	(995.2, 2647.9)	38	48.7	(23.27, 101.97)
	MnCC/13vPnC	34	23	(10.5, 50.6)	34	2696	(1831.0, 3968.5)	34	116.8	(54.54, 250.13)
23F	7vPnC/13vPnC	32	87	(34.1, 223.4)	32	2799	(2048.5, 3823.2)	32	32.1	(11.99, 85.81)
	MnCC/13vPnC	28	11	(5.0, 23.5)	28	5197	(3599.2, 7503.1)	28	481.0	(207.01, 1117.69)
Additional										
1	7vPnC/13vPnC	36	6	(4.3, 7.4)	36	440	(301.8, 641.2)	36	78.1	(50.42, 120.94)
	MnCC/13vPnC	33	5	(4.0, 6.6)	33	341	(221.9, 524.9)	33	66.5	(41.80, 105.75)
3	7vPnC/13vPnC	37	11	(6.9, 16.6)	37	111	(87.1, 141.1)	37	10.3	(6.80, 15.72)
	MnCC/13vPnC	33	11	(7.0, 18.2)	33	98	(75.2, 126.9)	33	8.6	(5.36, 13.94)
5	7vPnC/13vPnC	36	4	(3.6, 5.6)	36	277	(145.2, 526.4)	36	61.7	(32.75, 116.34)
	MnCC/13vPnC	35	4	(3.7, 5.0)	35	336	(175.4, 642.2)	35	78.2	(41.38, 147.80)

6A	7vPnC/13vPnC	35	17	(7.1, 39.7)	35	9029	(6255.0, 13034.0)	35	536.5	(212.04, 1357.19)
	MnCC/13vPnC	31	24	(8.9, 64.2)	31	10488	(7460.6, 14744.7)	31	438.1	(169.52, 1132.43)
7F	7vPnC/13vPnC	31	60	(17.7, 205.3)	31	7036	(4886.0, 10131.8)	31	116.9	(33.28, 410.33)
	MnCC/13vPnC	29	76	(21.1, 275.2)	29	6098	(4392.9, 8464.9)	29	80.0	(23.28, 274.82)
19A	7vPnC/13vPnC	33	76	(36.7, 157.5)	33	1869	(1099.8, 3177.3)	33	24.6	(11.30, 53.42)
	MnCC/13vPnC	33	39	(19.9, 78.1)	33	2424	(1696.6, 3462.4)	33	61.5	(28.73, 131.76)

a. Prespecified timing for blood sample.
b. n = Number of subjects with valid and determinate assay results for the specified serotype at both the prevaccination and postvaccination blood draws.
c. Geometric mean titers (GMTs) were calculated using all subjects with available data at both the prevaccination and postvaccination visits.
d. Confidence intervals (CIs) are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the titers, or the mean fold rise.
e. Geometric mean fold rises (GMFRs) were calculated (postvaccination/prevaccination) using all subjects with available data from both the prevaccination and postvaccination blood draws.

Kinetics

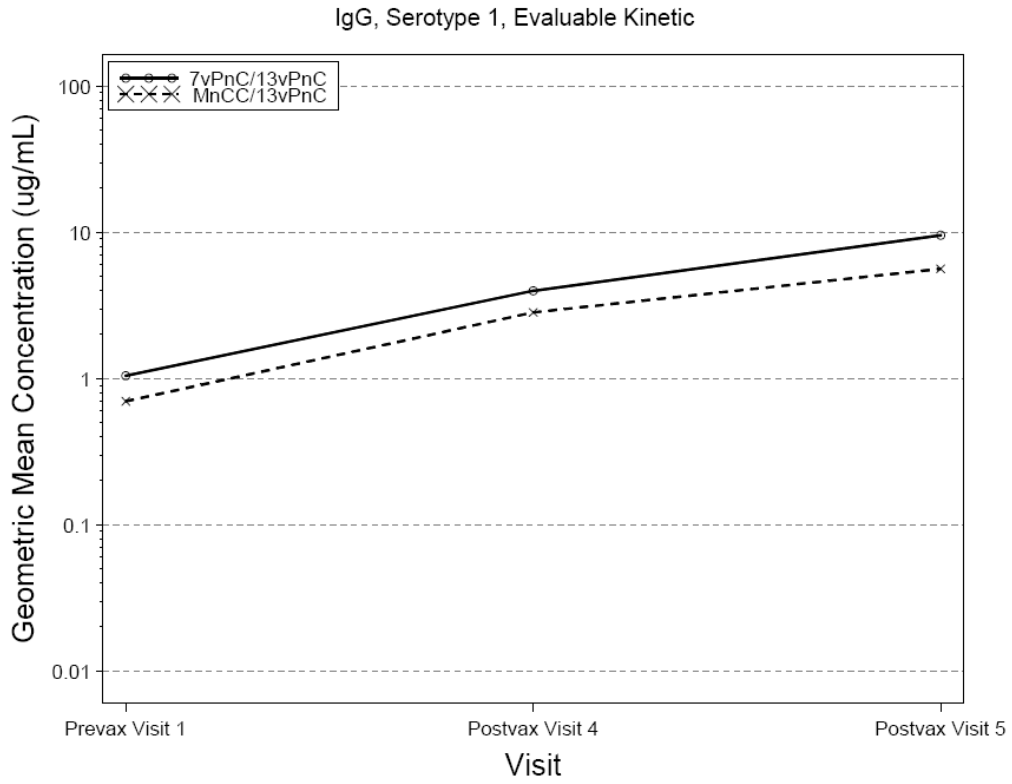
IgG Geometric Mean Concentrations

IgG concentrations over time for each of the serotypes in 13vPnC before vaccination with 13vPnC (visit 1) and after vaccination at visits 4 and 5 were presented for the evaluable kinetic population. Representative examples ar shown in Figures 16-27 and 16-29.

The pneumococcal IgG GMCs in the evaluable kinetic population at the prevaccination visit 1 and the postvaccination visits 4 and 5 are summarized in Table 9-14.

For all the 13 serotypes, GMCs increased from visit 1 to visit 4, and further increased to visit 5 in both vaccine groups.

16.27 Kinetic Curves, Serotype 1, IgG Antibody Concentrations - Evaluable Kinetic Population



16.29 Kinetic Curves, Serotype 4, IgG Antibody Concentrations - Evaluable Kinetic Population

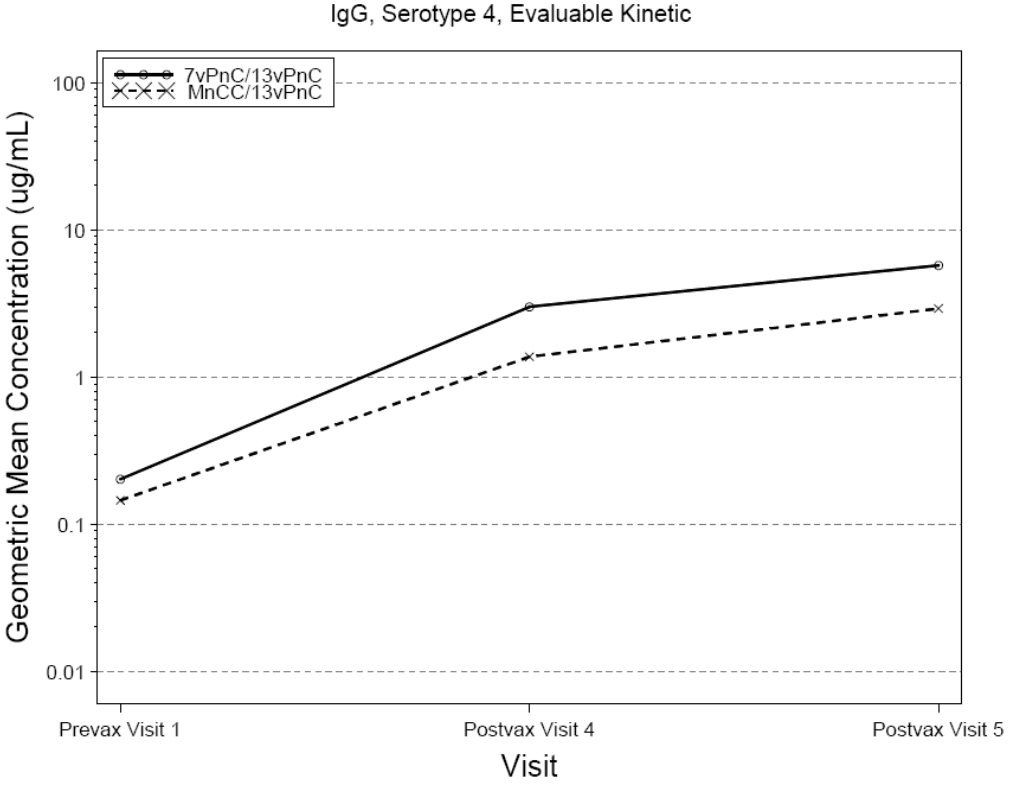


Table 9-14: Pneumococcal IgG GMCs (µg/mL) – Evaluable Kinetic Population

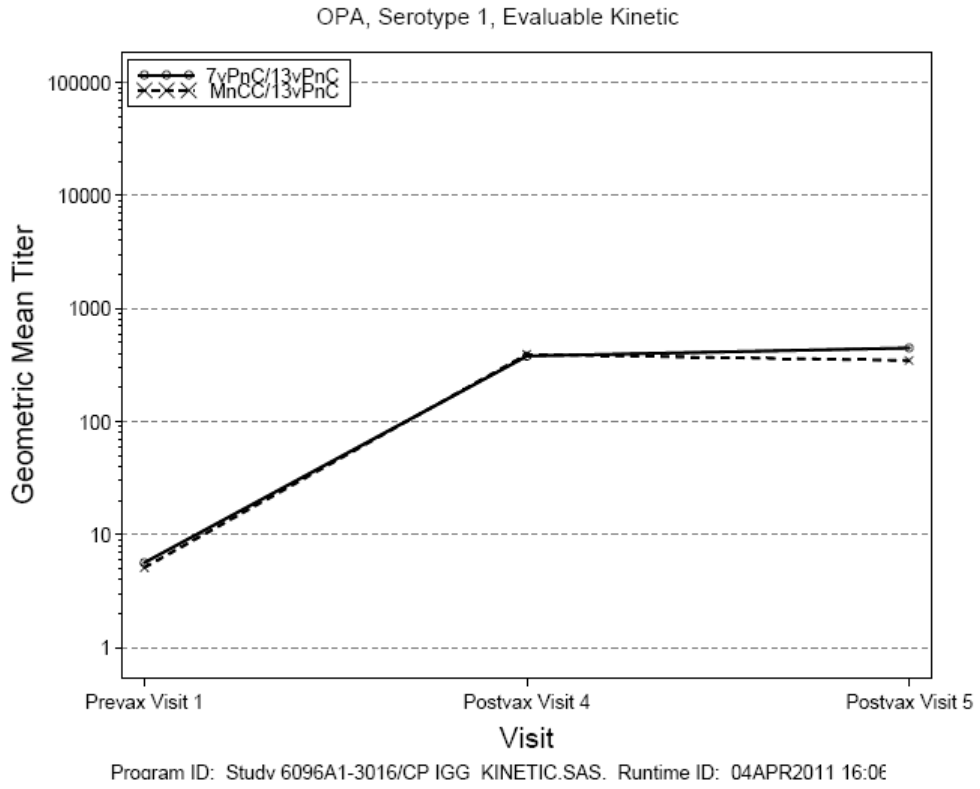
		Sampling Time[a]								
		Prevaccination (Visit 1)			Postvaccination (Visit 4)			Postvaccination (Visit 5)		
Serotype	Vaccine Group	n[b]	GMC[c]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])
7vPnC										
4	7vPnC/13vPnC	31	0.20	(0.12, 0.33)	38	3.00	(2.07, 4.35)	38	5.73	(4.21, 7.81)
	MnCC/13vPnC	25	0.15	(0.07, 0.29)	35	1.37	(0.90, 2.10)	35	2.92	(2.22, 3.83)
6B	7vPnC/13vPnC	38	5.89	(4.61, 7.51)	38	29.46	(20.74, 41.86)	38	66.72	(50.19, 88.70)
	MnCC/13vPnC	35	3.97	(2.78, 5.67)	35	9.42	(6.23, 14.24)	35	22.62	(14.56, 35.16)
9V	7vPnC/13vPnC	37	1.54	(1.19, 2.00)	38	5.75	(4.40, 7.51)	38	8.72	(6.68, 11.40)
	MnCC/13vPnC	35	1.69	(1.20, 2.38)	35	3.41	(2.51, 4.65)	35	4.70	(3.49, 6.33)
14	7vPnC/13vPnC	38	0.58	(0.39, 0.86)	38	10.25	(6.85, 15.33)	38	41.45	(27.72, 61.97)
	MnCC/13vPnC	35	0.79	(0.43, 1.43)	35	5.22	(2.76, 9.86)	35	18.50	(10.10, 33.90)
18C	7vPnC/13vPnC	37	0.75	(0.48, 1.18)	38	3.09	(2.22, 4.29)	38	5.72	(4.18, 7.82)
	MnCC/13vPnC	33	0.72	(0.46, 1.13)	35	3.45	(2.16, 5.52)	35	9.04	(5.98, 13.68)
19F	7vPnC/13vPnC	36	2.94	(2.08, 4.15)	38	7.66	(5.66, 10.36)	38	14.17	(9.54, 21.07)
	MnCC/13vPnC	33	1.98	(1.32, 2.96)	34	4.85	(3.09, 7.62)	34	15.80	(10.00, 24.96)
23F	7vPnC/13vPnC	38	2.51	(1.92, 3.27)	38	10.56	(7.69, 14.51)	38	17.20	(12.44, 23.77)
	MnCC/13vPnC	35	2.31	(1.70, 3.14)	35	6.51	(4.24, 10.01)	35	20.80	(13.07, 33.08)
Additional										
1	7vPnC/13vPnC	30	1.04	(0.71, 1.54)	38	3.98	(2.82, 5.62)	38	9.55	(6.46, 14.13)
	MnCC/13vPnC	32	0.70	(0.43, 1.15)	35	2.83	(1.86, 4.32)	35	5.63	(3.67, 8.64)
3	7vPnC/13vPnC	36	1.30	(0.83, 2.04)	38	2.02	(1.48, 2.76)	38	2.13	(1.58, 2.87)
	MnCC/13vPnC	32	1.07	(0.66, 1.73)	33	1.40	(0.95, 2.06)	33	1.71	(1.20, 2.44)
5	7vPnC/13vPnC	38	3.24	(2.45, 4.27)	38	5.40	(4.08, 7.15)	38	6.80	(4.75, 9.74)
	MnCC/13vPnC	34	3.83	(2.77, 5.31)	35	5.12	(3.60, 7.28)	35	7.52	(5.12, 11.04)
6A	7vPnC/13vPnC	38	3.78	(2.85, 5.03)	38	13.60	(9.01, 20.53)	38	29.11	(19.04, 44.50)
	MnCC/13vPnC	34	3.82	(2.79, 5.23)	35	7.25	(4.75, 11.06)	35	16.08	(10.18, 25.40)
7F	7vPnC/13vPnC	38	1.38	(0.93, 2.05)	38	4.70	(3.26, 6.78)	38	9.92	(7.03, 14.01)
	MnCC/13vPnC	34	1.12	(0.73, 1.72)	35	3.17	(2.24, 4.48)	35	5.75	(3.98, 8.33)
19A	7vPnC/13vPnC	38	7.05	(5.52, 8.99)	38	13.40	(10.30, 17.42)	38	21.29	(14.90, 30.43)
	MnCC/13vPnC	35	6.18	(4.57, 8.35)	35	12.03	(8.83, 16.39)	35	20.17	(15.28, 26.63)

a. Prespecified timing for blood sample.
b. n = Number of subjects with valid and determinate assay results for the specified serotype at all 3 blood draws.
c. Geometric mean concentrations (GMCs) were calculated using all subjects with available data at all 3 blood draws.
d. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.

OPA Geometric Mean Titers

OPA GMTs over time for each of the serotypes in 13vPnC at visit 1 and after vaccination at visits 4 and 5 were presented for the evaluable kinetic population. Representative examples are shown in Figures 16.40 and 16.42. The pneumococcal OPA GMTs in the evaluable kinetic population at the prevaccination visit 1 and the postvaccination visits 4 and 5 are summarized in Table 9-15.
In general, GMTs increased in both vaccine groups over time, the exception being serotypes 3, 4 and 9V for both vaccine groups, serotype 18C for the 7vPnC/13vPnC group and serotype 1 for the MnCC/13vPnC group.

16.40 Kinetic Curves, Serotype 1, OPA Antibody Titers - Evaluable Kinetic Population



Program ID: Study 6096A1-3016/CP IGG KINETIC.SAS. Runtime ID: 04APR2011 16:0

16.42 Kinetic Curves, Serotype 4, OPA Antibody Titers - Evaluable Kinetic Population

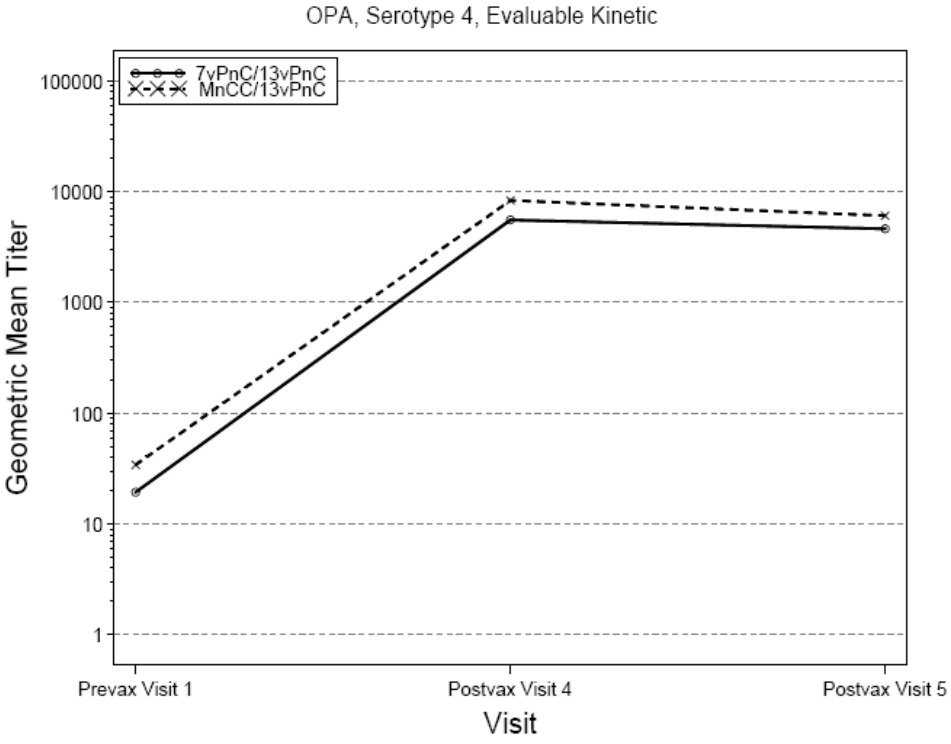


Table 9-15: Pneumococcal OPA GMTs – Evaluable Kinetic Population

		Sampling Time[a]								
		Prevaccination (Visit 1)			Postvaccination (Visit 4)			Postvaccination (Visit 5)		
Serotype	Vaccine Group	n[b]	GMT[c]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])
7vPnC										
4	7vPnC/13vPnC	23	19	(6.0, 62.8)	38	5567	(3202.5, 9678.7)	36	4626	(3322.5, 6441.2)
	MnCC/13vPnC	15	34	(6.0, 195.4)	34	8339	(6154.1, 11299.5)	32	6065	(4590.9, 8012.5)
6B	7vPnC/13vPnC	32	1034	(505.1, 2116.9)	38	8082	(5743.5, 11372.6)	37	11451	(8290.4, 15817.9)
	MnCC/13vPnC	27	288	(74.8, 1106.9)	33	6450	(4477.8, 9290.2)	35	10380	(7515.2, 14336.9)
9V	7vPnC/13vPnC	27	43	(13.4, 137.3)	38	6865	(4826.7, 9763.7)	38	6346	(5152.2, 7817.5)
	MnCC/13vPnC	31	126	(41.1, 387.0)	34	7806	(5491.4, 11095.6)	34	7555	(5916.7, 9646.8)
14	7vPnC/13vPnC	32	159	(63.7, 396.0)	37	3596	(2613.0, 4948.5)	38	5898	(4481.0, 7762.1)
	MnCC/13vPnC	30	286	(109.0, 750.7)	34	5994	(4246.9, 8460.1)	34	7031	(5195.6, 9515.5)
18C	7vPnC/13vPnC	37	54	(19.5, 149.5)	37	5833	(3770.5, 9023.7)	38	5090	(3428.4, 7557.7)
	MnCC/13vPnC	33	25	(8.4, 75.7)	35	5266	(3779.3, 7338.4)	35	6005	(4389.3, 8214.6)
19F	7vPnC/13vPnC	38	33	(15.1, 73.3)	35	1243	(620.6, 2489.8)	38	1623	(995.2, 2647.9)
	MnCC/13vPnC	35	22	(10.2, 47.3)	34	1855	(1055.8, 3258.2)	34	2696	(1831.0, 3968.5)
23F	7vPnC/13vPnC	33	79	(31.4, 201.3)	37	1575	(987.7, 2511.7)	37	2752	(2074.6, 3651.3)
	MnCC/13vPnC	28	11	(5.0, 23.5)	35	1141	(655.1, 1986.8)	35	4841	(3574.5, 6555.1)
Additional										
1	7vPnC/13vPnC	36	6	(4.3, 7.4)	37	379	(241.8, 594.9)	38	449	(312.8, 643.2)
	MnCC/13vPnC	34	5	(4.0, 6.5)	35	393	(257.2, 600.3)	34	347	(228.3, 527.4)
3	7vPnC/13vPnC	37	11	(6.9, 16.6)	38	117	(81.3, 167.5)	38	113	(89.2, 143.5)
	MnCC/13vPnC	33	11	(7.0, 18.2)	34	104	(75.4, 143.4)	35	99	(77.0, 126.3)
5	7vPnC/13vPnC	36	4	(3.6, 5.6)	38	200	(111.2, 358.6)	38	296	(158.8, 549.9)
	MnCC/13vPnC	35	4	(3.7, 5.0)	34	258	(132.3, 503.4)	35	336	(175.4, 642.2)
6A	7vPnC/13vPnC	35	17	(7.1, 39.7)	38	8534	(5631.9, 12931.6)	38	9458	(6674.2, 13404.0)
	MnCC/13vPnC	32	23	(8.7, 59.1)	35	6199	(4357.6, 8818.6)	34	10842	(7904.9, 14870.9)
7F	7vPnC/13vPnC	32	55	(16.7, 183.4)	37	4750	(3291.8, 6852.9)	37	6740	(4933.2, 9207.7)
	MnCC/13vPnC	29	76	(21.1, 275.2)	33	3760	(2106.7, 6709.5)	35	6050	(4515.0, 8106.7)
19A	7vPnC/13vPnC	33	76	(36.7, 157.5)	38	1504	(911.2, 2484.1)	38	2120	(1308.0, 3435.3)
	MnCC/13vPnC	33	39	(19.9, 78.1)	35	1761	(1242.8, 2496.0)	35	2340	(1667.0, 3285.4)

a. Prespecified timing for blood sample.
b. n = Number of subjects with valid and determinate assay results for the specified serotype at all 3 blood draws.
c. Geometric mean titers (GMTs) were calculated using all subjects with available data at all 3 blood draws.
d. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.

- Safety results

Safety was evaluated by the incidence of reactogenicity, adverse events (AEs), and serious adverse events (SAEs). The safety population (n=74) included all subjects who received at least 1 dose of the study vaccine (38 in the 7vPnC/13vPnC and 36 in the MnCC/13vPnC groups).
Reactogenicity (local reactions included redness, swelling, and tenderness at the site of the injection and systemic events included decreased appetite, irritability, increased sleep, decreased sleep, rash, fever, and use of antipyretic medications) were monitored daily for 4 days after vaccination. AEs and SAEs were collected for all subjects from the day of consent until the last visit (6-month follow-up).

Local Reactions
A total of 92.1% (n=35) of subjects in the 7vPnC/13vPnC group and 86.1% (n=31) of subjects in the MnCC/13vPnC group reported at least 1 local reaction during the 4 days after vaccination. Generally, the percentages of subjects with any local reactions were similar in both groups. Local reactions were mostly mild or moderate in severity.
The most frequently reported local reaction was tenderness; 92.1% (n=35) of subjects in the 7vPnC/13vPnC group and 86.1% (n=31) of subjects in the MnCC/13vPnC group.
Significant tenderness (ie, interfered with limb movement) was reported by 4 (10.5%) subjects in the 7vPnC/13vPnC group and 7 (19.4%) subjects in the MnCC/13vPnC group.

Systemic Events
The percentage of subjects reporting 1 or more systemic events was 38.9% (n=14) in the 7vPnC/13vPnC group and 42.9% (n=15) in the MnCC/13vPnC group. The percentages of subjects reporting any individual systemic event were generally similar between the 2 groups except for decreased appetite (7.9% [n=3] in the 7vPnC/13vPnC group and 16.7% [n=6] in the MnCC/13vPnC group). The most frequently reported systemic events were increased sleep (26.3% [n=10]) and irritability (18.4% [n=7]) in the 7vPnC/13vPnC group, and increased sleep (33.3% [n=12]) and decreased appetite (16.7% [n=6]) in the MnCC/13vPnC group. Most subjects did not report fever. Fever was reported in 1 (2.9%) subject in the 7vPnC/13vPnC group only; this was mild (≥38°C but ≤39°C) in severity. Overall, most subjects did not receive antipyretic medication to treat or prevent symptoms. Medication was used to treat symptoms in 3 (7.9%) subjects in the 7vPnC/13vPnC group only; no subjects in the MnCC/13vPnC group used medication to treat symptoms. None of the subjects in either group used medication to prevent symptoms.

Adverse Events
At least 1 AE was reported in 57.9% (n=22) of subjects in the 7vPnC/13vPnC group and 55.6% (n=20) of subjects in the MnCC/13vPnC group. Nearly all AEs reported were characterized as mild or moderate in severity; 1 AE (increased sleep) was assessed as severe. This event started on day 2 as moderate, then severe on day 3, and mild on days 4 to 6. In the 7vPnC/13vPnC group, the system organ classes most frequently reported were "general and administration site disorders" and "respiratory, thoracic and mediastinal disorders" (each 21.1%, n=8) whereas in the MnCC/13vPnC group, "injury, poisoning and procedural complications" and "nervous system disorders" were most frequently reported (22.2%, n=8 and 16.7%, n=6, respectively).

- MAH's conclusions

A single dose of 13vPnC was immunogenic in children aged 11 to 14 years, regardless of previous vaccination with 7vPnC or MnCC.
A subsequent childhood dose of 13vPnC showed a satisfactory safety and tolerability profile in subjects who were vaccinated with a primary series of 7vPnC or MnCC.
The data presented here add to the safety and immunogenicity database for this vaccine in older children, and do not change the risk-benefit assessment for Prevenar 13.

3. Discussion on clinical aspects
The current study presents results of a single dose of Prevenar 13 in subjects 11-14 years of age who received either Prevenar or a MnCC vaccine as infants. The results show that the vaccine is clearly immunogenic in both groups, and there were no major difference between the groups. The study population, healthy children 11-14 years, is not currently included in the indication for Prevenar 13,

but is generally not considered a risk group for pneumococcal infections, and therefore is not considered to benefit from vaccination. No safety issues were detected in this study. However, two questions regarding the lack of difference between the immune responses between the two groups are raised that needs clarification before the procedure can be considered fulfilled.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The data provided indicate that the vaccine is clearly immunogenic in both groups, but , two questions regarding the lack of difference between the immune responses between the two groups are raised that needs clarification before the procedure can be considered fulfilled.

- **Recommendation**

Fulfilled:

No further action required

Not fulfilled: X
Based on the data submitted, the MAH should provide responses to the questions below as part of this procedure P46 042. (see section IV "Additional clarifications requested").

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Based on the data submitted, the MAH should provide responses to the questions below as part of this procedure P46 041.

Question 1: With regard to the pre-challenge serological data: From the supportive tables (Section 15, tables 12/15, 23/25, 41/43) it appears that OPA antibody titres and GMTs are very similar between both groups on visit 1 (prior to vaccination), except for serotypes 6B, 18C and 23F. For the latter three the 7vPnC group consistently shows better protective values. The company is asked to comment on this and on the fact that there is no apparent difference in protection between groups with regard to the serotypes 4, 9V, 14 and 19F.

Question 2: There appears very little difference in quality and quantity of the immune response upon vaccination of both groups with Prevenar 13. The company is asked to comment on the apparent lack of anamnestic response, with regard to the 7vPnC serotypes, upon vaccination of the 7vPnC group with Prevenar 13.

The timetable as proposed by the Rapporteur is as follows:

a 30 day response timetable without clock stop will apply.