EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

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

Prevenar 13

(Pneumococcal saccharide conjugated vaccine, adsorbed)

Procedure No. EMEA/H/C/001104

P46 009

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

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I. INTRODUCTION

On 2011-06-02 the MAH submitted completed paediatric studies for Prevenar13, 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 proposed the following regulatory action: submission of a Type II variation to include a statement about catch-up vaccination in section 4.2 of the Prevenar 13 Summary of Product Characteristics (SPC).

The preliminary Assessment Report for this procedure was circulated on July 5, 2011. Comments were received from Belgium, which are added to the Discussion on clinical aspects.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the studies

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

II.2 Clinical aspects

1. Introduction

The MAH submitted final reports for:

6096A1-3021 A phase 3, open-label study to evaluate persistence of the antibody response elicited by pneumococcal conjugate vaccine in healthy children who have been previously immunized with a 4-dose series of a pneumococcal conjugate vaccine during infancy in study 6096a1-008-eu and the safety and immunogenicity of 13-valent pneumococcal conjugate vaccine administered at least 24 months after the last toddler dose of pneumococcal conjugate vaccine.

2. Clinical studies

6096A1-3021 A phase 3, open-label study to evaluate persistence of the antibody response elicited by pneumococcal conjugate vaccine in healthy children who have been previously immunized with a 4-dose series of a pneumococcal conjugate vaccine during infancy in study 6096a1-008-eu and the safety and immunogenicity of 13-valent pneumococcal conjugate vaccine administered at least 24 months after the last toddler dose of pneumococcal conjugate vaccine.

- **Description**

- **Methods**

  - Objective(s)

The primary objectives of the study were:

- To evaluate the antibody levels to the 13 pneumococcal vaccine serotypes not earlier than 24 months after the administration of the toddler dose in study 6096A1-008, as measured by serotype-specific (immunoglobulin G) IgG concentrations.
- To evaluate the immune response to 13 pneumococcal vaccine serotypes 1 month after a dose of the 13-valent pneumococcal conjugate vaccine (13vPnC) administered not earlier than 24 months after the toddler dose in study 6096A1-008, as measured by serotype-specific IgG concentrations.

The secondary objectives of the study were:

- To evaluate the antibody levels to the 13 pneumococcal vaccine serotypes not earlier than 24 months after the administration of the toddler dose in study 6096A1-008, as measured by serotype-specific opsonophagocytic activity (OPA).

- To evaluate the immune response to 13 pneumococcal vaccine serotypes 1 month after a dose of 13vPnC administered not earlier than 24 months after the toddler dose in study 6096A1-008, as measured by serotype-specific OPA antibody titers.

The safety objective of the study was:

- To evaluate the safety profile of 1 dose of 13vPnC administered to children previously vaccinated at least 24 months earlier with the toddler dose in study 6096A1-008, as measured by the incidence rates of local reactions, systemic reactions, and adverse events (AEs).

An exploratory objective of the study was:

- To evaluate the immune response to 13 pneumococcal vaccine serotypes in children previously vaccinated in study 6096A1-008, 4 to 7 days after a dose of 13vPnC administered not earlier than 24 months after the toddler dose, as measured by serotype-specific IgG concentrations.

- Study design

Study 6096A1-3021 was a phase 3, multicenter, open-label study in France, including eligible healthy children who had received a 4-dose vaccination series of pneumococcal conjugate vaccine as part of study 6096A1-008. In study 6096A1-008, vaccine groups were 13vPnC infant series/13vPnC toddler dose (13vPnC/13vPnC); 7-valent pneumococcal conjugate vaccine (7vPnC) infant series/7vPnC toddler dose (7vPnC/7vPnC); or 7vPnC infant series/13vPnC toddler dose (7vPnC/13vPnC). In this study, all subjects were to receive a fifth dose of 13vPnC at visit 2.

Blood samples were to be taken at visit 1 (prevaccination; >730 days after the toddler dose in study 6096A1-008 and >3 years of age), within 7 days prior to receiving the study vaccine (13vPnC; visit 2) and 1 month after (visit 4; 28 to 42 days after visit 2). In a subset of subjects whose parents/legal guardians consented to it, an additional blood sample was to be collected 4 to 7 days after vaccination with 1 dose of 13vPnC (visit 3).

- Study population /Sample size

Approximately 500 subjects were to be enrolled in the study. The sample size was not determined based on a power calculation, but on the number of subjects who could be enrolled from study 6096A1-008. A total of 262 eligible subjects from study 6096A1-008 consented to participate, were enrolled, and given a single dose

Diagnosis and Main Criteria for Inclusion: Subjects were enrolled in the study if they satisfied all of the following inclusion criteria: received all 4 assigned doses of the PnC vaccine as randomized and completed study 6096A1-008; were at least 24 months posttoddler dose and at least 3 years of age at visit 1; were healthy; and were available for the entire study period.

Subjects were excluded from participation in the study if they met any of the following criteria: vaccination with any licensed or investigational pneumococcal vaccine since completion of study 6096A1-008; history of culture-proven invasive disease caused by *Streptococcus pneumoniae* since the completion of study 6096A1-008, previous anaphylactic reaction to any vaccine or vaccine-related component; contraindication to vaccination with a pneumococcal conjugate vaccine (PnC); bleeding diathesis or condition associated with prolonged bleeding time; known or suspected immune deficiency or suppression since participation in study 6096A1-008; major known congenital malformation or serious chronic disorder; significant neurological disorder or history of seizure; receipt of any blood products, including immunoglobulin, within 90 days before the study; current participation in another investigational or interventional study; received any live vaccine within 28 days before administration of the first study vaccine.

- Treatments

In this study, all subjects were to receive 1 dose of 13vPnC at visit 2.

- Outcomes/endpoints

Immunogenicity Assessment Methods:

Blood samples for immunogenicity assessments were to be obtained up to 7 days before visit 2 (vaccination visit) and at visit 4 (28 to 42 days after the vaccination at visit 2). In a subset of subjects whose parents/legal guardians consented to it, an additional optional 5-mL blood sample was to be

collected 4 to 7 days after vaccination with 1 dose of 13vPnC (visit 3). Serotype-specific immunogenicity to the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) was to be assessed by enzyme-linked immunosorbent assay (ELISA) and OPA assays.

Safety Assessment Methods:
Safety parameters included physical examination, reactogenicity (solicited local reactions and systemic events including fever and the use of antipyretic medication); and unsolicited AEs and SAEs. Local reactions (redness [erythema], swelling [induration], and pain) at the site of the 13vPnC vaccine injection were monitored daily for 7 days (day 1 to day 7) after vaccination. Systemic events (fever, vomiting, diarrhea, and fatigue) were monitored daily and recorded in the e-diary for 7 days after each vaccination (day 1 to day 7). In addition, the use of antipyretic medications to prevent or treat symptoms was collected daily in the e-diary during the active safety observation periods (day 1 to day 7) after the vaccination. A subject's AEs and SAEs were recorded from the signing of the ICF to visit 4 (1 month after the vaccination).

- Statistical Methods

Analysis Populations:
Immunogenicity analyses were performed for 2 populations, the evaluable immunogenicity population (primary immunogenicity population) and the all-available immunogenicity population. The primary immunogenicity population was the evaluable immunogenicity population, defined
As:

1. Eligible subjects who were randomized.
2. Had blood drawn within required time frames (within 7 days prior to 13vPnC vaccination, 3 to 9 days after the vaccination, 27 to 56 days after the vaccination).
3. Had at least 1 valid and determinate assay result for the proposed analysis.
4. Received no prohibited vaccines.
5. Had no major protocol violations as determined by the global trial leader or global medical monitor.

Protocol violations were identified before any immunogenicity analysis was carried out.

The all-available immunogenicity population consisted of subjects who had at least 1 valid and determinate assay result for the proposed analysis.

Immunogenicity:
The primary endpoint was the serotype-specific IgG concentration 1 month after the single dose of 13vPnC.
The secondary endpoints included: the serotype-specific IgG concentration prior to the 13vPnC dose, 4 to 7 days after the 13vPnC dose; OPA titers collected on all available samples of study 6096A1-008, prior to the 13vPnC dose, 1 month after the 13vPnC dose; the proportion of subjects with OPA titer ≥ the lower limit of quantitation (LLOQ) for each of the 13 serotypes 1 month after the 13vPnC dose. *This analysis was changed; instead of the proportion of subjects with an OPA titer ≥1:8 one month after the 13vPnC dose (for serotype 7F, the proportion of subjects with an OPA titer ≥1:2048), the proportion of subjects with an OPA titer ≥LLOQ 1 month after the 13vPnC dose was presented in this CSR*.

The pneumococcal IgG serotype concentrations were logarithmically transformed for analysis. Within each group and for each antibody concentration separately, geometric means of the antibody concentrations from each of the blood draws were calculated. Two (2)-sided, 95% confidence intervals (CIs) were constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using the Student t distribution. To assess the within-subject post-13vPnC and pre-13vPnC differences in concentration, the fold rise in geometric mean concentration (GMC) from pre-13vPnC to post-13vPnC and 95% 2-sided CI were estimated for each group using the logarithmically transformed assay results.

The antibody concentrations over time were described for each serotype and each group by GMCs and corresponding 2-sided 95% CIs: pre-13vPnC dose, 4 to 7 days post-13vPnC dose, and 1 month post-13vPnC dose. All pairwise comparisons among the 3 groups were made at each time point using geometric mean ratios and 95% CIs.

Serotype-specific fold rise in antibody concentration from the pre-13vPnC dose to the 4 to 7 days post-13vPnC dose were derived for each subject and summarized using geometric mean fold rises (GMFRs) along with 2-sided 95% CI. The fold rise from the pre-13vPnC dose to 1 month after the 13vPnC dose was summarized similarly. All pairwise comparisons of GMFR among the 3 groups were made by computing the ratios of the GMFR of the 2 corresponding groups, along with 2-sided 95% CIs. The empirical reverse cumulative distribution curves (RCDCs) of pneumococcal IgG concentrations prior to the 13vPnC dose and 1 month after the 13vPnC dose from all 3 groups were presented graphically for each serotype.

For each of the 13 serotypes and for each group, OPA geometric mean titers (GMTs) and corresponding 95% CIs were calculated for the post-toddler dose, prior to the 13vPnC dose and 1 month after the 13vPnC dose. All pairwise comparisons among the 3 groups were made at each time point using geometric mean ratios and 95% CIs.

Fold rises in OPA assay results from the pre-13vPnC dose to 1 month after 13vPnC dose were summarized and all pairwise comparisons among the 3 groups were made in the same manner as with IgG concentrations.

In addition, the proportion of subjects with an OPA titer ≥LLOQ 1 month after the 13vPnC dose, along with exact, unconditional, 2-sided 95% CIs, were to be provided for each of the 13 serotypes and each group. All pairwise comparisons among the 3 groups were made by providing differences in proportion along with exact, 2-sided 95% CIs.

Serum OPA for the 13 pneumococcal serotypes were determined for all subjects in the immunogenicity subset for each blood sample. Results were reported as antibody titers.

Assessor's comment: There were two primary objectives, IgG responses before and after the fifth vaccination given not less than 24 months after the toddler dose. However, there is only one primary endpoint, serotype specific IgG 1 month after the fifth dose. As all data are presented, this is considered of minor importance.
The change of OPA analysis is explained as follows (summarised): "The OPA assay method to be used was not specified in the protocol. In study 6096A1-008, the dribble OPA (dOPA) was used. To increase the relatively low throughput of the dOPAs, the assays were simplified and automated The modified OPA assays are referred to as mcOPAs. Precision of the mcOPA assays was also improved by instituting replicate testing of each clinical serum sample. In the current study, all sera were assayed using the mcOPA assay (available sera from study 6096A1-008 were reassayed using the mcOPA assay).

The lowest titer that can be determined in OPA assays is a titer of 1:8 (limit of detection, LOD) and is the same for each serotype-specific OPA assay. However, to quantify functional antibodies in the OPA assays with appropriate precision and accuracy, the lower limit of quantitation (LLOQ) was determined for each serotype-specific OPA assay during assay validation. The LLOQ for each serotype-specific OPA assay was used as a cutoff to determine serum response for the immunogenicity subjects. Previously, an OPA serum response was determined using an OPA titer cutoff of 1:8 for all serotype-specific dOPA assays in exploratory analyses for 13vPnC assessments in support of an infant/young child indication.

However, the additional, more stringent qualification and validation of the improved mcOPA assays used in this study did not support 1:8 for the quantitation of a serum response and thus the following established cutoffs (LLOQs) were used for the mcOPA assay: serotype 1, 1:18; serotype 3, 1:12; serotype 4, 1:21; serotype 5, 1:29; serotype 6A, 1:37; serotype 6B, 1:43; serotype 7F, 1:210; serotype 9V, 1:345; serotype l4, 1:35; serotype 18C, 1:31; serotype 19A, 1:18; serotype 19F, 1:48; and serotype 23F, 1:13.

Therefore, based on the new LLOQs determined for the mcOPAs, instead of the proportion of subjects with an OPA titer ≥1:8 one month after the 13vPnC dose (for serotype 7F, the proportion of subjects with an OPA titer ≥1:2048), the proportion of subjects with an OPA titer ≥LLOQ 1 month after the 13vPnC dose is presented."

The change of OPA methodology has been assessed previously, and is considered acceptable, and thus the chosen analysis is endorsed.

Safety:
The safety variables collected for this study were local reactions (redness, swelling, and pain at the site of the 13vPnC injection), systemic events (fever, vomiting, diarrhea, fatigue, and use of antipyretic medications), and AEs. Fever was defined as a temperature of ≥38.0°C (100.4°F). The proportion of subjects with local reactions and systemic events reported on any day within the 7-day period after the vaccination was summarized for each vaccine group. 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 summarized by vaccine group for each vaccination separately. All summaries showed, by vaccine group, the number and percentage of subjects experiencing at least 1 event and the number of events. Pairwise differences in incidence rates of local reactions, systemic events, and AEs among the 13vPnC/13vPnC/13vPnC, 7vPnC/13vPnC/13vPnC, and 7vPnC/7vPnC/13vPnC groups were reported.

- **Results**

- Recruitment/ Number analysed

According to the protocol, approximately 500 subjects were to participate in this study at approximately 39 sites. This was based on the previous study (6096A1-008) data. Enrollment at each site was to be based upon the ability of the site personnel to recruit eligible subjects who had completed study 6096A1-008. All investigators who participated in study 6096A1-008 had been offered participation in this study and those who agreed were to recruit subjects. Some investigators declined participation, thereby decreasing the number of participating sites and potential subjects. Participating investigators were to offer participation to study 6096A1-3021 to all subjects enrolled at their site in study 6096A1-008 and who fulfilled the eligibility criteria for the current study, 6096A1-3021. A subject eligibility list was prepared by programming and provided to the participating investigators in the previous study.
A total of 262 eligible subjects from study 6096A1-008 consented to participate, were enrolled, and given a single dose of 13vPnC. The distribution of subjects across the 3 treatment groups followed the randomization ratio of 2:1:1 from study 6096A1-008. The disposition of subjects is presented in Table 8-1.
Of the 262 enrolled subjects, 260 subjects completed the study. Two (2) subjects (1 subject in the 13vPnC/13vPnC/13vPnC group and 1 subject in the 7vPnC/7vPnC/13vPnC group) were withdrawn from the study as they were lost to follow-up.

Table 8-1: Disposition of All Subjects

	Vaccine Group (as Enrolled)							
	13v/13v/13v		7v/7v/13v		7v/13v/13v		Total	
	n	%	n	%	n	%	n	%
Consented[a]	130	100.0	65	100.0	67	100.0	262	100.0
Enrolled[b]	130	100.0	65	100.0	67	100.0	262	100.0
Vaccinated	130	100.0	65	100.0	67	100.0	262	100.0
Completed study	129	99.2	64	98.5	67	100.0	260	99.2
Withdrawn from study	1	0.8	1	1.5	0	0.0	2	0.8
Reason for withdrawal								
Lost to Follow-up	1	0.8	1	1.5	0	0.0	2	0.8

Note: Subject 3021-033-000564, a screen failure in Study 008 (008-036-001556), is not included.
a. The values in this row are used as the denominator for percentages for screened only subjects.
b. The values in this row are used as the denominator for percentages for vaccine groups.

Of the 262 enrolled subjects who received 13vPnC, 257 subjects (98.1%) were included in the all-available immunogenicity population, 235 subjects (89.7%) were included in the evaluable immunogenicity population, and 84 subjects (32.1%) were included in the visit 3 optional blood sample evaluable immunogenicity population.

Four subjects were excluded from the all-available immunogenicity population because they were misdosed in Study 6096A1-008. One additional subject was excluded from the all-available immunogenicity population because no original informed consent form was available at the site. Twenty-seven subjects were excluded from the evaluable immunogenicity population. Most frequently subjects were excluded from this analysis set based on blood being drawn more than 56 days after vaccination at visit 4 or no valid or determinate assay result at visit 4. All subjects excluded from the all-available immunogenicity population were also excluded from the evaluable immunogenicity population.

- Efficacy results

Antibody persistence

Pneumococcal IgG Geometric Mean Concentrations

Pneumococcal IgG GMCs before vaccination ('predose' in the tables; up to 7 days prior to visit 2, ie after the 4-dose infant and toddler vaccination series but prior to the fifth vaccine dose at >3 years of age) are presented for the evaluable immunogenicity population in Table 9-3.

Table 9-3: Comparison of Pneumococcal IgG GMCs (µg/mL) Predose – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled)									Ratio[d] (95% CI[e])		
	13v/13v/13v			7v/7v/13v			7v/13v/13v					
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	13v/13v/13v to 7v/7v/13v	13v/13v/13v to 7v/13v/13v	7v/7v/13v to 7v/13v/13v
7vPnC												
4	120	0.17	(0.15,0.21)	57	0.23	(0.18,0.30)	58	0.18	(0.15,0.22)	0.75 (0.56, 1.00)	0.96 (0.73, 1.28)	1.29 (0.92, 1.79)
6B	120	2.86	(2.35, 3.48)	57	4.10	(2.96, 5.68)	58	3.21	(2.37, 4.36)	0.70 (0.49, 1.00)	0.89 (0.62, 1.27)	1.27 (0.84, 1.94)
9V	120	0.72	(0.60, 0.85)	57	0.92	(0.72, 1.17)	58	0.71	(0.58, 0.87)	0.78 (0.58, 1.03)	1.01 (0.76, 1.33)	1.29 (0.93, 1.80)
14	120	0.77	(0.61, 0.98)	57	0.74	(0.52, 1.06)	58	0.59	(0.42, 0.83)	1.04 (0.69, 1.58)	1.30 (0.86, 1.97)	1.25 (0.77, 2.03)
18C	120	0.21	(0.17, 0.25)	57	0.36	(0.28, 0.47)	58	0.23	(0.18, 0.28)	0.58 (0.42, 0.78)	0.91 (0.67, 1.23)	1.58 (1.11, 2.25)
19F	120	2.22	(1.67, 2.95)	56	2.11	(1.43, 3.11)	58	1.44	(1.04, 2.02)	1.05 (0.66, 1.68)	1.54 (0.97, 2.44)	1.46 (0.85, 2.51)
23F	120	1.26	(1.00, 1.58)	57	1.56	(1.19, 2.05)	58	1.18	(0.92, 1.52)	0.80 (0.56, 1.15)	1.06 (0.74, 1.52)	1.32 (0.87, 2.01)
Additional												
1	120	0.35	(0.29, 0.43)	54	0.14	(0.09, 0.20)	58	0.28	(0.23, 0.34)	2.59 (1.80, 3.73)	1.26 (0.88, 1.79)	0.49 (0.32, 0.74)
3	117	0.50	(0.35, 0.71)	56	0.47	(0.29, 0.75)	58	0.42	(0.30, 0.58)	1.06 (0.61, 1.87)	1.19 (0.68, 2.09)	1.12 (0.59, 2.15)
5	120	1.28	(1.07, 1.53)	57	1.12	(0.89, 1.41)	58	1.41	(1.19, 1.67)	1.15 (0.87, 1.52)	0.91 (0.69, 1.20)	0.79 (0.57, 1.10)
6A	120	4.05	(3.25, 5.04)	57	1.89	(1.50, 2.38)	58	2.47	(1.91, 3.21)	2.14 (1.52, 3.02)	1.64 (1.16, 2.30)	0.76 (0.51, 1.14)
7F	120	0.65	(0.55, 0.78)	55	0.21	(0.15, 0.30)	58	0.77	(0.62, 0.96)	3.11 (2.23, 4.33)	0.84 (0.61, 1.17)	0.27 (0.19, 0.40)
19A	120	6.16	(4.88, 7.79)	57	3.38	(2.60, 4.41)	58	4.63	(3.43, 6.26)	1.82 (1.25, 2.66)	1.33 (0.91, 1.94)	0.73 (0.47, 1.13)

a. n = Number of subjects with a determinate IgG antibody concentration to the given serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
d. Ratio of GMCs.
e. CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures ((13v/13v/13v - 7v/7v/13v) or (13v/13v/13v - 7v/13v/13v) or (7v/7v/13v - 7v/13v/13v)).

Before vaccination, GMCs for the 7 common serotypes were generally comparable for the 3 groups. In all 3 groups, the lowest GMCs were determined for serotype 4 and the highest GMCs were determined for serotype 6B. For the 7vPnC/7vPnC/13vPnC to 7vPnC/13vPnC/13vPnC pairwise comparison, all GMC ratios were >1.0 for the 7 common serotypes. GMC ratios with 95% CIs excluding 1 were only seen for serotype 18C. For this serotype the GMC in the 7vPnC/7vPnC/13vPnC group was significantly higher than in the 13vPnC/13vPnC/13vPnC or 7vPnC/13vPnC/13vPnC groups.

For the 6 additional serotypes, most GMCs before vaccination were lower in the 7vPnC/7vPnC/13vPnC group compared to the other 2 vaccine groups. In all 3 groups, the lowest GMCs were determined for serotype 1, and the highest GMCs were determined for serotype 19A. The GMC ratios were >1 for all 13vPnC/13vPnC/13vPnC to 7vPnC/7vPnC/13vPnC pairwise comparisons, with 95% CIs excluding 1 for serotypes 1, 6A, 7F, 19A. Statistically significantly higher GMCs were also shown in the 13vPnC/13vPnC/13vPnC group compared to the 7vPnC/13vPnC/13vPnC for serotype 6A and in the

7vPnC/13vPnC/13vPnC group compared to the 7vPnC/7vPnC/13vPnC group for serotypes 1 and 7F. GMCs for serotypes 3 and 5 were essentially comparable across all 3 study groups.

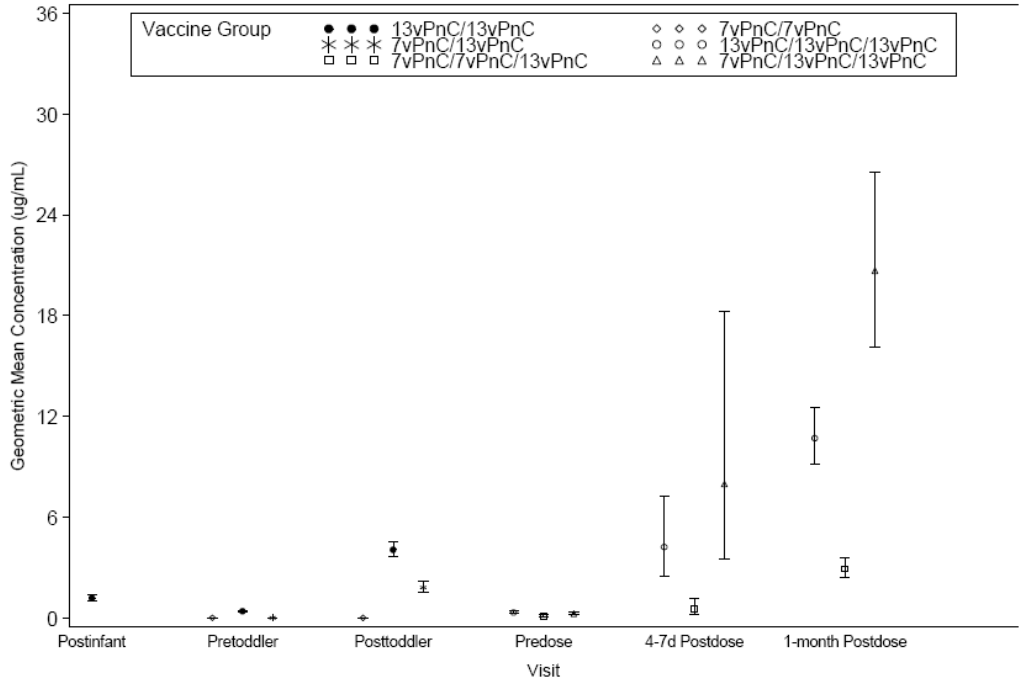
The GMCs and GMC ratios before vaccination for the all-available immunogenicity population were overall comparable to those observed for the evaluable immunogenicity population.

For the 7 common serotypes, the GMCs in each group had decreased from the values after the toddler dose (presented in CSR for study 008) to before the 13vPnC dose.
Generally, for the 6 additional serotypes, the GMCs had decreased from the values after the toddler dose in the 13vPnC/13vPnC/13vPnC and 7vPnC/13vPnC/13vPnC groups (exception: serotype 5 and serotype 6A in the 13vPnC/13vPnC/13vPnC group), ie the groups that had received 13vPnC as toddler dose, but had slightly increased in the 7vPnC/7vPnC/13vPnC group (exception: serotype 19A).

Pneumococcal IgG GMCs and 95% CIs at the postinfant, pretoddler, and posttoddler visits (study 6096A1-008), and at the visit before vaccination in study 6096A1-008 are presented graphically by serotype for the evaluable immunogenicity population, examples in Figures 16.1, 16.2 and 16.3. Note that postinfant assays were only performed in infants who received 13vPnC during the infant series; 7vPnC sera were not assayed for pneumococcal responses.

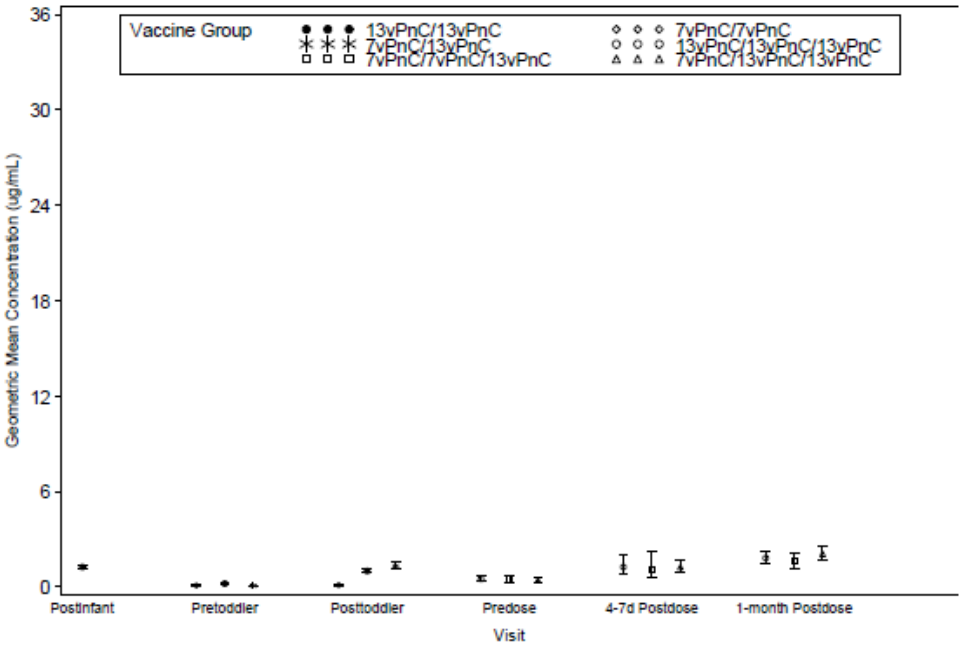
16.1 IgG Serotype 1, GMC and 95% CI – Evaluable Immunogenicity Population

IgG Serotype 1, GMC and 95% CI, Evaluable Population

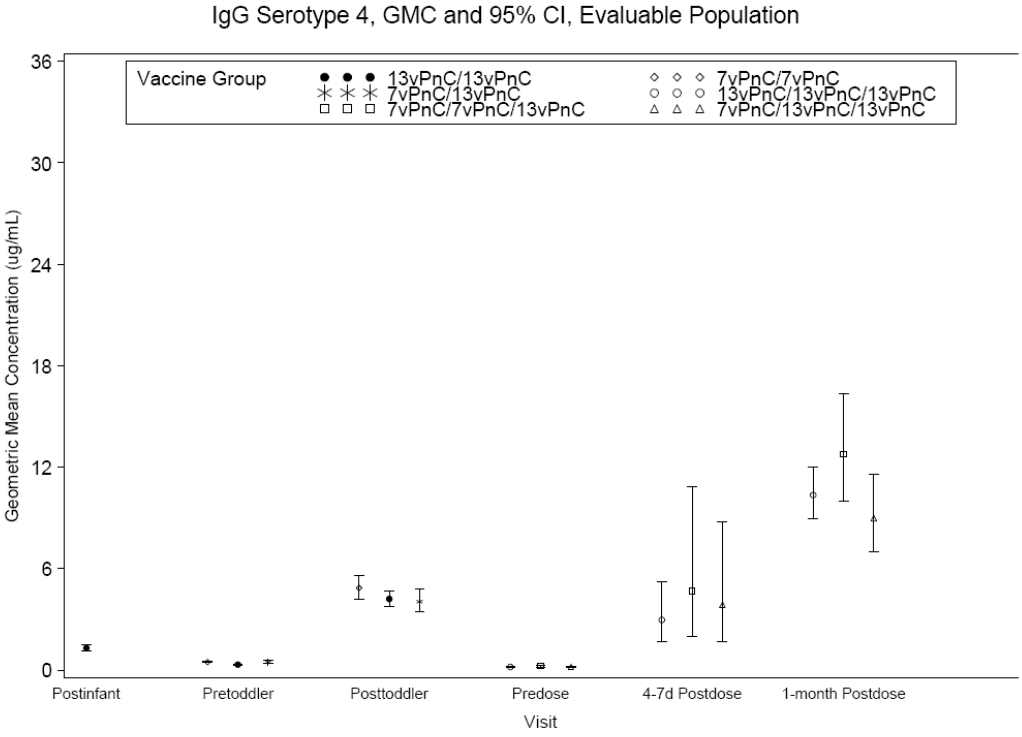


16.2 IgG Serotype 3, GMC and 95% CI – Evaluable Immunogenicity Population

IgG Serotype 3, GMC and 95% CI, Evaluable Population



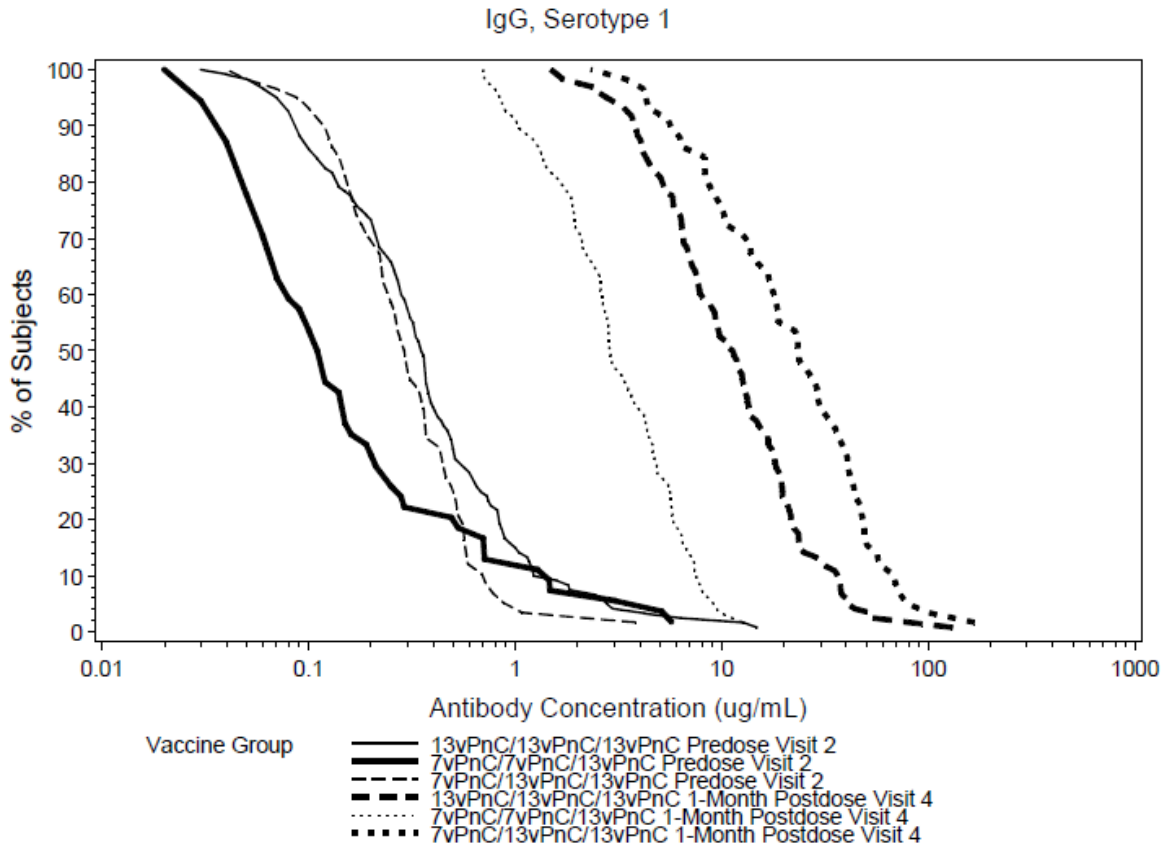
16.3 IgG Serotype 4, GMC and 95% CI – Evaluable Immunogenicity Population



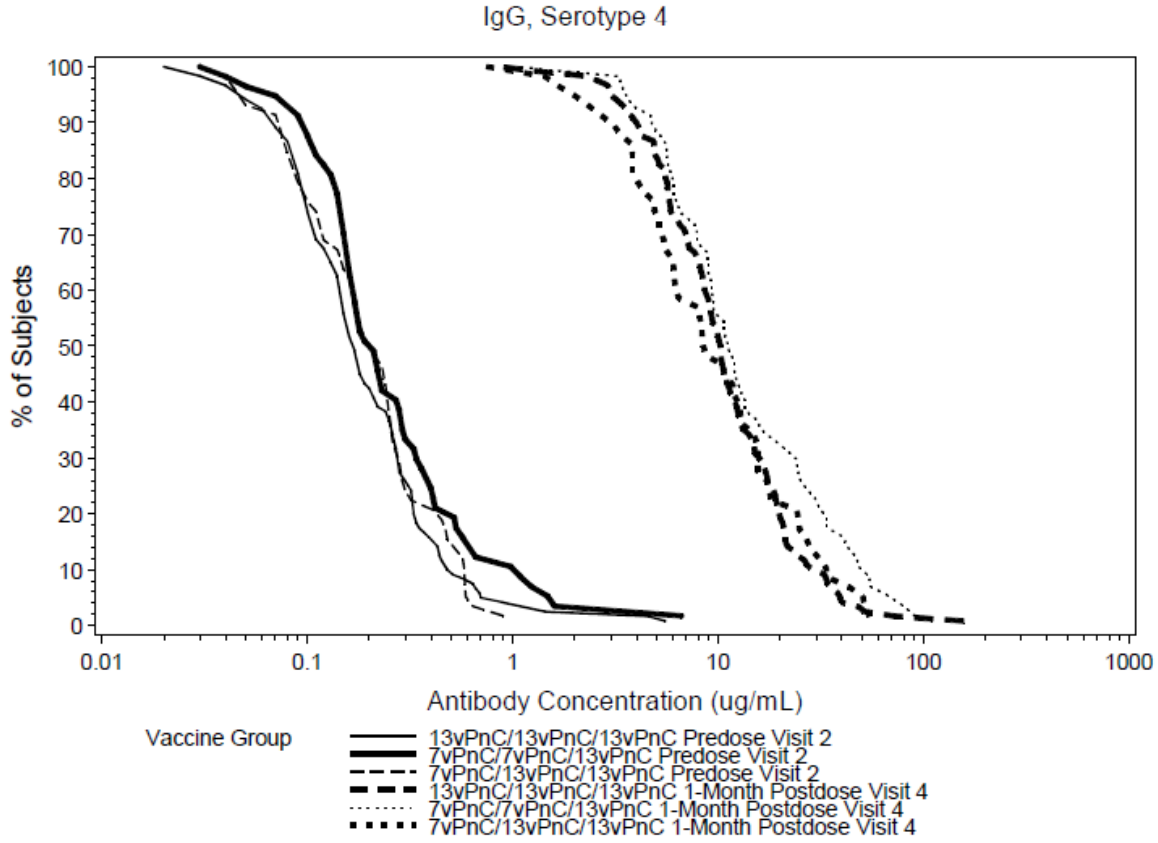
Pneumococcal IgG Concentration Response - Reverse Cumulative Distribution Curves

Examples of RCDCs are shown by antibody concentration and serotype in Supportive Figures 16.27 and 16.29. For all 3 groups at all concentration levels, the percentage of subjects achieving any given level of response was generally higher at 1 month after vaccination than before vaccination. Both before vaccination and 1 month after the 13vPnC dose, the RCDCs were comparable for the 7 common serotypes and higher for the 6 additional serotypes for the vaccine groups who received 13vPnC at the toddler dose (exception: serotype 3).

16.27 Reverse Cumulative Distribution Curve, IgG Serotype 1 – Evaluable Immunogenicity Population



16.29 Reverse Cumulative Distribution Curve, IgG Serotype 4 – Evaluable Immunogenicity Population



Pneumococcal OPA Geometric Mean Titers

Pneumococcal OPA GMTs before vaccination (up to 7 days prior to visit 2) are presented for the evaluable immunogenicity population in Table 9-4.

Before vaccination, OPA GMTs for the 7 common serotypes were generally comparable for the 3 groups. In all 3 groups, the highest OPA GMTs were determined for serotype 6B. OPA GMT ratios with 95% CIs excluding 1 (upper limit of the CI <1) were seen for serotype 4 in the 13vPnC/13vPnC/13vPnC to 7vPnC/7vPnC/13vPnC and to 7vPnC/13vPnC/13vPnC pairwise comparisons and additionally for serotype 18C in the 13vPnC/13vPnC/13vPnC to 7vPnC/7vPnC/13vPnC pairwise comparison.

For the 6 additional serotypes, OPA GMTs before vaccination were generally lower in the 7vPnC/7vPnC/13vPnC group compared to the 13vPnC/13vPnC/13vPnC and 7vPnC/13vPnC/13vPnC groups, and comparable or higher in the 7vPnC/13vPnC/13vPnC group compared to the 13vPnC/13vPnC/13vPnC group, with the exception of serotype 6A. In all 3 groups, the lowest GMTs were determined for serotype 5, with OPA GMTs to serotype 5 of 4 in each study group. The OPA GMT ratios were >1 for all 13vPnC/13vPnC/13vPnC to 7vPnC/7vPnC/13vPnC pairwise comparisons (except for serotype 5), reaching statistical significance for serotypes 6A and 19A. OPA GMT ratios were <1 for all 7vPnC/7vPnC/13vPnC to 7vPnC/13vPnC/13vPnC pairwise comparisons. GMT ratios with the upper limit of the 95% CI <1 were shown for group 13vPnC/13vPnC/13vPnC compared to group 7vPnC/13vPnC/13vPnC for serotypes 1 and 7F, and for group 7vPnC/7vPnC/13vPnC compared to group 7vPnC/13vPnC/13vPnC group for serotypes 1, 6A, 7F and 19A.

Table 9-4: Comparison of Pneumococcal OPA GMTs Predose – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled)									Ratio[d] (95% CI[e])		
	13v/13v/13v			7v/7v/13v			7v/13v/13v					
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	13v/13v/13v to 7v/7v/13v	13v/13v/13v to 7v/13v/13v	7v/7v/13v to 7v/13v/13v
7vPnC												
4	40	8	(4.4, 13.1)	14	46	(7.8, 268.5)	19	45	(10.6, 190.6)	0.2 (0.04, 0.73)	0.2 (0.04, 0.64)	1.0 (0.19, 5.46)
6B	38	245	(92.6, 646.9)	16	247	(49.1, 1241.8)	21	332	(84.4, 1304.3)	1.0 (0.17, 5.85)	0.7 (0.15, 3.72)	0.7 (0.10, 5.37)
9V	40	43	(16.3, 111.9)	18	36	(8.6, 149.1)	21	52	(14.6, 187.8)	1.2 (0.23, 6.25)	0.8 (0.17, 3.92)	0.7 (0.11, 4.43)
14	39	98	(39.7, 242.9)	16	40	(9.2, 174.2)	20	49	(14.4, 163.9)	2.4 (0.48, 12.35)	2.0 (0.45, 9.05)	0.8 (0.13, 5.14)
18C	42	14	(6.9, 27.7)	17	76	(15.7, 363.0)	19	28	(7.2, 109.7)	0.2 (0.04, 0.80)	0.5 (0.12, 2.03)	2.7 (0.48, 14.92)
19F	43	48	(20.8, 112.5)	17	49	(13.0, 182.6)	21	40	(14.0, 112.5)	1.0 (0.23, 4.36)	1.2 (0.31, 4.84)	1.2 (0.23, 6.65)
23F	43	52	(22.5, 120.3)	16	61	(13.1, 284.3)	21	178	(54.6, 578.7)	0.9 (0.17, 4.17)	0.3 (0.07, 1.24)	0.3 (0.06, 2.08)
Additional												
1	44	6	(4.5, 7.5)	18	5	(3.4, 6.5)	22	10	(6.9, 15.0)	1.3 (0.79, 1.97)	0.6 (0.38, 0.88)	0.5 (0.27, 0.77)
3	42	20	(11.8, 34.6)	17	10	(4.4, 22.2)	21	18	(12.1, 28.0)	2.0 (0.85, 4.90)	1.1 (0.49, 2.48)	0.5 (0.20, 1.45)
5	44	4	(NE, NE)	18	4	(NE, NE)	22	4	(3.6, 5.6)	1.0 (0.87, 1.15)	0.9 (0.79, 1.03)	0.9 (0.76, 1.06)
6A	44	170	(72.8, 395.5)	16	10	(3.4, 31.4)	21	75	(22.3, 253.9)	16.5 (3.56, 76.14)	2.3 (0.56, 9.06)	0.1 (0.02, 0.78)
7F	39	60	(22.5, 157.8)	16	47	(10.0, 225.2)	21	389	(112.0, 1351.1)	1.3 (0.22, 7.07)	0.2 (0.03, 0.74)	0.1 (0.02, 0.84)
19A	41	118	(58.2, 239.7)	18	25	(7.4, 82.0)	20	124	(46.4, 330.2)	4.8 (1.35, 16.98)	1.0 (0.28, 3.23)	0.2 (0.05, 0.85)

Abbreviation: NE=Not estimable.

a. n = Number of subjects with a determinate OPA antibody titer to the given 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.
e. CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures ((13v/13v/13v - 7v/7v/13v) or (13v/13v/13v - 7v/13v/13v) or (7v/7v/13v - 7v/13v/13v)).

The OPA GMTs and GMT ratios before vaccination (up to 7 days prior to visit 2) for the all-available immunogenicity population were overall comparable to those observed for the evaluable immunogenicity population.

For the 7 common serotypes, the OPA GMTs in each group had decreased from the values after the toddler dose (presented in CSR for study 008) to before the 13vPnC dose in study 6096A1-3021 (up to 7 days prior to visit 2). For the 6 additional serotypes, the GMTs had generally decreased from the values after the toddler dose in the 13vPnC/13vPnC/13vPnC and 7vPnC/13vPnC/13vPnC groups, ie the groups that had received 13vPnC as toddler dose, but had slightly increased in the 7vPnC/7vPnC/13vPnC group (exception serotypes 5 and 6A). Refer to Supportive Table 15.14 for additional details on posttoddler OPA GMT analyses.

15.14 Comparison of Pneumococcal OPA GMTs Posttoddler Dose – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled)									Ratio[d] (95% CI[e])		
	13v/13v/13v			7v/7v/13v			7v/13v/13v					
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	13v/13v/13v to 7v/7v/13v	13v/13v/13v to 7v/13v/13v	7v/7v/13v to 7v/13v/13v
7vPnC												
4	49	1231	(801.1, 1892.3)	34	1976	(1543.1, 2531.0)	18	1163	(723.9, 1867.4)	0.6 (0.37, 1.06)	1.1 (0.55, 2.03)	1.7 (0.85, 3.39)
6B	44	1857	(1131.4, 3048.1)	32	2007	(1146.5, 3513.0)	16	2444	(1537.7, 3883.0)	0.9 (0.46, 1.85)	0.8 (0.32, 1.81)	0.8 (0.33, 2.05)
9V	43	1470	(914.3, 2362.3)	31	1333	(849.8, 2089.4)	17	925	(306.9, 2788.8)	1.1 (0.53, 2.31)	1.6 (0.65, 3.90)	1.4 (0.56, 3.71)
14	39	758	(521.4, 1103.0)	32	1052	(822.2, 1344.8)	13	916	(544.1, 1541.7)	0.7 (0.46, 1.14)	0.8 (0.45, 1.52)	1.1 (0.61, 2.15)
18C	49	2999	(2237.1, 4019.7)	35	3871	(2807.8, 5337.9)	20	4259	(2629.5, 6898.5)	0.8 (0.50, 1.20)	0.7 (0.42, 1.19)	0.9 (0.52, 1.58)
19F	38	437	(271.9, 701.4)	29	142	(57.8, 350.8)	13	405	(100.4, 1630.0)	3.1 (1.17, 8.06)	1.1 (0.31, 3.80)	0.4 (0.10, 1.30)
23F	50	1100	(672.1, 1801.2)	35	1614	(991.0, 2628.9)	17	1785	(1139.1, 2797.0)	0.7 (0.35, 1.32)	0.6 (0.26, 1.44)	0.9 (0.37, 2.20)
Additional												
1	55	136	(100.9, 184.6)	30	4	(NE, NE)	26	54	(29.3, 99.2)	34.1 (21.05, 55.29)	2.5 (1.53, 4.20)	0.1 (0.04, 0.13)
3	51	185	(156.1, 219.1)	28	5	(3.9, 7.6)	25	330	(262.4, 415.2)	33.9 (24.82, 46.31)	0.6 (0.41, 0.77)	0.0 (0.01, 0.02)
5	56	84	(61.2, 114.4)	32	4	(NE, NE)	27	75	(41.3, 135.1)	20.9 (12.95, 33.76)	1.1 (0.67, 1.86)	0.1 (0.03, 0.09)
6A	53	1650	(1194.9, 2277.8)	25	164	(52.5, 513.0)	25	2083	(1276.7, 3397.6)	10.1 (4.44, 22.76)	0.8 (0.35, 1.79)	0.1 (0.03, 0.20)
7F	57	1440	(995.6, 2083.5)	28	7	(3.7, 15.4)	25	6354	(4343.5, 9295.5)	192.1 (99.47, 370.80)	0.2 (0.11, 0.45)	0.0 (0.00, 0.00)
19A	56	563	(403.4, 785.7)	28	14	(6.8, 30.3)	23	794	(507.5, 1241.6)	39.3 (20.48, 75.34)	0.7 (0.35, 1.42)	0.0 (0.01, 0.04)

Abbreviation: NE=Not estimable.

a. n = Number of subjects with a determinate OPA antibody titer to the given 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.

e. CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures ((13v/13v/13v - 7v/7v/13v) or (13v/13v/13v - 7v/13v/13v) or (7v/7v/13v - 7v/13v/13v)).

Antibody Response To Vaccination

Pneumococcal IgG Geometric Mean Concentrations

Four (4) to 7 days after vaccination

The pneumococcal IgG GMCs at 4 to 7 days after vaccination ('postdose' in tables) are presented for the evaluable immunogenicity population in Table 9-5.

At day 4 to 7 after 13vPnC administration, GMCs for the 7 common serotypes were all increased as compared to the GMCs before vaccination and were generally comparable in the 3 vaccine groups.

For the 6 additional serotypes, the GMCs were generally comparable in the 13vPnC/13vPnC/13vPnC and the 7vPnC/13vPnC/13vPnC groups, but lower in the 7vPnC/7vPnC/13vPnC group, with the exception of GMCs for serotype 3 which remained essentially comparable across all 3 study groups.

All of the 95% CIs on the GMC ratios for the 13vPnC/13vPnC/13vPnC to 7vPnC/13vPnC/13vPnC pairwise comparison included 1. However, 95% CIs for the ratios in all of the 13vPnC/13vPnC/13vPnC to 7vPnC/7vPnC/13vPnC and 7vPnC/7vPnC/13vPnC to 7vPnC/13vPnC/13vPnC pairwise comparisons excluded 1, indicating that GMC mean values were consistently lower in the 7vPnC/7vPnC/13vPnC than in the other vaccine groups (exception: serotype 3 for the 13vPnC/13vPnC/13vPnC to 7vPnC/7vPnC/13vPnC pairwise comparison, and serotypes 3 and 6A for the 7vPnC/7vPnC/13vPnC to 7vPnC/13vPnC/13vPnC pairwise comparison) .

Table 9-5: Comparison of Pneumococcal IgG GMCs (µg/mL) 4-7 Days Postdose – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled)									Ratio[d] (95% CI[e])		
	13v/13v/13v			7v/7v/13v			7v/13v/13v					
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	13v/13v/13v to 7v/7v/13v	13v/13v/13v to 7v/13v/13v	7v/7v/13v to 7v/13v/13v
7vPnC												
4	44	2.96	(1.67, 5.24)	18	4.66	(2.01, 10.82)	22	3.85	(1.70, 8.74)	0.63 (0.23, 1.76)	0.77 (0.30, 1.99)	1.21 (0.38, 3.86)
6B	44	17.78	(12.50, 25.30)	18	19.15	(8.84, 41.48)	22	16.26	(8.10, 32.66)	0.93 (0.43, 1.99)	1.09 (0.54, 2.22)	1.18 (0.50, 2.79)
9V	43	3.49	(2.39, 5.09)	18	3.15	(1.75, 5.66)	22	3.20	(1.86, 5.50)	1.11 (0.56, 2.19)	1.09 (0.58, 2.06)	0.98 (0.46, 2.13)
14	44	5.55	(3.32, 9.30)	18	5.67	(2.29, 13.99)	22	4.52	(2.14, 9.52)	0.98 (0.38, 2.55)	1.23 (0.50, 3.00)	1.25 (0.42, 3.72)
18C	44	2.31	(1.36, 3.91)	18	3.34	(1.66, 6.72)	22	2.51	(1.33, 4.73)	0.69 (0.29, 1.68)	0.92 (0.40, 2.10)	1.33 (0.49, 3.64)
19F	44	11.70	(7.21, 19.00)	18	6.88	(2.98, 15.86)	22	8.51	(4.38, 16.55)	1.70 (0.70, 4.12)	1.37 (0.60, 3.14)	0.81 (0.30, 2.21)
23F	44	5.24	(3.49, 7.87)	18	5.82	(2.97, 11.40)	22	6.28	(3.50, 11.26)	0.90 (0.43, 1.89)	0.83 (0.42, 1.67)	0.93 (0.40, 2.16)
Additional												
1	44	4.24	(2.48, 7.26)	18	0.56	(0.27, 1.18)	22	8.00	(3.51, 18.23)	7.53 (2.86, 19.78)	0.53 (0.22, 1.31)	0.07 (0.02, 0.21)
3	44	1.24	(0.79, 1.95)	18	1.12	(0.56, 2.25)	22	1.24	(0.90, 1.72)	1.11 (0.53, 2.30)	1.00 (0.50, 1.97)	0.90 (0.39, 2.07)
5	44	6.00	(4.16, 8.66)	18	1.43	(0.99, 2.06)	22	9.81	(5.29, 18.19)	4.20 (2.18, 8.09)	0.61 (0.33, 1.13)	0.15 (0.07, 0.31)
6A	44	13.86	(9.69, 19.83)	18	4.46	(2.18, 9.12)	22	7.37	(3.95, 13.78)	3.11 (1.51, 6.40)	1.88 (0.96, 3.69)	0.60 (0.27, 1.37)
7F	44	3.55	(2.35, 5.36)	18	1.23	(0.69, 2.21)	22	3.08	(1.72, 5.51)	2.88 (1.39, 5.98)	1.15 (0.58, 2.28)	0.40 (0.17, 0.92)
19A	44	13.07	(9.63, 17.74)	18	5.09	(3.17, 8.19)	22	10.50	(7.12, 15.50)	2.57 (1.50, 4.39)	1.24 (0.75, 2.05)	0.48 (0.26, 0.89)

a. n = Number of subjects with a determinate IgG antibody concentration to the given serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
d. Ratio of GMCs.
e. CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures ((13v/13v/13v - 7v/7v/13v) or (13v/13v/13v - 7v/13v/13v) or (7v/7v/13v - 7v/13v/13v)).

One (1) month after vaccination

One of the primary objectives was to evaluate the immune response to 13 pneumococcal vaccine serotypes 1 month after a dose of 13vPnC administered not earlier than 24 months after the toddler dose in study 6096A1-008, as measured by serotype-specific IgG concentrations. The pneumococcal IgG GMCs approximately 1 month after vaccination (visit 4) are presented for the evaluable immunogenicity population in Table 9-6.

For the 7 common serotypes, GMCs measured at visit 4 (27 through 56 days after 13vPnC) in the evaluable immunogenicity population were generally comparable for the 3 groups. In all 3 groups, the lowest GMCs were determined for serotype 18C, and the highest GMCs were determined for serotype 6B. Overall, the GMC ratios ranged from 0.62 (serotype 6B in the 13vPnC/13vPnC/13vPnC to 7vPnC/7vPnC/13vPnC pairwise comparison) to 1.44 (serotype 6B in the 7vPnC/7vPnC/13vPnC to 7vPnC/13vPnC/13vPnC pairwise comparison), with the upper limit of the 95% CI for the ratio <1 only for serotypes 6B and 18C for the 13vPnC/13vPnC/13vPnC to 7vPnC/7vPnC/13vPnC pairwise comparison, and with the lower CI limit >1 for serotypes 4 and 6B for the 7vPnC/7vPnC/13vPnC to 7vPnC/13vPnC/13vPnC pairwise comparison.

For the 6 additional serotypes, the GMCs were higher in the 13vPnC/13vPnC/13vPnC and 7vPnC/13vPnC/13vPnC groups than in the 7vPnC/7vPnC/13vPnC group, with the exception of GMCs for serotype 3 which remained comparable across all 3 study groups.
The GMC ratios were >1.0 for all serotypes for the 13vPnC/13vPnC/13vPnC to 7vPnC/7vPnC/13vPnC pairwise comparison and <1.0 for all 7vPnC/7vPnC/13vPnC to 7vPnC/13vPnC/13vPnC pairwise comparisons, indicating that GMC mean values were consistently higher for the 13vPnC/13vPnC/13vPnC and 7vPnC/13vPnC/13vPnC groups than for the 7vPnC/7vPnC/13vPnC group. The 95% CIs for the ratios excluded 1 for serotypes 1 and 5 (all 3 pairwise comparisons); for serotype 6A (13vPnC/13vPnC/13vPnC to 7vPnC/7vPnC/13vPnC pairwise comparison only); and for serotypes 7F and 19A (13vPnC/13vPnC/13vPnC to 7vPnC/7vPnC/13vPnC pairwise comparison and 7vPnC/7vPnC/13vPnC to 7vPnC/13vPnC/13vPnC pairwise comparison). The 95% CIs for GMC ratios

also excluded 1 (upper limits <1) for the 13vPnC/13vPnC/13vPnC to 7vPnC/13vPnC/13vPnC pairwise comparison for serotypes 1 and 5.

In all groups and all serotypes, GMCs further increased from 4 to 7 days after vaccination to 1 month after vaccination.

Table 9-6: Comparison of Pneumococcal IgG GMCs (µg/mL) 1 Month Postdose – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled)									Ratio[d] (95% CI[e])		
	13v/13v/13v			7v/7v/13v			7v/13v/13v					
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	13v/13v/13v to 7v/7v/13v	13v/13v/13v to 7v/13v/13v	7v/7v/13v to 7v/13v/13v
7vPnC												
4	120	10.34	(8.94, 11.97)	57	12.79	(10.00, 16.35)	58	8.98	(6.98, 11.56)	0.81 (0.61, 1.07)	1.15 (0.87, 1.52)	1.42 (1.03, 1.96)
6B	120	31.62	(27.02, 37.01)	57	51.07	(38.65, 67.49)	58	35.38	(27.25, 45.93)	0.62 (0.46, 0.84)	0.89 (0.66, 1.20)	1.44 (1.02, 2.04)
9V	120	6.76	(5.90, 7.73)	57	6.50	(5.31, 7.95)	58	6.19	(5.04, 7.61)	1.04 (0.82, 1.32)	1.09 (0.86, 1.39)	1.05 (0.79, 1.39)
14	120	21.55	(18.41, 25.24)	57	21.15	(16.89, 26.48)	58	20.73	(16.45, 26.12)	1.02 (0.77, 1.34)	1.04 (0.79, 1.37)	1.02 (0.74, 1.40)
18C	120	4.56	(3.93, 5.29)	56	6.12	(4.89, 7.65)	58	5.35	(4.27, 6.71)	0.75 (0.57, 0.97)	0.85 (0.65, 1.11)	1.14 (0.84, 1.56)
19F	120	16.59	(13.57, 20.28)	57	12.07	(9.35, 15.59)	58	15.09	(11.17, 20.39)	1.37 (0.97, 1.94)	1.10 (0.78, 1.55)	0.80 (0.54, 1.19)
23F	120	8.68	(7.50, 10.03)	57	10.87	(8.30, 14.22)	58	9.10	(7.34, 11.28)	0.80 (0.61, 1.05)	0.95 (0.73, 1.25)	1.19 (0.87, 1.64)
Additional												
1	120	10.72	(9.17, 12.52)	57	2.96	(2.45, 3.59)	58	20.69	(16.14, 26.53)	3.62 (2.76, 4.74)	0.52 (0.40, 0.68)	0.14 (0.10, 0.20)
3	120	1.81	(1.46, 2.23)	56	1.60	(1.19, 2.17)	58	2.07	(1.66, 2.59)	1.13 (0.80, 1.59)	0.87 (0.62, 1.23)	0.77 (0.52, 1.15)
5	120	10.00	(8.63, 11.58)	57	2.86	(2.37, 3.46)	58	19.20	(14.93, 24.70)	3.49 (2.68, 4.54)	0.52 (0.40, 0.68)	0.15 (0.11, 0.20)
6A	120	23.09	(19.50, 27.33)	57	14.38	(10.53, 19.64)	58	18.60	(13.87, 24.93)	1.61 (1.15, 2.23)	1.24 (0.89, 1.72)	0.77 (0.53, 1.13)
7F	118	8.23	(7.11, 9.52)	56	5.04	(4.16, 6.11)	58	8.02	(6.66, 9.67)	1.63 (1.28, 2.08)	1.03 (0.81, 1.30)	0.63 (0.47, 0.83)
19A	120	17.10	(14.54, 20.11)	57	8.58	(6.70, 10.99)	58	16.46	(13.42, 20.19)	1.99 (1.51, 2.63)	1.04 (0.79, 1.37)	0.52 (0.38, 0.72)

a. n = Number of subjects with a determinate IgG antibody concentration to the given serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
d. Ratio of GMCs.
e. CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures ((13v/13v/13v - 7v/7v/13v) or (13v/13v/13v - 7v/13v/13v) or (7v/7v/13v - 7v/13v/13v)).

Pneumococcal OPA Geometric Mean Titers

A comparison of pneumococcal OPA GMTs measured approximately 1 month after vaccination (visit 4) is shown in Table 9-11.

For the 7 common serotypes, OPA GMTs measured at visit 4 (27 through 56 days after 13vPnC) in the evaluable immunogenicity population were generally comparable for the 3 groups. In all 3 groups, the lowest OPA GMTs were determined for serotype 19F. The highest OPA GMTs were determined for serotype 18 in the 13vPnC/13vPnC/13vPnC group and for serotype 6B in the 7vPnC/7vPnC/13vPnC, and 7vPnC/13vPnC/13vPnC groups. The GMT ratios ranged from 0.7
to 1.3, with the 95% CI for the ratio excluding 1 only for serotype 6B (13vPnC/13vPnC/13vPnC to 7vPnC/7vPnC/13vPnC pairwise comparison).

OPA GMTs for serotype 3 were clearly higher in the 13vPnC/13vPnC/13vPnC and 7vPnC/13vPnC/13vPnC groups as compared to the 7vPnC/7vPnC/13vPnC group, which contrasts with the comparable IgG response to serotype 3 that was described in all 3 study groups.

At 1 month after vaccination, OPA GMTs in all vaccine groups were generally higher than before vaccination and for the majority of serotypes also higher than at the posttoddler visit.

Table 9-11: Comparison of Pneumococcal OPA GMTs 1 Month Postdose – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled)									Ratio[d] (95% CI[e])		
	13v/13v/13v			7v/7v/13v			7v/13v/13v					
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	13v/13v/13v to 7v/7v/13v	13v/13v/13v to 7v/13v/13v	7v/7v/13v to 7v/13v/13v
7vPnC												
4	117	5465	(4698.9, 6356.4)	53	5208	(4301.7, 6304.2)	55	5487	(4236.9, 7106.4)	1.0 (0.80, 1.38)	1.0 (0.76, 1.30)	0.9 (0.69, 1.30)
6B	117	6684	(5638.4, 7924.4)	57	10042	(7697.5, 13101.6)	56	8983	(7006.9, 11516.8)	0.7 (0.49, 0.90)	0.7 (0.55, 1.01)	1.1 (0.79, 1.59)
9V	116	5120	(4456.1, 5882.6)	54	4052	(3291.0, 4989.7)	55	5221	(4110.4, 6630.7)	1.3 (0.98, 1.63)	1.0 (0.76, 1.27)	0.8 (0.58, 1.05)
14	115	2780	(2374.7, 3254.6)	54	3079	(2450.6, 3869.4)	55	2979	(2232.9, 3973.4)	0.9 (0.67, 1.21)	0.9 (0.70, 1.25)	1.0 (0.73, 1.46)
18C	117	7711	(6589.6, 9023.3)	54	7091	(5655.9, 8889.9)	57	8431	(6740.3, 10545.7)	1.1 (0.83, 1.43)	0.9 (0.70, 1.20)	0.8 (0.61, 1.15)
19F	118	1319	(1030.5, 1689.5)	57	1721	(1316.8, 2250.3)	57	1914	(1350.6, 2712.5)	0.8 (0.51, 1.15)	0.7 (0.46, 1.03)	0.9 (0.56, 1.44)
23F	118	2427	(2063.6, 2855.0)	53	2411	(1792.5, 3242.4)	56	2673	(2091.2, 3417.3)	1.0 (0.74, 1.37)	0.9 (0.67, 1.23)	0.9 (0.63, 1.29)
Additional												
1	119	613	(525.2, 715.7)	56	197	(161.4, 239.4)	57	1212	(968.0, 1516.9)	3.1 (2.40, 4.06)	0.5 (0.39, 0.66)	0.2 (0.12, 0.22)
3	118	244	(214.7, 276.4)	56	173	(139.5, 214.5)	58	291	(239.4, 353.7)	1.4 (1.11, 1.78)	0.8 (0.66, 1.06)	0.6 (0.45, 0.78)
5	118	455	(385.7, 537.9)	55	390	(281.2, 541.8)	54	728	(545.0, 972.2)	1.2 (0.84, 1.62)	0.6 (0.45, 0.87)	0.5 (0.36, 0.79)
6A	117	5580	(4593.6, 6777.0)	55	5596	(4276.6, 7321.2)	55	5982	(4450.7, 8041.1)	1.0 (0.71, 1.40)	0.9 (0.66, 1.31)	0.9 (0.63, 1.39)
7F	118	4323	(3794.4, 4925.1)	56	8048	(6500.9, 9962.2)	54	4056	(3092.2, 5321.2)	0.5 (0.41, 0.70)	1.1 (0.82, 1.38)	2.0 (1.46, 2.69)
19A	116	1212	(1048.1, 1400.7)	53	1249	(956.5, 1632.3)	54	1568	(1249.7, 1966.1)	1.0 (0.74, 1.28)	0.8 (0.59, 1.02)	0.8 (0.58, 1.10)

a. n = Number of subjects with a determinate OPA antibody titer to the given 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.
e. CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures ((13v/13v/13v - 7v/7v/13v) or (13v/13v/13v - 7v/13v/13v) or (7v/7v/13v - 7v/13v/13v)).

Proportion of Subjects Achieving Pneumococcal OPA Antibody Titers ≥ LLOQ

For the 7 common serotypes, the proportions of subjects achieving OPA titers ≥LLOQ at 1 month after vaccination were comparable for all 3 groups. The percentage of responders to all 7 common serotypes was 100% in all 3 study groups except for serotype 19F (98.3% in the 13vPnC/13vPnC/13vPnC group and 98.2% in the 7vPnC/13vPnC/13vPnC group).

For the 6 additional serotypes, the proportions of subjects achieving OPA titers ≥LLOQ at 1 month after vaccination were comparable for all 3 groups. The percentage of responders to serotypes 1, 6A, 7F, and 19A was 100% in all 3 study groups, the percentage of responders to serotype 3 ranged from 98.2% (7vPnC/7vPnC/13vPnC group) to 100% in the 2 other groups, and the percentage of responders to serotype 5 ranged from 96.4% (7vPnC/7vPnC/13vPnC group) to 100% in the 7vPnC/13vPnC/13vPnC group.

Assessor's comment: The results of this study provide new data on antibody persistence and responses to a fifth dose of Prevenar 13. IgG GMCs were presented, but not proportion of subjects obtaining antibody levels ≥0.35 µg/mL. From the RCDCs it is evident that for all serotypes except serotype 3 100% of the subjects achieved this threshold after the fifth booster dose, in all three groups.
The antibody persistence data showed that the GMC point estimates for the 7 common serotypes were higher for in the 7v/7v/13v group compared to the two other groups, especially the 13v/13v/13v group. The clinical relevance of this difference is unknown. There was good evidence of a memory response to the fifth dose in all groups for all serotypes, with responses that exceeded those to the toddler dose, except serotype 3 (see fig 16.2).

- Safety results

Local Reactions:

Local reactions (pain, swelling, and redness) at the site of the pneumococcal conjugate injection were monitored daily for a total of 7 days after the vaccination. The frequencies of local reactions were comparable for the 3 groups, with 70.1% of subjects in the 13vPnC/13vPnC/13vPnC group, 66.7% of subjects in the 7vPnC/7vPnC/13vPnC group, and 72.2% of subjects in the 7vPnC/13vPnC/13vPnC group reporting at least 1 local reaction during the 7 days after vaccination.

The local reaction most frequently reported after 13vPnC administration was pain at the injection site, reported for 55.4% of subjects in the 13vPnC/13vPnC/13vPnC group, 55.8% of subjects in the 7vPnC/7vPnC/13vPnC group, and 64.2% of subjects in the 7vPnC/13vPnC/13vPnC group. Most local reactions were mild or moderate in severity. Severe pain at the injection site (ie, prevented daily activities) was reported for 1) subject in each group, (1.1%, 2.3% and 2.2%). There were no statistically significant differences between the groups in the incidences of mild, moderate, and severe occurrences of pain, swelling, and redness.

Systemic Events:

The percentage of subjects reporting 1 or more systemic event was 50.5% in the 13vPnC/13vPnC/13vPnC group, 58.9% in the 7vPnC/7vPnC/13vPnC group, and 42.9% in the 7vPnC/13vPnC/13vPnC group.

Fever was defined as a temperature of greater than or equal to 38.0°C. Most subjects with fever had a temperature of ≤39.0°C, only 1 subject (2.2% of subjects) in the 7vPnC/13vPnC/13vPnC group had fever >40.0°C.

The systemic event reported most frequently was fatigue. It was reported for 40.8% of subjects in the 13vPnC/13vPnC/13vPnC group, 51.9% of subjects in the 7vPnC/7vPnC/13vPnC group, and 31.3% of subjects in the 7vPnC/13vPnC/13vPnC group. The severity of fatigue was mild or moderate for the majority of subjects. Severe fatigue was reported for 3.3% of subjects in the 13vPnC/13vPnC/13vPnC group, 2.3% in the 7vPnC/7vPnC/13vPnC group, and 2.2% of subjects in the 7vPnC/13vPnC/13vPnC group.

The percentage of subjects reporting any systemic events, fever, vomiting, and diarrhea were generally comparable for the 3 groups. Fatigue occurred with a statistically significantly higher incidence in the 7vPnC/7vPnC/13vPnC group (51.9% of subjects) compared with the 7vPnC/13vPnC/13vPnC group (31.3% of subjects). A statistically significantly higher number of subjects used antipyretic medication in the 7vPnC/7vPnC/13vPnC group (44.2%) compared to subjects in the 13vPnC/13vPnC/13vPnC group (19.8%) and subjects in the 7vPnC/13vPnC/13vPnC group

(21.3%). Although a higher number of subjects reported fever ≤40°C in the 7vPnC/7vPnC/13vPnC group compared with the 13vPnC/13vPnC/13vPnC group and the 7vPnC/13vPnC/13vPnC group, this difference was not statistically significant.

Adverse Events:
At least 1 AE was reported for 13.1% of subjects in the 13vPnC/13vPnC/13vPnC group, 9.4% of subjects in the 7vPnC/7vPnC/13vPnC group, and 7.8% of subjects in the 7vPnC/13vPnC/13vPnC group.
The AEs reported were consistent with childhood illnesses considered common in this age group.
The system organ class "infections and infestations" was reported most frequently in all 3 groups: for 12.3% of subjects in the 13vPnC/13vPnC/13vPnC group, 7.8% of subjects in the 7vPnC/7vPnC/13vPnC group, and 6.3% of subjects in the 7vPnC/13vPnC/13vPnC group AEs in this category were reported. The only AE (preferred term) reported by more than 2% of subjects in any group was nasopharyngitis which was reported by 2.3% of subjects in the 13vPnC/13vPnC/13vPnC group. The incidence of AEs was not statistically significantly different between the groups overall or for any individual AE.

Serious adverse events
No death occurred during the course of the study. No subjects reported SAEs during the course of the study. No subjects were withdrawn from the study because of adverse events

Assessor's comment. No new safety signal was detected in study 3021. The adverse reactions were similar to what has been reported for Prevenar 13 in other studies.

MAH's Overall Conclusions of the Study:
At least 2 years after a toddler dose of pneumococcal conjugate vaccine, antibody persistence for the 7 common serotypes was generally comparable regardless of the vaccination regimen received during the infant series and toddler dose. Antibody levels for the 6 additional serotypes were comparable or higher in the 7vPnC/13vPnC/13vPnC group compared to the 13vPnC/13vPnC/13vPnC group, with the exception of serotype 6A, and higher than in the 7vPnC/7vPnC/13vPnC subjects that had not previously received 13vPnC.

One dose of 13vPnC was immunogenic when given in children at approximately 3.4 years of age regardless of previous PnC vaccination regimen. The immunogenicity response to the 7 common serotypes was similar in all three groups. The antibody response to the 6 additional serotypes was higher in subjects who had previously received at least 1 dose of 13vPnC. Additionally, the rapid increase in pneumococcal immunogenicity response observed at 4 to 7 days after vaccination is indicative of a memory response induced by previous 13vPnC vaccination.

In this study, a fifth dose of PnC vaccine administered in children of approximately 3 years of age who had previously received a 4-dose series of pneumococcal conjugate vaccine as infants and toddlers, showed an acceptable safety profile.

3. Discussion on clinical aspects

In general the MAH's conclusions are endorsed. The submitted study is of interest as it demonstrates the extent of persistence and memory up to 24 months after the toddler dose, which has not been shown previously. The MAH has stated that a type II variation will be submitted to update section 4.2 of the SPC, though the exact content of the change has not been stated. The data demonstrate that 24 months after the toddler dose, the antibody levels have declined to levels similar to before the toddler dose. The immune responses following an additional dose 24 months after the toddler dose clearly demonstrate the presence of immunological memory, regardless of whether Prevenar or Prevenar 13 was used for priming. The results of the study have been described according to the protocol, and in that sense this submission is considered fulfilled. The information obtained from this study is clearly relevant to the prescribers, and the proposal to submit a type II variation in endorsed. Further details regarding this study, e.g. proportion of subjects achieving ≥0.35µg/mL IgG as measured by ELISA or OPA titres above the defined LLOQs, may be required during the assessment of the type II variation.

MS comments:
Comments were submitted by BE. They are partly endorsed.

1. BE did not accept the MAH's conclusion that the antibody persistence was generally comparable between the groups, and specifically refer to statistically significant differences between the groups.

The Rapporteur agrees that there are slight but statistically significant differences between the groups, and the MAH has also clearly stated these differences (serogroup 18C for ELISA IgG GMCs and serogroups 4 and 18C for OPA GMTs). Thus, in the opinion of the Rapporteur no further action regarding this question is necessary at this stage.

2. BE did not endorse the Rapporteur's comment that the GMC point estimates for the 7 common serotypes were higher for the 7v/7v/13v group compared to the other two groups, especially the 13v/13v/13v group. The BE assessor comments that the point estimates were in fact lower for two serotypes.

The Rapporteur agrees that the point estimates were in fact slightly lower in two cases, but the differences were very small and not statistically significant and it is therefore not correct to state that the GMCs were in fact lower in one group or the other. The only significantly different results between the groups point in the direction of lower titres in the 13v/13v/13v group. This can also be expected, as it is reasonable that there is some immune interference with increasing number of serotypes. This has been described previously for Prevenar 13 vs Prevenar, and for Synflorix vs Prevenar. It is also a well known phenomenon when increasing the number of antigens using concomitant vaccinations with several different vaccines.

3. BE did not endorse the comment that the clinical relevance of the difference between the groups is unknown, as differences in clinical protection are only expected to occur when differences in efficacy parameters are statistically significant.

The Rapporteur does not agree with this comment. A small difference in GMC or GMT is unlikely to have an impact on the clinical protection but it may very well be statistically significant if the study is adequately powered to detect small differences. Likewise, a difference between groups that is not statistically significant may in fact prove to be important, if the difference is large. The lack of statistical significance may be the result of an underpowered study, rather than a true lack of difference between the groups. The Rapporteur still consider the clinical relevance of differences in GMCs and GMTs unknown, as it is currently not known if high antibody levels are required for protection, or if the presence of immunological memory provides sufficient protection.

4. BE commented that the persistence of antibody to the additional serotypes was not commented in the PVAR. The following comment was given:
   When considering persistence of IgG against serotypes 3 and 5 (Table 9-3), it should be noted that pre-dose GMC are strictly comparable across the three vaccine groups. In other words, priming and boosting with the 13v vaccine (or priming with the 7v and boosting with the 13v) results in GMC that are comparable to the GMC obtained after priming and boosting with the 7 valent Prevenar vaccine that does not provide any protection against these serotypes. When considering functional antibody (Table 9-4), comparable pre-dose GMT are observed for serotypes 1, 3, 5 and 7F between the 13v/13v/13v and the 7v/7v/13v schedule.

The rapporteur agrees with this comment. However, regarding serogroup 3, several previously reported studies have noted relatively poor memory responses to this serogroup, and the responses are very often similar to the primary responses. The rapporteur would like to emphasise that it is not possible to conclude that 7v Prevenar is able to prime against any additional serogroups based on these results.

5. BE proposed the two following requests for supplementary information:

1. The proportion of subjects showing GMT ≥ LLOQ for serotypes 4 and 18C at the pre-dose time point in the 13v/13v/13v, 7v/7v/13v and 7v/13v/13v groups should be submitted.

2. 2. No clinical protection at the pre-dose time point (=24 months after the toddler dose) is expected for additional serotypes 1, 3 and 5 in the 13v/13v/13v group since GMT were very low and strictly comparable with those of the 7v/7v/13v group, not expected to provide any clinical protection. The proportion of subjects showing GMT ≥ LLOQ for serotypes 1, 3 and 5 at the pre-dose time point in the 13v/13v/13v, 7v/7v/13v and 7v/13v/13v groups should be submitted and the need for a fifth vaccine dose should be discussed.

The Rapporteur prefers not to prolong this procedure with additional questions, as a type II variation is proposed by the MAH. As stated above, the MAH has submitted the results of the study according to the study protocol, and by that the FUM is considered fulfilled. The additional information will be requested in the upcoming type II variation.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

This procedure is considered fulfilled as the MAH has submitted the full report for paediatric study 6096A1-3021, and has committed to submission of a type II variation.

- **Recommendation**

Fulfilled: X

Type II variation to be requested from the MAH by 2011-11-18

Not fulfilled:

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable