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

(Suspension for injection, Pneumococcal saccharide conjugated vaccine, adsorbed)

Procedure No. EMEA/H/C/000323

P46 132

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

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I. EXECUTIVE SUMMARY

The MAH submitted the immunogenicity and safety data from study 6114A1-4000-CN (B1841008): A phase 4, open-label trial to assess the safety, tolerability, and immunogenicity of Prevenar in older infants and young children in China who are naïve to previous pneumococcal vaccination.
Immunogenicity and safety data were discussed in sufficient detail by the MAH and do not warrant further investigation.

No SmPC and PL changes are proposed.

II. RECOMMENDATION[1]

No further action required.

III. INTRODUCTION

On June 24 2013 the MAH submitted a completed paediatric study for Prevenar, 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 and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

Information on the pharmaceutical formulation used in the study

Suspension for injection identical to the currently approved pharmaceutical formulation.

Clinical aspects

1. Introduction

The MAH submitted a final report for:

Study 6114A1-4000-CN (B1841008): A phase 4, open-label trial to assess the safety, tolerability, and immunogenicity of Prevenar in older infants and young children in China who are naïve to previous pneumococcal vaccination. The data in this report include the 12 month follow up following completion of vaccination.

2. Clinical study

Study 6114A1-4000-CN (B1841008): A phase 4, open-label trial to assess the safety, tolerability, and immunogenicity of Prevenar in older infants and young children in China who are naïve to previous pneumococcal vaccination.

- **Description**

Prevenar was approved in China in May 2008 for immunization against IPD in infants and young children. Based on Chinese data on pneumococcal disease and nasopharyngeal carriage, Prevenar is likely to protect Chinese infants from a large proportion of IPD.
Furthermore, as the majority of serotypes responsible for IPD are likely to be penicillin resistant, use of Prevenar may help to decrease rates of PRSP in the population. Prevenar is also approved in China for catch-up vaccinations in previously unvaccinated older infants and young children aged 7 months through 5 years. The present study is being conducted as part of the Prevenar post-approval commitment to provide safety, tolerability, and immunogenicity data on Prevenar catch-up

[1] *The recommendation from section V can be copied in this section*

vaccinations in older infants and young children in China. It also addresses requests for data on serum antibody concentrations in unvaccinated children.

- **Methods**

  - Objective(s)

    Primary objectives

    - To assess the serotype-specific pneumococcal immune responses induced by Prevenar when measured 1 month after the last dose of Prevenar in each age group.
    - To assess the pre-vaccination antibody levels to the 7 pneumococcal serotypes in Prevenar in each age group.

    Secondary objectives

    - To assess the serotype-specific pneumococcal immune responses induced by Prevenar when measured as follows:
      - 1 month after the third dose of Prevenar in Group 1.
      - 1 month after the second dose of Prevenar in Group 2.
      - 1 month after the first dose of Prevenar in Group 3.
    - To assess the antibody levels to the 7 pneumococcal vaccine serotypes 12 months after the last dose of Prevenar in each age group.

  - Study design

This was a phase 4, open-label, single center study. A total of 505 healthy Chinese infants and children were planned to be enrolled into 1 of 4 groups based on their age at enrollment as follows:
• Group 1 (100 subjects): 121 to <212 days of age and receive 4 doses of Prevenar.
• Group 2 (100 subjects): 212 days to <12 months of age (before the first birthday) and receive 3 doses of Prevenar.
• Group 3 (125 subjects): 12 to <24 months of age (before the second birthday) and receive 2 doses of Prevenar.
• Group 4 (180 subjects): 24 to <72 months of age (before the sixth birthday) and receive 1 dose of Prevenar.
Prevenar is the investigational product that was used in this study. It is licensed in China for use in infants aged 3 to 6 months, usually in a 3-4-5 month schedule, and at 12 to 15 months of age. Prevenar is also licensed for use in previously unvaccinated older children aged 7 months to 5 years in China.
Pre-vaccination antibody levels to the 7 pneumococcal vaccine serotypes in Prevenar were assessed for each age group.
Immune responses to the 7 pneumococcal vaccine serotypes were assessed approximately 1 month after the last dose of Prevenar and will be assessed again approximately 12 months after the last dose of Prevenar for each age group. Immune responses to the 7 pneumococcal vaccine serotypes were also assessed approximately 1 month after the third dose of Prevenar in Group 1, 1 month after the second dose of Prevenar in Group 2, and 1 month after the first dose of Prevenar in Group 3.
The approximate duration of subject participation in the study for each age group, including follow-up of antibody persistence up to approximately 12 months after the last dose of Prevenar, was to be as follows:
• Group 1 (121 to <212 days of age): up to 24.5 months.
• Group 2 (212 days to <12 months of age): up to 23.5 months.
• Group 3 (12 to <24 months of age): up to 17.5 months.
• Group 4 (24 to <72 months of age): up to 15 months.
It is planned that the study will be completed in approximately 29.5 months. The end of the study will be the last visit of the last subject.

  - Study population /Sample size

Sample size estimation was based on the variation in IgG first use concentrations observed in previous Prevenar studies (D118-P16 and P18) and in the 13vPnC clinical program (Studies 6096A1-003, 004, 006, 007, 008, 009, 011, 500, 501, 3000, 3002, 3005, 3007, and 3008). Observed standard deviations (SDs) on the natural logarithmic scale ranged up to 1.15 across the Prevenar serotypes. It is assumed this variability may increase with age. A responder rate of at least 94.9% was assumed for these calculations.
A sufficient number of subjects were to be enrolled to ensure approximately 80 subjects for groups 1 and 2, 100 subjects for group 3, and 144 subjects for group 4, provide safety and evaluable immunogenicity data. These sample sizes were estimated to provide estimates of the GMC within 25%

precision and responder rates with 5% precision in each group separately using 95% confidence intervals (CIs). Assuming a dropout rate of at most 20%, 505 subjects overall (100 in groups 1 and 2, 125 in group 3, and 180 in group 4) was considered to be sufficient to ensure the required number of evaluable subjects for immunogenicity and safety analysis.

- Treatments

Subjects in group 1, group 2, group 3, and group 4 received 4, 3, 2, and 1 doses of Prevenar, respectively, as outlined below:

Table 2. Immunization Schedule

	Vaccination 1	Vaccination 2	Vaccination 3	Vaccination 4
Group 1	Visit 1	28 to 42 days after Visit 1	28 to 42 days after Visit 2	12 to 15 months of age (At least 28 days after Visit 4)
Group 2	Visit 1	28 to 42 days after Visit 1	12 to 16 months of age (At least 28 days after Visit 3)	N/A
Group 3	Visit 1	56 to 70 days after Visit 1	N/A	N/A
Group 4	Visit 1	N/A	N/A	N/A

N/A=Not applicable

Immunogenicity Evaluation

For all subjects, blood samples (approximately 5 mL) were collected prior to the first vaccination, approximately 1 month after the last dose of Prevenar, and approximately 12 months (365 to 410 days) after the last dose of Prevenar. A blood sample was also collected approximately 1 month after the third dose of Prevenar for Group 1, 1 month after the second dose of Prevenar for Group 2, and 1 month after the first dose of Prevenar for Group 3.

The total volume of blood collected from each subject was approximately 20 mL for Groups 1, 2, and 3, and 15 mL for Group 4.

All serum samples were shipped to Pfizer, Pearl River, New York, United States of America. Serum concentrations of anticapsular IgG as measured by enzyme-linked immunosorbent assay for the 7 pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) were to be determined in all subjects for each blood sample and expressed as micrograms per milliliter (µg/mL). The assay employs 2 absorbents: a C polysaccharide-containing cell wall extract plus serotype 22F capsular polysaccharide.

Safety Evaluation

The safety of 7vPnC (Prevenar) in this study was determined based on clinically important related AEs, AEs that require withdrawal, protocol-related AEs, and SAEs observed.

Subjects were observed for at least 20 minutes after each vaccination for any significant acute reactions. Observations after vaccination were to be performed according to local immunization practice.

- Statistical Methods

1. Statistical and Analysis Plans

Statistical analysis methods are described briefly here. Detailed information on statistical analyses is provided in the statistical analysis plan (SAP) dated 23 Apr 2010 and SAP memo dated 12 Jul 2011 in the appendix titled Statistical Analysis Report (SAP included).

2. Statistical Analysis of Demographic Data

Demographic characteristics, including gender, race and age at the time of first vaccination (in months) were summarized by group using descriptive statistics.

3. Statistical Analysis of Immunogenicity

3.1. Immunogenicity Populations

For the immunogenicity data from the first three blood draws for groups 1, 2 and 3 and the immunogenicity data from the first two blood draws for group 4 (not including the immunogenicity data from the 12-month follow-up visit blood draw visit), immunogenicity analyses were performed for 2 populations.

The evaluable immunogenicity population consisted of eligible subjects in the age range who had received all the assigned vaccination(s), had blood drawn within required time frames, had at least 1 valid and determinate assay result for the proposed analysis, had received no prohibited vaccines, and had no other major protocol violations. The all-available immunogenicity population consisted of

subjects who had at least 1 valid and determinate assay result for the proposed analysis. Both the evaluable and all-available immunogenicity populations were considered as primary immunogenicity populations.
For the timings of blood draws (except the prevaccination blood draw for Vaccination 1), 1 day before and 14 days after the protocol-specified timings were permitted for determination of evaluability.

3.2. Immunogenicity Analyses

The number and percentage of subjects enrolled and included in each immunogenicity population was tabulated for each group and the total sample. The denominator for the percentages was the total number of subjects in the given group, or the total sample as appropriate. Reasons for exclusion from the immunogenicity population were also summarized using the number and percentage of subjects. Subjects with no assay results for any serotype were classified under "subjects excluded from the all-available immunogenicity population" and not under "no valid or determinate assay result".

3.2.1. Geometric Means

Within each group, geometric means of the pneumococcal IgG antibody concentrations (GMCs) were calculated at each visit that had a blood draw. For all groups, the geometric mean fold rises (GMFRs) in antibody concentration (postvaccination/prevaccination) were summarized by geometric means, and CIs were also computed using the logarithmically transformed assay results. Only subjects with both pre- and postvaccination results were included in the derivation of GMFRs.

3.2.2. Proportion of Subjects Achieving Defined Levels

Within each group and for each serotype separately before and after each appropriate vaccination, the proportion of subjects achieving an antibody concentration at least as large as 0.35 µg/mL was computed for each blood sample. For each serotype, exact, unconditional, 2-sided 95% CIs on the proportion were calculated.

3.2.3. Reverse Cumulative Distribution Curves

Reverse cumulative distribution curves (RCDCs) are presented graphically by group for each serotype-specific pneumococcal IgG antibody concentration. The RCDCs for each group were plotted pre- and postvaccination IgGs on the same graph, distinguishable by symbol and/or line style choice.

4. Statistical Analysis of Safety

4.1. Safety Population

All subjects who received at least 1 dose of Prevenar were included in the safety population.

4.2. Safety Analyses

The safety of 7vPnC (Prevenar) in this study was determined based on findings from clinically important related AEs, AEs that require withdrawal, protocol-related AEs and SAEs.

4.2.1. Physical Examinations

Baseline physical examination information was summarized. The number and percentage of subjects enrolled, and those with each type of finding (performed [subcategories: abnormal, normal] or not performed) for the physical examination were tabulated for each age group or the total sample. The denominator for the percentages was the number in the group or the total sample.

4.2.2. Adverse Events

Adverse events were categorized according to MedDRA (version 14.1). The relation between AEs and the study vaccine (7vPnC) was characterized as related or not related as described in the protocol. The severity of AEs was characterized as mild, moderate, or severe. Any deaths were to be included in the last category, namely severe. In Groups 1 and 2, AEs were to be summarized during the infant series and following the toddler dose for each group separately. In Group 3, AEs were to be summarized during the 2-dose series and in Group 4, AEs were to be summarized following vaccination. All summaries were to be shown, by group, the number and percentage of subjects experiencing at least 1 event and the number of events. Additional summaries by AE severity and by vaccine relationship were to be produced.
All safety analyses were produced for each age group separately. No comparisons were made among the four age groups.
Separate summaries were to be produced for clinically important related AEs, AEs requiring withdrawal, protocol related AEs and SAEs.

➢ Results

- Recruitment/ Number analysed

A total of 506 subjects were enrolled in this study, 505 (99.8%) of which received at least 1 dose of vaccine. The total number of planned doses were administered in 90.0% of subjects in group 1 (4 doses), 88.1% of subjects in group 2 (3 doses), 94.4% of subjects in group 3 (2 doses), and 100.0% of subjects in group 4 (1 dose), respectively. A total of 93.1% of subjects completed the study up to

the time-point of the blood draw one month after the last vaccination. The remaining 6.9% of subjects were withdrawn before the blood draw one month after the last vaccination.
Twenty one (21, 4.2%) subjects withdrew during the 12-month follow-up. A total of 450 (88.9%) subjects completed the study, including the 12-month follow-up visit. Reasons for withdrawal during the 12-month follow-up included, 1 (0.8%) subject in Group 3 who died, and 20 (4.0%) subjects who were no longer willing to participate; 6 (6.0%) subjects in Group 1 and 3 (2.4%) and 11 (6.1%) subjects in Groups 3 and Group 4, respectively.

- Baseline data

Table 8 presents the demographic summary for the evaluable immunogenicity population. In total, 223 (47.8%) male subjects and 244 (52.2%) female subjects were included in the evaluable immunogenicity population. The distribution of gender within the individual groups was similar, with slightly more females than males in groups 1 and 4. All participating subjects were Asian. The mean (SD) age at dose 1 was within the protocol specified age range for groups 1 (5.3 months), 2 (9.8 months), 3 (17.5 months) and 4 (44.5 months).

Table 8. Demographic Characteristics – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled)									
	7vPnC Group 1 N[a]=88		7vPnC Group 2 N[a]=87		7vPnC Group 3 N[a]=115		7vPnC Group 4 N[a]=177		Total N[a]=467	
	n	%	n	%	n	%	n	%	n	%
Sex										
Female	50	56.8	43	49.4	58	50.4	93	52.5	244	52.2
Male	38	43.2	44	50.6	57	49.6	84	47.5	223	47.8
Race										
Asian	88	100.0	87	100.0	115	100.0	177	100.0	467	100.0
Age at dose 1 (months)										
n	88		87		115		177		467	

Mean (SD)	5.3 (0.9)	9.8 (1.4)	17.5 (4.2)	44.5 (13.0)	24.0 (18.5)
Median	5.1	10.0	17.6	45.1	17.8
Min, max	4.0, 7.0	7.0, 12.0	12.0, 23.9	24.6, 71.5	4.0, 71.5
Age at dose 2 (months)					
n	88	87	115		290
Mean (SD)	6.4 (0.9)	10.8 (1.5)	19.6 (4.1)		13.0 (6.3)
Median	6.2	11.0	19.7		11.8
Min, max	5.0, 8.1	8.0, 13.4	14.0, 26.2		5.0, 26.2
Age at dose 3 (months)					
n	88				88
Mean (SD)	7.4 (0.9)				7.4 (0.9)
Median	7.3				7.3
Min, max	6.0, 9.3				6.0, 9.3
Age at toddler dose (months)					
n	88	87			175
Mean (SD)	13.6 (0.9)	14.5 (1.6)			14.0 (1.4)
Median	13.5	14.7			13.8
Min, max	12.0, 15.7	12.0, 18.0			12.0, 18.0

Abbreviations: 7vPnC = 7-valent pneumococcal conjugate vaccine; max = maximum; min = minimum; n = number of subjects; N = total number of subjects in group; SD = standard deviation.
a. The values in this row are used as the denominators for percentages.
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- Efficacy results

1. Populations Analyzed

A total of 506 subjects were enrolled; 505 (99.8%) of whom were included in the all-available immunogenicity population and 467 (92.3%) of whom were included in the evaluable immunogenicity population. At the 12-month follow-up, 450 (88.9%) subjects were included in the all-available immunogenicity population and 433 (85.6%) subjects were included in the evaluable immunogenicity population.

2. Primary Immunogenicity Outcomes

2.1. Immune Response 1 Month After Last Dose of Study Vaccine

2.1.1. Geometric Mean Concentration and Geometric Mean Fold Rise

Pneumococcal IgG GMCs for groups 1 and 2 following the last vaccination (toddler dose) are presented in Table 18 for the evaluable immunogenicity population. GMCs of serotype-specific IgG appeared similar across the two groups for the 7 serotypes, with highest levels observed for serotype 14. GMCs one month after the toddler dose ranged from 4.05 to 12.75 µg/mL for group 1, and 4.02 to 13.02 µg/mL for group 2.

Table 18. Pneumococcal IgG GMCs (µg/mL) After Toddler Dose – Groups 1 and 2 – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled)					
	7vPnC Group 1			7vPnC Group 2		
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])
4	88	6.90	(5.61, 8.48)	87	7.16	(6.09, 8.42)
6B	88	8.01	(6.24, 10.30)	87	5.79	(4.64, 7.23)
9V	88	4.11	(3.40, 4.96)	87	4.64	(3.93, 5.47)
14	88	12.75	(10.32, 15.76)	87	13.02	(10.89, 15.57)
18C	88	4.65	(3.81, 5.69)	87	4.65	(3.86, 5.61)
19F	87	4.05	(3.07, 5.36)	87	4.02	(3.05, 5.31)
23F	88	4.75	(3.77, 5.99)	87	3.95	(3.19, 4.89)

Abbreviations: 7vPnC = 7-valent pneumococcal conjugate vaccine; CI = confidence interval; GMC = geometric mean concentration; n = number of subjects.

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 confidence levels based on the Student t distribution for the mean logarithm of the concentrations.

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Pneumococcal IgG GMCs for groups 3 and 4 following the last vaccination are presented in Table 19 for the evaluable immunogenicity population. As for groups 1 and 2, the highest GMCs were observed for serotype 14 in groups 3 and 4. GMCs ranged from 4.03 to 11.98 µg/mL for group 3 and 4.53 to 9.86 µg/mL for group 4.

Table 19. Pneumococcal IgG GMCs (µg/mL) 1 Month After the Last Vaccination – Groups 3 and 4 – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled)					
	7vPnC Group 3			7vPnC Group 4		
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])
4	115	7.53	(6.70, 8.46)	177	9.45	(8.38, 10.65)
6B	114	4.81	(3.89, 5.96)	177	6.36	(5.32, 7.59)
9V	115	4.67	(4.18, 5.21)	177	6.14	(5.42, 6.95)
14	115	11.98	(10.51, 13.65)	177	9.86	(8.03, 12.10)
18C	115	5.40	(4.78, 6.10)	177	7.39	(6.41, 8.51)
19F	115	4.03	(3.26, 4.98)	177	4.53	(3.73, 5.49)
23F	115	4.18	(3.51, 4.96)	177	5.64	(4.84, 6.57)

Abbreviations: 7vPnC = 7-valent pneumococcal conjugate vaccine; CI = confidence interval; GMC = geometric mean concentration; n = number of subjects.

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 confidence levels based on the Student t distribution for the mean logarithm of the concentrations.

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The antibody response for group 3, one month after the last (second) vaccination is presented in Table 20. For all serotypes, the lower limit of the 95% CI for the GMFR was greater than 1.0, indicating that the IgG GMC was notably higher after the last dose of study vaccine than before vaccination in group

3. The lowest response was found for serotype 6B, while the greatest response was observed for serotype 4. Across the 7 serotypes, the GMFR ranged from 17.00 to 425.21.

Table 20. Pneumococcal IgG GMCs (µg/mL) and GMFRs 1 Month After the Last Vaccination for 7vPnC Group 3 – Evaluable Immunogenicity Population

	Sampling Time								
	Before Vaccination			After Vaccination					
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	n[a]	GMFR[d]	(95% CI[c])
4	115	0.02	(0.01, 0.02)	115	7.53	(6.70, 8.46)	115	425.21	(330.20, 547.56)
6B	99	0.27	(0.21, 0.35)	99	4.62	(3.71, 5.76)	99	17.00	(12.64, 22.87)
9V	113	0.17	(0.13, 0.21)	113	4.64	(4.15, 5.18)	113	27.53	(22.00, 34.44)
14	115	0.03	(0.02, 0.04)	115	11.98	(10.51, 13.65)	115	384.28	(283.22, 521.41)
18C	114	0.02	(0.02, 0.03)	114	5.39	(4.76, 6.09)	114	222.79	(175.92, 282.14)
19F	115	0.13	(0.10, 0.17)	115	4.03	(3.26, 4.98)	115	31.54	(22.96, 43.44)
23F	102	0.17	(0.12, 0.23)	102	4.22	(3.50, 5.10)	102	25.31	(18.98, 33.75)

Abbreviations: 7vPnC = 7-valent pneumococcal conjugate vaccine; CI = confidence interval; GMC = geometric mean concentration; GMFR = geometric mean fold rise; n = number of subjects.

a. n = Number of subjects with a determinate IgG antibody concentration to the given serotype.

b. Geometric mean concentrations (GMCs) were calculated using all Group 3 subjects with available data from both prevaccination and postvaccination blood draws.

c. Confidence intervals (CIs) are back transforms of confidence levels based on the Student t distribution for the mean logarithm of the concentrations, or the mean fold rise.

d. Geometric mean fold rises (GMFRs) were calculated using all Group 3 subjects with available data from both the prevaccination and postvaccination blood draws.

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The antibody response for group 4, one month after vaccination is presented in Table 21 for the evaluable immunogenicity population. For all serotypes, the lower limit of the 95% CI for the GMFR was greater than 1.0, indicating that the IgG GMC was notably higher after vaccination than before vaccination in group 4. The lowest response was found for serotype 6B, while the greatest response was observed for serotype 4. Across the 7 serotypes, the GMFR ranged from 4.90 to 147.54.

Table 21. Pneumococcal IgG GMCs (µg/mL) and GMFRs 1 Month After Vaccination for 7vPnC Group 4 – Evaluable Immunogenicity Population

	Sampling Time								
	Before Vaccination			After Vaccination					
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	n[a]	GMFR[d]	(95% CI[c])
4	172	0.06	(0.05, 0.08)	172	9.40	(8.31, 10.64)	172	147.54	(119.12, 182.73)
6B	177	1.30	(1.08, 1.55)	177	6.36	(5.32, 7.59)	177	4.90	(4.17, 5.77)
9V	177	0.66	(0.56, 0.77)	177	6.14	(5.42, 6.95)	177	9.33	(8.02, 10.86)
14	177	0.36	(0.26, 0.50)	177	9.86	(8.03, 12.10)	177	27.38	(20.93, 35.82)
18C	172	0.12	(0.10, 0.16)	172	7.42	(6.42, 8.57)	172	59.55	(48.56, 73.03)
19F	169	0.71	(0.57, 0.89)	169	4.60	(3.77, 5.62)	169	6.45	(5.13, 8.09)
23F	174	0.88	(0.74, 1.04)	174	5.66	(4.84, 6.61)	174	6.45	(5.42, 7.68)

Abbreviations: 7vPnC = 7-valent pneumococcal conjugate vaccine; CI = confidence interval; GMC = geometric mean concentration; GMFR = geometric mean fold rise; n = number of subjects.

a. n = Number of subjects with a determinate IgG antibody concentration to the given serotype.

b. Geometric mean concentrations (GMCs) were calculated using all Group 4 subjects with available data from both prevaccination and postvaccination blood draws.

c. Confidence intervals (CIs) are back transforms of confidence levels based on the Student t distribution for the mean logarithm of the concentrations, or the mean fold rise.

d. Geometric mean fold rises (GMFRs) were calculated using all Group 4 subjects with available data from both the prevaccination and postvaccination blood draws.

Program ID: Study 6114A1-4000/CP IMM_IGG_GMFR.SAS. Runtime ID: 05APR2012 13:40

2.1.2. Proportion of Subjects Achieving Predefined Pneumococcal Antibody Concentration

The percentage of subjects achieving a pneumococcal IgG concentration ≥0.35 µg/mL following the toddler dose in groups 1 and 2 is summarized in Table 22 for the evaluable immunogenicity population. The majority of subjects (>90%) in groups 1 and 2 achieved an IgG concentration ≥0.35 µg/mL for all 7 serotypes, following the toddler dose. Across the 7 serotypes, proportion of subjects achieving an IgG level ≥0.35 µg/mL ranged from 93.1 to 100.0% for group 1 and from 94.3 to 100.0% for group 2. Results for the all-available immunogenicity population are presented in Supportive Table 2.9 in Section 11 attachment. Results were similar to results for the evaluable immunogenicity population.

Table 22. Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After Toddler Dose – Groups 1 and 2 – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled)							
	7vPnC Group 1				7vPnC Group 2			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
4	88	87	98.9	(93.8, 100.0)	87	87	100.0	(95.8, 100.0)
6B	88	87	98.9	(93.8, 100.0)	87	87	100.0	(95.8, 100.0)
9V	88	88	100.0	(95.9, 100.0)	87	87	100.0	(95.8, 100.0)
14	88	88	100.0	(95.9, 100.0)	87	87	100.0	(95.8, 100.0)
18C	88	87	98.9	(93.8, 100.0)	87	86	98.9	(93.8, 100.0)
19F	87	81	93.1	(85.6, 97.4)	87	82	94.3	(87.1, 98.1)
23F	88	86	97.7	(92.0, 99.7)	87	86	98.9	(93.8, 100.0)

Abbreviations: 7vPnC = 7-valent pneumococcal conjugate vaccine; CI = confidence interval; GMC = geometric mean concentration; n = number of subjects.
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 upon the observed proportion of subjects.
Program ID: Study 6114A1-4000/CP IMM_IGG_RESP.SAS. Runtime ID: 05APR2012 13:42

The percentage of subjects achieving a pneumococcal IgG concentration ≥0.35 µg/mL following the last dose of study vaccine in groups 3 and 4 is summarized in Table 22 for the evaluable immunogenicity population. The majority of subjects (>95%) in groups 3 and 4 achieved an IgG concentration ≥0.35 µg/mL for all 7 serotypes, following the last dose of study vaccine. Across the 7 serotypes, proportion of subjects achieving an IgG level ≥0.35 µg/mL ranged from 96.5 to 100.0% for group 3 and from 97.2 to 100.0% for group 4.

Table 23. Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL 1 Month After the Last Vaccination – Groups 3 and 4 – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled)							
	7vPnC Group 3				7vPnC Group 4			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
4	115	115	100.0	(96.8, 100.0)	177	177	100.0	(97.9, 100.0)
6B	114	113	99.1	(95.2, 100.0)	177	177	100.0	(97.9, 100.0)
9V	115	115	100.0	(96.8, 100.0)	177	177	100.0	(97.9, 100.0)
14	115	115	100.0	(96.8, 100.0)	177	176	99.4	(96.9, 100.0)
18C	115	115	100.0	(96.8, 100.0)	177	177	100.0	(97.9, 100.0)
19F	115	111	96.5	(91.3, 99.0)	177	172	97.2	(93.5, 99.1)
23F	115	114	99.1	(95.3, 100.0)	177	176	99.4	(96.9, 100.0)

Abbreviations: 7vPnC = 7-valent pneumococcal conjugate vaccine; CI = confidence interval; n = number of subjects; N = total number of subjects.
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 upon the observed proportion of subjects.
Program ID: Study 6114A1-4000/CP IMM_IGG_RESP.SAS. Runtime ID: 20APR2012 09:20

2.2. Prevaccination Antibody Levels to the 7 Pneumococcal Serotypes in Prevenar

2.2.1. Geometric Mean Concentration

Pneumococcal IgG GMCs for groups 1 to 4 prior to first vaccination are presented in Table 24. For all 7 serotypes, IgG GMCs were generally higher in group 4 than in groups 1 through 3, which were comparable. However, it was observed that the GMC for serotype 14 in group 1 was notably higher, than in groups 2 and 3 and the GMC for serotype 18C was also slightly higher in group 1; this may be explained by maternal antibodies.

Table 24. Pneumococcal IgG GMCs (µg/mL) Prior to First Vaccination for 7vPnC Groups 1 to 4 – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled)											
	7vPnC Group 1			7vPnC Group 2			7vPnC Group 3			7vPnC Group 4		
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])
4	88	0.01	(0.01, 0.02)	87	0.01	(0.01, 0.02)	115	0.02	(0.01, 0.02)	172	0.06	(0.05, 0.08)
6B	86	0.12	(0.10, 0.15)	64	0.16	(0.12, 0.22)	100	0.27	(0.21, 0.35)	177	1.30	(1.08, 1.55)
9V	88	0.10	(0.08, 0.12)	84	0.10	(0.08, 0.13)	113	0.17	(0.13, 0.21)	177	0.66	(0.56, 0.77)
14	88	0.16	(0.12, 0.22)	87	0.04	(0.03, 0.05)	115	0.03	(0.02, 0.04)	177	0.36	(0.26, 0.50)
18C	88	0.04	(0.03, 0.06)	87	0.02	(0.01, 0.02)	114	0.02	(0.01, 0.03)	172	0.12	(0.10, 0.16)
19F	88	0.11	(0.09, 0.14)	85	0.09	(0.07, 0.12)	115	0.13	(0.10, 0.17)	169	0.71	(0.57, 0.89)
23F	85	0.07	(0.06, 0.09)	75	0.08	(0.06, 0.11)	102	0.17	(0.12, 0.23)	174	0.88	(0.74, 1.04)

Abbreviations: 7vPnC = 7-valent pneumococcal conjugate vaccine; CI = confidence interval; GMC = geometric mean concentration; n = number of subjects.

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 confidence levels based on the Student t distribution for the mean logarithm of the concentrations.

Program ID: Study 6114A1-4000/CP IMM_IGG_GMC.SAS. Runtime ID: 05APR2012 13:39

2.2.2. Proportion of Subjects Achieving Predefined Pneumococcal Antibody Concentration

The percentage of subjects achieving a pneumococcal IgG concentration ≥0.35 µg/mL before vaccination in groups 1 and 2 is summarized in Table 25 for the evaluable immunogenicity population. The proportion of subjects achieving an IgG concentration ≥0.35 µg/mL ranged from 0.0 to 29.5% in group 1 and 0.0 to 28.1% in group 2. Analogous with GMC data, a higher proportion of patients achieved an IgG antibody concentration ≥0.35 µg/mL in group 1 (29.5%) than in groups 2 (4.6%) and group 3 (9.6%) for serotype 14 (Table 25 and Table 26).

Results for the all-available immunogenicity population are presented in Supportive Table 2.12 in Section 11 attachment. Results were similar to results for the evaluable immunogenicity population.

Table 25. Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL Before Vaccination – Groups 1 and 2 – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled)							
	7vPnC Group 1				7vPnC Group 2			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
4	88	0	0.0	(0.0, 4.1)	87	0	0.0	(0.0, 4.2)
6B	86	9	10.5	(4.9, 18.9)	64	18	28.1	(17.6, 40.8)
9V	88	11	12.5	(6.4, 21.3)	84	11	13.1	(6.7, 22.2)
14	88	26	29.5	(20.3, 40.2)	87	4	4.6	(1.3, 11.4)
18C	88	2	2.3	(0.3, 8.0)	87	1	1.1	(0.0, 6.2)
19F	88	12	13.6	(7.2, 22.6)	85	12	14.1	(7.5, 23.4)
23F	85	3	3.5	(0.7, 10.0)	75	10	13.3	(6.5, 23.2)

Abbreviation: 7vPnC = 7-valent pneumococcal conjugate vaccine; CI = confidence interval; n = number of subjects; N = total number of subjects.
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 upon the observed proportion of subjects.
Program ID: Study 6114A1-4000/CP IMM_IGG_RESP.SAS. Runtime ID: 05APR2012 13:42

The percentage of subjects achieving a pneumococcal IgG concentration ≥0.35 µg/mL before vaccination in groups 3 and 4 is summarized in Table 26 for the evaluable immunogenicity population. The proportion of subjects achieving an IgG concentration ≥0.35 µg/mL ranged from 2.6 to 49.0% in group 3 and 11.0 to 85.9% in group 4 across the 7 serotypes. A higher proportion of subjects in group 4 than in group 3 had an IgG concentration ≥0.35 µg/mL for all 7 serotypes. In group 4 >70% had an IgG antibody concentration ≥0.35 µg/mL for 4 of the 7 serotypes (6B, 9V, 19F and 23F) before vaccination.

Table 26. Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL Before Vaccination – Groups 3 and 4 – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled)							
	7vPnC Group 3				7vPnC Group 4			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
4	113	3	2.6	(0.5, 7.4)	172	19	11.0	(6.8, 16.7)
6B	100	49	49.0	(38.9, 59.2)	177	152	85.9	(79.9, 90.6)
9V	113	33	29.2	(21.0, 38.5)	177	129	72.9	(65.7, 79.3)
14	115	11	9.6	(4.9, 16.5)	177	88	49.7	(42.1, 57.3)
18C	114	4	3.5	(1.0, 8.7)	172	45	26.2	(19.8, 33.4)
19F	115	26	22.6	(15.3, 31.3)	169	121	71.6	(64.2, 78.3)
23F	102	37	36.3	(27.0, 46.4)	174	135	77.6	(70.7, 83.5)

Abbreviations: 7vPnC = 7-valent pneumococcal conjugate vaccine; CI = confidence interval; n = number of subjects; N = total number of subjects.
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 upon the observed proportion of subjects.
Program ID: Study 6114A1-4000/CP IMM_IGG_RESP.SAS. Runtime ID: 05APR2012 13:42

2.3. Immunogenicity outcomes at 12-month follow-up

2.3.1. Geometric Mean Concentration and Geometric Mean Fold Rise
2.3.1.1. Pneumococcal IgG GMCs (µg/mL) at 12-Month Follow-up

Pneumococcal IgG GMCs in the evaluable immunogenicity population at the 12-month follow-up are presented in Table 11. Serotype-specific IgG GMCs for the 7 serotypes were similar across groups 1, 2 and 3, with generally higher values observed in group 4. GMCs at 12-month follow-up ranged from 0.78 µg/mL to 3.22 µg/mL for group 1, 0.65 µg/mL to 2.31 µg/mL for group 2, 0.96 µg/mL to 2.61 µg/mL for group 3 and 1.27 µg/mL to 5.19 µg/mL for group 4.

Table 11. Pneumococcal IgG GMCs (µg/mL) at 12-Month Follow-up - All Groups 12-Month Follow-up Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled)											
	7vPnC Group 1			7vPnC Group 2			7vPnC Group 3			7vPnC Group 4		
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])
4	81	0.78	(0.62, 0.98)	79	0.65	(0.52, 0.82)	111	0.96	(0.80, 1.14)	162	1.27	(1.11, 1.45)
6B	81	3.22	(2.41, 4.29)	78	2.31	(1.77, 3.03)	109	2.38	(1.89, 3.00)	161	4.20	(3.40, 5.19)
9V	81	1.26	(1.00, 1.59)	79	0.98	(0.79, 1.21)	111	1.44	(1.20, 1.71)	162	2.23	(1.94, 2.56)
14	81	1.84	(1.40, 2.41)	79	2.18	(1.62, 2.94)	111	2.61	(2.09, 3.27)	162	5.19	(4.25, 6.33)
18C	81	0.87	(0.69, 1.10)	79	0.71	(0.59, 0.85)	111	0.98	(0.84, 1.15)	162	1.46	(1.24, 1.72)
19F	80	1.25	(0.95, 1.64)	76	1.29	(0.85, 1.95)	109	1.39	(1.03, 1.88)	166	2.85	(2.28, 3.56)
23F	81	1.38	(1.07, 1.77)	78	1.20	(0.91, 1.59)	110	1.79	(1.45, 2.21)	162	2.49	(2.13, 2.92)

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 transforms of confidence levels based on the Student t distribution for the mean logarithm of the concentrations.
Program ID: Study B1841008/t_bdr_immugmc.SAS. Runtime ID: 16APR13 13:41

2.3.1.2. Pneumococcal IgG GMCs (µg/mL) and GMFRs at 12-Month Follow-up Compared to Prevaccination

Pneumococcal IgG GMCs and GMFRs in the evaluable immunogenicity population at the 12-month follow-up compared to before vaccination are presented in Table 12. For all serotypes, the lower limit of the 95% CI for the GMFR was greater than 1.0, indicating that the IgG GMC was significantly higher at the 12-month follow-up than before vaccination in all groups. Prevaccination IgG GMCs for group 4 were observed higher compared to other groups for the 7 serotypes. This could be explained by prior exposure to *S pneumoniae* in older subjects. Across the 7 serotypes, the GMFR ranged from 10.06 to 52.86 for group 1, 8.97 to 55.55 for group 2, 7.99 to 88.27 for group 3 and 2.86 to 21.01 for group 4. GMFRs at 12-month follow-up were generally higher in groups 1, 2 and 3 for the majority of serotypes when compared to group 4 as a result of higher prevaccination IgG GMCs.

Table 12. Pneumococcal IgG GMCs (µg/mL) and GMFRs at 12-Month Follow-up Compared to Before Vaccination for 12-Month Follow-up Evaluable Immunogenicity Population

		Sampling Time								
		Before Vaccination			12-Month Follow-up					
Vaccine Group	Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	n[a]	GMFR[d]	(95% CI[c])
7vPnC Group 1	4	81	0.01	(0.01, 0.02)	81	0.78	(0.62, 0.98)	81	52.86	(37.61, 74.31)
	6B	79	0.13	(0.10, 0.15)	79	3.19	(2.39, 4.27)	79	25.52	(18.57, 35.07)
	9V	81	0.10	(0.08, 0.12)	81	1.26	(1.00, 1.59)	81	12.73	(9.41, 17.24)
	14	81	0.18	(0.13, 0.25)	81	1.84	(1.40, 2.41)	81	10.19	(7.84, 13.19)
	18C	81	0.04	(0.03, 0.06)	81	0.87	(0.69, 1.10)	81	19.75	(14.00, 27.87)
	19F	80	0.12	(0.10, 0.16)	80	1.25	(0.95, 1.64)	80	10.06	(6.85, 14.77)
	23F	79	0.07	(0.06, 0.09)	79	1.38	(1.08, 1.77)	79	18.80	(13.26, 26.66)
7vPnC Group 2	4	79	0.01	(0.01, 0.02)	79	0.65	(0.52, 0.82)	79	50.54	(37.47, 68.18)
	6B	58	0.17	(0.12, 0.24)	58	2.57	(1.85, 3.58)	58	15.58	(10.18, 23.83)
	9V	76	0.11	(0.08, 0.14)	76	0.97	(0.78, 1.21)	76	8.97	(6.84, 11.77)
	14	79	0.04	(0.03, 0.05)	79	2.18	(1.62, 2.94)	79	55.55	(37.23, 82.87)
	18C	79	0.02	(0.01, 0.02)	79	0.71	(0.59, 0.85)	79	45.07	(33.12, 61.33)
	19F	74	0.10	(0.07, 0.13)	74	1.20	(0.81, 1.78)	74	12.62	(8.67, 18.39)
	23F	67	0.09	(0.06, 0.12)	67	1.16	(0.85, 1.60)	67	13.50	(9.56, 19.04)
7vPnC Group 3	4	111	0.02	(0.01, 0.02)	111	0.96	(0.80, 1.14)	111	52.19	(39.75, 68.53)
	6B	95	0.27	(0.20, 0.35)	95	2.13	(1.67, 2.71)	95	7.99	(5.98, 10.67)
	9V	109	0.17	(0.13, 0.22)	109	1.43	(1.19, 1.71)	109	8.40	(6.55, 10.77)
	14	111	0.03	(0.02, 0.04)	111	2.61	(2.09, 3.27)	111	88.27	(63.53, 122.63)
	18C	110	0.02	(0.02, 0.03)	110	0.98	(0.84, 1.14)	110	41.14	(32.18, 52.59)

	19F	109	0.12	(0.09, 0.17)	109	1.39	(1.03, 1.88)	109	11.15	(7.87, 15.80)
	23F	97	0.16	(0.12, 0.22)	97	1.82	(1.46, 2.28)	97	11.39	(8.31, 15.61)
7vPnC Group 4	4	157	0.06	(0.05, 0.07)	157	1.25	(1.09, 1.44)	157	21.01	(17.04, 25.91)
	6B	161	1.33	(1.10, 1.61)	161	4.20	(3.49, 5.04)	161	3.16	(2.70, 3.70)
	9V	162	0.66	(0.56, 0.79)	162	2.23	(1.94, 2.56)	162	3.35	(2.93, 3.83)
	14	162	0.33	(0.23, 0.47)	162	5.19	(4.25, 6.33)	162	15.67	(11.43, 21.47)
	18C	158	0.13	(0.10, 0.16)	158	1.45	(1.23, 1.72)	158	11.43	(9.18, 13.92)
	19F	150	0.70	(0.55, 0.89)	150	2.92	(2.32, 3.68)	150	4.19	(3.19, 5.51)
	23F	159	0.89	(0.74, 1.06)	159	2.54	(2.16, 2.98)	159	2.86	(2.39, 3.42)

a. n = Number of subjects with a determinate IgG antibody concentration to the given serotype.
b. Geometric mean concentrations (GMCs) of each Group were calculated using all subjects with available data from both before vaccination and 12-month follow-up blood draw.
c. Confidence intervals (CIs) are back transforms of confidence levels based on the Student t distribution for the mean logarithm of the concentrations, or the mean fold rise.
d. Geometric mean fold rises (GMFRs) of each Group were calculated using all subjects with available data from both before vaccination and 12-month follow-up blood draw.
Program ID: Study B1841008/t_bdr_immugmcfr.SAS. Runtime 15APR13 13:41

2.3.1.3. Pneumococcal IgG GMCs (µg/mL) and GMFRs at 12-Month Follow-up Compared to 1 Month after Toddler Dose/Last Vaccination

Pneumococcal IgG GMCs and GMFRs in the evaluable immunogenicity population at the 12-month follow-up compared to 1 month after the toddler dose/last vaccination are presented in Table 13. For all serotypes, GMCs were significantly higher at 1 month after the toddler dose/last vaccination compared to those at the 12-month follow-up, consistent with normal waning of antibody concentrations over time. Across the 7 serotypes, the GMFR ranged from 0.12 to 0.41 for group 1, 0.09 to 0.42 for group 2, 0.13 to 0.49 for group 3 and 0.13 to 0.64 for group 4.

Higher prevaccination level of IgG GMCs were observed in group 4, consistent with previous exposure to *S pneumoniae* in older subjects. The IgG GMC's of subjects in group 4 were generally numerically higher than the ones in other groups both at 1 month after the toddler dose/last vaccination, and at 12-month follow-up. There were no formal statistical GMC comparisons planned between groups for this study. Older subjects, such as those in group 4 are expected to have a more developed immune system. Together with previous immunologic exposure, suggested by higher prevaccination IgG GMCs, this would explain a more robust immune response in older subjects following vaccination.

Vaccine Group	Serotype	Sampling Time: One Month After Toddler Dose/Last Vaccination n[a]	GMC[b]	(95% CI[c])	12-Month Follow-up n[a]	GMC[b]	(95% CI[c])	n[a]	GMFR[d]	(95% CI[c])
	19F	76	4.21	(3.12, 5.70)	76	1.29	(0.85, 1.95)	76	0.31	(0.21, 0.44)
	23F	78	3.80	(3.03, 4.77)	78	1.20	(0.91, 1.59)	78	0.32	(0.26, 0.39)
7vPnC Group 3	4	111	7.63	(6.80, 8.56)	111	0.96	(0.80, 1.14)	111	0.13	(0.11, 0.15)
	6B	108	4.88	(3.91, 6.08)	108	2.38	(1.88, 3.00)	108	0.49	(0.39, 0.62)
	9V	111	4.70	(4.21, 5.25)	111	1.44	(1.20, 1.71)	111	0.31	(0.26, 0.36)
	14	111	11.76	(10.31, 13.43)	111	2.61	(2.09, 3.27)	111	0.22	(0.18, 0.28)
	18C	111	5.41	(4.78, 6.13)	111	0.98	(0.84, 1.15)	111	0.18	(0.16, 0.21)
	19F	109	4.28	(3.46, 5.30)	109	1.39	(1.03, 1.88)	109	0.33	(0.25, 0.43)
	23F	110	4.16	(3.51, 4.94)	110	1.79	(1.[illegible]5, [illegible])	110	0.43	(0.35, 0.53)
7vPnC Group 4	4	162	9.64	(8.50, 10.93)	162	1.27	(1.11, 1.45)	162	0.13	(0.12, 0.15)
	6B	161	6.57	(5.46, 7.92)	161	4.20	(3.49, 5.04)	161	0.64	(0.55, 0.74)
	9V	162	6.37	(5.60, 7.23)	162	2.23	(1.94, 2.56)	162	0.35	(0.31, 0.39)
	14	162	9.32	(7.53, 11.[illegible])	162	5.19	(4.25, 6.33)	162	0.56	(0.46, 0.67)
	18C	162	7.42	(6.3[illegible], 8.62)	162	1.46	(1.24, 1.72)	162	0.20	(0.18, 0.22)
	19F	156	4.8[illegible]	(3.95, 5.98)	156	2.85	(2.28, 3.56)	156	0.59	(0.48, 0.72)
	23F	16[illegible]	5.77	(4.90, 6.80)	162	2.49	(2.13, 2.92)	162	0.43	(0.37, 0.50)

a. n = Number of subjects with a determinate IgG antibody concentration to the given serotype.
b. Geometric mean concentrations (GMCs) of each Group were calculated using all subjects with available data from both one month after toddler/last vaccination and 12-month follow-up blood draw.
c. Confidence intervals (CIs) are back transforms of confidence levels based on the Student t distribution for the mean logarithm of the concentrations, or the mean fold rise.
d. Geometric mean fold rises (GMFRs) of each Group were calculated using all subjects with available data from both one month after toddler/last vaccination and 12-month follow-up blood draw.
Based on Supportive Table 2.4 in Section 11 attachment.

2.3.2. Proportion of Subjects Achieving Predefined Pneumococcal Antibody Concentration

2.3.2.1. Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL at 12-Month Follow-up

The percentage of subjects in the evaluable immunogenicity population achieving a pneumococcal IgG concentration ≥0.35 µg/mL at the 12-month follow-up is summarized in Table 14. The majority of subjects (>70%) achieved an IgG concentration ≥0.35 µg/mL for each of the 7 serotypes at the 12-month follow-up. In group 4, >90% of subjects achieved an IgG concentration ≥0.35 µg/mL for each of the 7 serotypes. Across the 7 serotypes, the proportion of subjects achieving an IgG level ≥0.35

µg/mL ranged from 77.8% to 97.5% for group 1, 70.9% to 97.5% for group 2, 78.9% to 98.2% for group 3 and 94.4% to 100.0% for group 4.

2.3.2.2. Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.15, ≥0.20 µg/mL at 12-Month Follow-up

Overall, >95% of subjects achieved an IgG concentration ≥0.15 µg/mL for each of the 7 serotypes, at the 12-month follow-up. Similarly, >90% of subjects achieved an IgG concentration ≥0.20 µg/mL for each of the 7 serotypes, at the 12-month follow-up, except for serotype 19F in group 2. A total of 86.8% of subjects achieved an IgG concentration ≥0.20 µg/mL for serotype 19F.

2.3.3. Reverse Cumulative Distribution Curves and Antibody Response Curves

To provide a descriptive means to compare distributions of the immune response elicited by 7vPnC, serotype-specific anti-capsular polysaccharide IgG concentration RCDCs and antibody response curves for each of the 7 serotypes, from before the first vaccination to the 12-month follow-up time point, are respectively displayed in Figures 3.1 to 3.28 and Figures 3.29 to 3.49 in Section 11 attachment.

For all serotypes in all groups the RCDC curves showed that across the full range of responses, IgG concentrations were lower than those after the last vaccination, but remained above pre-vaccination levels.

2.3.4. Immunogenicity Conclusions for the 12 month follow up

• Antibody levels as measured by IgG GMCs to the 7 pneumococcal serotypes were increased significantly at 12-month follow-up, relative to prevaccination antibody levels, in all age groups.

• Overall, >95% of subjects achieved an IgG concentration ≥0.15 µg/mL, >86% of subjects achieved an IgG concentration ≥0.20 µg/mL and >70% of subjects in groups 1 through 4 achieved an IgG concentration ≥0.35 µg/mL for each of the 7 serotypes at 12-month follow-up.

• Higher IgG GMCs were generally observed for group 4 (older subjects) compared to groups 1, 2 and 3 at prevaccination and at 1 month after the toddler dose/last vaccination, and at the 12-month follow-up, consistent with more developed immune system in older subjects and possible previous exposure to *S pneumoniae.*

• Antibody levels to the 7 pneumococcal serotypes were statistically significantly lower at the 12-month follow-up compared to antibody levels at 1 month after the toddler dose/last vaccination, which is consistent with normal waning of antibody levels over time. However, antibody levels at 12-month follow-up were still consistently higher when compared to prevaccination antibody levels.

- Safety results

1. Adverse Events

1.1. Summary of Adverse Events

Overall, a total of 13 AEs were reported in 12 subjects. Adverse events were reported for 4 subjects each in groups 1 and 2, 3 subjects in group 3 and 1 subject in group 4. One event was reported for each subject, except for one subject in group 3 for whom 2 events were reported. The most common AE was pyrexia (9 events in 8 subjects). Other AEs included 1 event each of drug eruption, enteritis, hypersensitivity and dermatitis allergic. The majority of AEs were mild (8 events), 4 AEs were moderate and one event was severe. One SAE of enteritis was reported in one subject in group 1; all other AEs were non-serious. All AEs were considered related to the study vaccine, except for the one reported SAE mentioned above. No protocol-related AEs, no AEs leading to withdrawal and no deaths were reported during the study. A by-subject summary of AEs during the study is presented in Table 35.

Table 35. Summary of Adverse Events by Subject

Vaccine Group	Subject	System Organ Class	Preferred Term	Vax #	Onset Date	Rel Day[a]	Dur (days)	Severity	Vax Rel[b]	Action Study Treatment Dose	Action Subject	Outcome	SAE Flag
7vPnC Group 1	10011014	GASTR	Enteritis	1	06NOV2010	12	7	SEV	NO	N	T	Resolved (12NOV2010)	YES
	10011041	SKIN	Drug eruption	1	28OCT2010	2	44	MOD	YES	N	N	Resolved (10DEC2010)	NO
	10011105	GENRL	Pyrexia	1	18NOV2010	4	2	MILD	YES	N	N	Resolved (19NOV2010)	NO
	10011110	GENRL	Pyrexia	1	15NOV2010	1	2	MILD	YES	N	T	Resolved (16NOV2010)	NO
7vPnC Group 2	10011169	GENRL	Pyrexia	1	18NOV2010	1	2	MILD	YES	N	T	Resolved (19NOV2010)	NO
	10011201	GENRL	Pyrexia	1	18NOV2010	1	3	MILD	YES	N	N	Resolved (20NOV2010)	NO
	10011207	GENRL	Pyrexia	1	18NOV2010	1	2	MILD	YES	N	T	Resolved (19NOV2010)	NO
	10011218	GENRL	Pyrexia	1	18NOV2010	1	2	MILD	YES	N	T	Resolved (19NOV2010)	NO
7vPnC Group 3	10011130	GENRL	Pyrexia	1	16NOV2010	1	3	MOD	YES	N	T	Resolved (18NOV2010)	NO
				2	23JAN2011	2	2	MOD	YES	N	T	Resolved (24JAN2011)	NO
	10011287	INFEC	Hypersensitivity	1	27NOV2010	2	3	MILD	YES	N	T	Resolved (29NOV2010)	NO
	10011288	SKIN	Dermatitis allergic	2	27JAN2011	2	36	MOD	YES	N	T	Resolved (03MAR2011)	NO
7vPnC Group 4	10011005	GENRL	Pyrexia	1	12SEP2010	2	1	MILD	YES	N	T	Resolved (12SEP2010)	NO

Abbreviations: 7vPnC = 7-valent pneumococcal conjugate vaccine; Dur=duration ; GASTR=gastrointestinal disorders; GENRL=general disorders and administration site conditions ; INFEC=immune system disorders; MOD=moderate ; N=no action taken); SAE=serious adverse event; SEV=severe; SKIN=skin and subcutaneous tissue disorders; T=treatment given; Vax=vaccination.

a. Rel Day is calculated from the date of last vaccination.

b. Relationship to study vaccine as assessed by the investigator.

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Source: Listing 34, Appendix 10.15.7, Section 10

At the 12 month follow up, 3 severe SAEs were observed for 1 subject in group 3 at the 12-month follow-up. The subject died as a result of these events, none of which were considered related to the study vaccine. No other AEs were reported at the 12-month follow-up.

2. Safety Conclusions

Based on the low incidence of AEs and their general lack of severity, the study vaccine as administered in this study appears to be safe and well-tolerated.

There were no AEs that required withdrawal, no protocol-related AEs, and only 4 SAE (not considered related to the study vaccine) in 2 subjects .

3. Discussion on clinical aspects

This B1841008 (6114A1-4000-CN) study assessed the safety, tolerability and immunogenicity of Prevenar in older infants and young children in China who are naive to previous pneumococcal vaccination. Prevenar was administered in four age groups in this study:

- Group 1 (100 subjects): 121 to <212 days of age; received 4 doses of Prevenar.
- Group 2 (100 subjects): 212 days to <12 months of age; received 3 doses of Prevenar.
- Group 3 (125 subjects): 12 to <24 months of age; received 2 doses of Prevenar.
- Group 4 (180 subjects): 24 to <72 months of age; received 1 dose of Prevenar.

The primary objectives of the study were to assess the serotype-specific pneumococcal immune responses induced by Prevenar when measured 1 month after the last dose of Prevenar, and to assess the prevaccination antibody levels to the 7 pneumococcal serotypes in Prevenar in each age group. Additionally, the serotype-specific pneumococcal immune responses induced by Prevenar, was assessed 1 month after the third dose of Prevenar in group 1, 1 month after the second dose of Prevenar in group 2 and 1 month after the first dose of Prevenar in group 3.

Immunogenicity analysis was performed for 2 populations, the evaluable immunogenicity population and the all-available immunogenicity population. The evaluable immunogenicity population consisted of eligible subjects in the age range who had received all the assigned vaccination(s), had blood drawn

within required time frames, had at least 1 valid and determinate assay result for the proposed analysis, had received no prohibited vaccines, and had no other major protocol violations. The all-available immunogenicity population consisted of subjects who had at least 1 valid and determinate assay result for the proposed analysis. Both the evaluable and all-available immunogenicity populations were considered as primary immunogenicity populations. Safety analysis was performed on the safety population, which consisted of all subjects who received at least 1 dose of Prevenar. A total of 506 subjects were enrolled in this study, 505 (99.8%) of which received at least 1 dose of vaccine. One subject (10011248) was enrolled into group 2, but was never vaccinated. The total number of planned doses were administered in 90.0% of subjects in group 1 (4 doses), 88.1% of subjects in group 2 (3 doses), 94.4% of subjects in group 3 (2 doses), and 100.0% of subjects in group 4 (1 dose), respectively. A total of 93.1% of subjects completed the study up to the time-point of the blood draw one month after the last vaccination. The remaining 6.9% of subjects were withdrawn before the blood draw one month after the last vaccination.

Prevaccination antibody levels of the 7 pneumococcal serotypes were low in the younger age groups, but increased with age, particularly in group 4. As subjects were at least 4 months of age at the time of enrollment in this study, we did not observe the typical decreasing curve which is attributed to the maternal antibody decay at 6 months of age in overall 7 serotypes that is seen in unvaccinated infants enrolled at 2 months of age. However, it was observed that the GMC for serotype 14 in group 1 was notably higher than in groups 2 and 3 and the GMC for serotype 18C was also slightly higher in group 1, this may be explained by maternal antibodies. Across the 7 serotypes, a greater proportion of subjects in groups 3 and 4 had an IgG concentration of ≥0.35 µg/mL for 4 of the 7 serotypes (6B, 9V, 19F and 23F) than subjects in groups 1 and 2 before vaccination. In group 4, >70% of subjects achieved an IgG antibody concentration ≥0.35 µg/mL for 4 of the 7 serotypes (6B, 9V, 19F and 23F) before vaccination. This could be explained by prior exposure to *S pneumoniae* in older subjects (groups 3 and 4).

Antibody levels were higher than prevaccination levels, 1 month after the infant series in groups 1 and 2 and 1 month after the first dose of Prevenar in group 3, across the 7 pneumococcal serotypes. For all serotypes, the lower limit of the 95% CI for GMFR was greater than 1.0, indicating that the IgG GMC was higher following the infant series for groups 1 and 2, and following the first vaccination for group 3. The proportion of subjects achieving an IgG concentration ≥0.35 µg/mL ranged from 92.0 to 100.0% in group 1 and 94.3 to 100.0% in group 2 across the 7 serotypes following the infant series. The proportion of subjects achieving an IgG concentration ≥0.35 µg/mL ranged from 89.4 to 100.0% across the 7 serotypes following the first dose of study vaccine in group 3.

Antibody levels of the 7 pneumococcal serotypes increased notably 1 month following the last vaccination, relative to prevaccination levels, in all age groups. GMCs at one month following the toddler dose ranged from 4.05 to 12.75 µg/mL for group 1, 4.02 to 13.02 µg/mL for group 2, 4.03 to 11.98 µg/mL for group 3 and 4.53 to 9.26 µg/mL for group 4. Overall, >90% of subjects in groups 1 through 4 achieved an IgG concentration ≥0.35 µg/mL for all 7 serotypes, following the last dose of study medication.

In the U.S. and Europe, Prevenar is approved for concomitant administration with other pediatric vaccines (DTwP, DTaP, Hib, IPV, OPV, hepatitis B vaccines, MMR, varicella vaccine). However, according to the current package insert for Prevenar in China, it is not recommended to administer this vaccine simultaneously with other vaccines of planned or routine children immunization program. Hence, this study was designed to not allow nonstudy vaccines being given within 7 days after Prevenar administration and administration of the study vaccine was to be delayed if the subject received any non-live vaccine within the previous 7 days or live vaccine within the previous 28 days. Overall, 90 (17.8%) of all subjects received at least one dose of nonstudy vaccine within 7 days of one of their scheduled doses of study vaccine. The highest percentage of subjects receiving nonstudy vaccine within 7 days of study vaccine was observed in group 1 (60.0% subjects) and group 2 (20.8% of subjects). The higher percentage of nonstudy vaccinations in younger patients is expected, given that quite a number of vaccinations are advised to be administered at this age. Although these concomitant vaccinations were treated as protocol deviations in this report, it was judged that such deviations would not impact the safe use of Prevenar and interfere the immunogenicity response of Prevenar based on the available safety data in this study and the study results in previous clinical trials. In group 1, in which the highest percentage of subjects (60.0%) was administered nonstudy vaccines within 7 days of study vaccine, the number of AEs observed was very low (4 AEs were observed in 4 [4.0%] subjects).

In conclusion, Prevenar catch-up vaccinations given to older infants and young children naïve to pneumococcal vaccines resulted in a robust immune response to all serotypes. The vaccine was well tolerated in infants and children in different age groups. This study has demonstrated that Prevenar given as a catch up regimen in different age groups (121 to <212 days, 212 days to <12 months, 12 to <24 months and 24 to <72 months) was well tolerated and produces a robust immune response as

characterized by antibody geometric mean concentrations (GMC) and geometric mean fold rise (GMFR).

In addition to the primary analysis showing that IgG GMCs of the 7 pneumococcal serotypes were significantly higher 1 month after the last vaccination, relative to prevaccination antibody concentrations, in all age groups, it was shown that at the 12-month follow-up, IgG GMCs of the 7 pneumococcal serotypes were still significantly higher than prevaccination antibody concentrations. However IgG GMCs of the 7 pneumococcal serotypes at 12-month follow-up were lower than antibody concentrations at 1 month after the toddler dose/last vaccination, consistent with natural waning of antibodies.
Overall, >90% of subjects in groups 1 through 4 achieved an IgG concentration ≥0.35 µg/mL for each of the 7 serotypes, after the last dose of study vaccine. In comparison, >70% of subjects in groups 1 through 4 achieved an IgG concentration ≥0.35 µg/mL for each of the 7 serotypes at the 12-month follow-up.
Higher IgG GMCs were generally observed for group 4 (older subjects) compared to groups 1, 2 and 3 at prevaccination and at 1 month after dosing, and at the 12-month follow-up, consistent with a more developed immune system in older subjects and possible previous exposure to *S pneumoniae*.
Except for one death that was considered unrelated to the study vaccine, no other AEs were reported at 12-month follow-up. Based on this, the study vaccine as administered in this study appears to be safe and well-tolerated.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The MAH submitted the immunogenicity and safety data from study 2114A1-4000-CN (B1841008): A phase 4, open-label trial to assess the safety, tolerability, and immunogenicity of Prevenar in older infants and young children in China who are naïve to previous pneumococcal vaccination.
Immunogenicity and safety data were discussed in sufficient detail by the MAH and do not warrant further investigation.

- **Recommendation**

No further action required.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable.