EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 February 2015
EMA/123675/2015
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Prevenar

(Suspension for injection
Pneumococcal saccharide conjugated vaccine, adsorbed)

Procedure No. EMEA/H/C/000323

P46 129

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

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I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

II. RECOMMENDATION

The data from this study do not warrant any changes to the SmPC or PIL.

III. INTRODUCTION

On 6 February 2012, 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

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

No investigational product was administered during the study period.

IV.2 Clinical aspects

1. Introduction

The MAH submitted a final report for: A study to evaluate pneumococcal antipolysaccharide antibody concentrations in subjects that participated in the Wyeth Prevenar Safety and Immunogenicity Study 0887X-101518 (Protocol B1841009 [6114A1-4001-CN])

2. Clinical study

- **Description**

This study has been conducted as a postapproval commitment following approval of Prevenar by the Chinese State Food and Drug Administration (SFDA) for immunization against invasive pneumococcal disease in infants and young children.
Prevenar, a 7-valent pneumococcal conjugate vaccine (7vPnC), contains polysaccharides from serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. Based on Chinese data on pneumococcal disease and nasopharyngeal carriage, serotypes 23F, 19F, 6A, 6B, 14, 15, 3, 18C, 23A, and 9V are the most common in China. Prevenar is therefore likely to protect Chinese infants from a large proportion of invasive pneumococcal diseases.
In 2005, a Phase 3 safety and immunogenicity study (Wyeth study 0887X-101518) was conducted, in which Chinese infants were assigned to 1 of 3 groups to receive either Prevenar alone (group 1), Prevenar given concomitantly with a diphtheria, tetanus and acellular pertussis (DTaP) vaccine (group 2), or DTaP alone (group 3).
The Chinese State Food and Drug Administration (SFDA) has requested that an additional study be conducted as a postapproval commitment, to evaluate postvaccination antibody concentrations in children aged up to 5 years. This follow-up study (B1841009 [6114A1-4001-CN]) assessed the postvaccination pneumococcal antipolysaccharide antibody concentrations in children who previously completed Wyeth study 0887X-101518, at a time point at least 36 months after the last vaccination. It also compared antibody levels in subjects who received Prevenar in this study to those subjects who received DTaP alone (control group) at a single time point.

- **Methods**

- Objective(s)

Primary objective

The primary objective of the study was to evaluate the antibody levels to the 7 pneumococcal vaccine serotypes at least 36 months after administration of the toddler vaccination in groups 1 and 2 in Wyeth study 0887X-101518, as measured by serotype-specific immunoglobulin G (IgG)concentrations.

Secondary objective

The secondary objective of the study was to compare the antibody levels to the 7 pneumococcal vaccine serotypes in subjects who received 7vPnC (groups 1 and 2) with those who did not receive 7vPnC (group 3) in Wyeth study 0887X-101518.

- Study design

All eligible subjects who completed the Wyeth safety and immunogenicity study 0887X-101518 were invited to participate in this Phase 4, open-label study, at a timepoint at least 3 years after their last vaccination in study 0887X-101518. Subjects had a blood sample (approximately 5 mL) drawn at enrollment; subjects participated in the study for approximately 1 day.

No vaccines were administered during the study. However, subjects were assessed according to the vaccine group they were assigned to in Wyeth study 0887X-101518: 7vPnC alone (group 1), 7vPnC given concomitantly with diphtheria, tetanus and acellular pertussis (DTaP) (group 2), or DTaP alone (group 3). Subjects in all 3 groups were vaccinated in the preceding study at 3 months (vaccination 1), 4 months (vaccination 2), and 5 months (vaccination 3) of age (designated the infant series), with the subjects in groups 1 and 2 (groups that received 7vPnC) also vaccinated at 12 to 15 months of age (vaccination 4) (designated the toddler vaccination).

- Study population /Sample size

Of the 652 subjects who completed the Wyeth safety and immunogenicity study 0887X-101518, 336 were screened for participation in this study and 335 were enrolled. One of the screened subjects did not meet the entrance criteria and did not enroll. Of the 335 subjects enrolled, 123 subjects were in group 1, 121 subjects were in group 2, and 91 subjects were in group 3. All enrolled subjects completed this 1-day study.

- Treatments

No investigational product was administered during the study period.

- Outcomes/endpoints

Efficacy endpoint: not applicable

Safety endpoint: The protocol defined AEs and SAEs that were collected throughout the study. Adverse events were categorized according to MedDRA. If an event increased in severity, then a stop date was to be entered and a new event reported with a new severity. The start date of the new event was to be the same as the stop date for the previous event.

Immunogenicity endpoint: The primary endpoint is the serotype-specific IgG concentration at the blood draw. Immunogenicity variables collected for this study are the results of assays performed on the blood samples collected. The results of these assays are antibody concentrations.

Indicator variables will be derived for each of the 7 serotypes in 7vPnC for the following criterion: serotype-specific IgG antibody concentration ≥0.35 µg/mL.

All indicator variables will be derived as follows:

=., if the value is missing or otherwise unavailable

=1, if the value meets the specified criteria

=0, if the value does not meet the specified criteria

- Statistical Methods

Statistical Analysis of Immunogenicity - Immunogenicity Populations

Immunogenicity analyses were performed for 2 populations in this study. The primary immunogenicity population in this study was the evaluable immunogenicity population, defined as eligible subjects who had blood drawn within required time frames, had at least 1 valid and determinate assay result for the proposed analysis, received no prohibited vaccines, and had no major protocol violations. Although specific prohibited vaccines were not pre-specified in the protocol, non-live vaccines/live vaccines within 28 days prior to enrollment were to be reviewed by the clinical scientist and used to assess whether subjects should be included in the evaluable immunogenicity population. The all-available immunogenicity population consisted of subjects who had at least 1 valid and determinate assay result for the proposed analysis.

Ad hoc analyses were also conducted on 2 subsets, Subset A and Subset B.

*Subset A (called “Infant-Toddler-3/4 years after”) included those subjects who had valid IgG values at ‘before infant series’, ‘after infant series’, ‘before toddler vaccination’, ‘after toddler vaccination’, and

'3 years after last vaccination' for group 1 and 2, and 'before infant series', 'after infant series', and '3 years after last vaccination' for group 3.
*Subset B (called "Toddler-3/4 years after") included subjects who had valid IgG values at 'before toddler vaccination', 'after toddler vaccination', and '3 years after last vaccination' for group 1 and 2.

Comparisons of Immunogenicity
The immunologic comparisons were between group 1 (7vPnC) and group 2 (7vPnC + DTaP), and between groups 1 and 2 combined and group 3 (DTaP) at 3 years after the last vaccination. These between-group comparisons using immunogenicity data collected in this study were performed for the evaluable and the all-available immunogenicity populations. Within-group comparisons were also made for the following intervals:
* From after the infant series to 3 years after the last vaccination
* From after the toddler vaccination to 3 years after the last vaccination
Because there was no evaluable population defined during the preceding study, comparisons of immunogenicity data collected during the preceding study (ie, after the infant series or after the toddler vaccination) were only performed for the all-available population.
The ad hoc analyses of Subset A and Subset B were performed for the comparisons at 3 years after the last vaccination.

Methods of Analysis - Geometric Means
Geometric means of the pneumococcal IgG concentrations (GMCs) were calculated at each visit that had a blood draw. For all groups, the geometric mean fold changes (GMFCs) in antibody concentration at different timepoints were summarized by geometric mean IgG concentration and confidence intervals (CIs), computed using the logarithmically transformed assay results.
Only subjects with results at both timepoints were included in the derivation of GMFCs. For between-group comparisons, ratios of the GMCs for the groups being compared were calculated by back transforming the difference between vaccine groups on the logarithmic scale. For within-group comparisons, the GMFCs for the timepoints were calculated by back transforming the difference in GMC within vaccine groups on the logarithmic scale.
The analyses in this study are descriptive. The protocol and SAP did not prespecify an analysis to demonstrate superiority of the immune response. However, the same criteria used for other vaccine studies were used to evaluate antibody concentrations in this study. Response to a serotype was considered to be statistically significantly greater for 1 vaccine group over another if the lower limit of the 95% CI for the ratio of GMCs was greater than 1.0. The response to a serotype was considered statistically significantly lower if the upper limit of the 95% CI for the ratio of GMCs was less than 1.0. Significant within-group differences in GMC were also assessed using these criteria.

➢ **Results**

- Recruitment/ Number analysed

All eligible subjects who completed the 0887X-101518 study were allowed to participate in this study. All analyses were descriptive and no formal power calculation was done.
Disposition of study subjects is summarized in Table 6-1. Of the 652 subjects who completed the preceding study, 336 were screened for participation in this study and 335 enrolled. One of the screened subjects did not meet the entrance criteria and did not enroll. Of the 335 subjects enrolled (123 in group 1, 121 in group 2, and 91 in group 3), all completed this 1-day study.

Table 6-1: Disposition of Subjects

	Vaccine Group (as Enrolled)									
	Screened Only		Group 1 (7vPnC)		Group 2 (7vPnC + DTaP)		Group 3 (DTaP)		Total	
	n	%	n	%	n	%	n	%	n	%
Enrolled in 0887X-101518 study[a]	N.A.		300		296		204		800	
Completed 0887X-101518 study[b]	N.A.		236	78.7	238	80.4	178	87.3	652	81.5
Screened[c]	1	N.A.	123	52.1	121	50.8	91	51.1	336	51.5
Enrolled[d]	0	0.0	123	100.0	121	100.0	91	100.0	335	100.0
Not enrolled	1	100.0	0	0.0	0	0.0	0	0.0	1	0.3
Reason for not enrolled										
Does not meet entrance criteria	1	100.0	0	0.0	0	0.0	0	0.0	1	0.3
Evaluable Immunogenicity Population	0	0.0	123	100.0	121	100.0	91	100.0	335	100.0
All-Available Immunogenicity Population	0	0.0	123	100.0	121	100.0	91	100.0	335	100.0
Safety Population	0	0.0	123	100.0	121	100.0	91	100.0	335	100.0
Completed	0	0.0	123	100.0	121	100.0	91	100.0	335	100.0

a. The values in this row are used as the denominators for percentages for subjects who completed the 0887X-101518 study.
b. The values in this row are used as the denominators for percentages for subjects who screened for the current study.
c. For column of 'Screened Only', the value in this row is used as the denominators for percentages for screened only subjects
d. The values in this row are used as the denominators for percentages for subjects who enrolled in the study.
Program ID: Study B1841009 (6114A1-4001)/CP CS_DISP.SAS. File ID: CS_DISP.HTM. Runtime ID: 07NOV2011 17:01

- Baseline data

Subjects were not randomized in this study; they remained in the same groups that they were assigned to in the preceding study (study 0887X-101518). A unique subject number for each subject was assigned at enrollment.

The demographic characteristics of subjects in the safety population are summarized in Table 6-2. The 3 vaccine groups were similar with respect to sex, race, and age at the time of the blood draw. All subjects were Asian and ≥4 years of age at the time of blood draw, with a mean age of 5.04 years. The percentage of males (55.5%) was slightly higher than the percentage of females (44.5%).

Table 6-2: Demographic Characteristics – Safety Population

	Vaccine Group (as Enrolled)							
	Group 1 (7vPnC) N=123		Group 2 (7vPnC + DTaP) N=121		Group 3 (DTaP) N=91		Total N=335	
	n	%	n	%	n	%	n	%
Sex								
Male	68	55.3	68	56.2	50	54.9	186	55.5
Female	55	44.7	53	43.8	41	45.1	149	44.5
Race								
Asian	123	100.0	121	100.0	91	100.0	335	100.0
Age (years) at time of blood draw								
≥ 4 years	123	100.0	121	100.0	91	100.0	335	100.0
Mean	5.04		5.04		5.04		5.04	
Median	5.00		5.00		5.10		5.00	
SD	0.144		0.157		0.151		0.150	
Min, max	4.7, 5.4		4.7, 5.4		4.7, 5.4		4.7, 5.4	

Program ID: Study B1841009 (6114A1-4001)/CP CS_DEMO.SAS. File ID: CS_DEMO_SAF.HTM. Runtime ID: 07NOV2011 17:01

- Efficacy results

Not applicable

- Immunogenicity results

* At 3 years after the last vaccination, for IgG GMCs, group 1 (7vPnC) demonstrated a similar antibody concentration as group 2 (7vPnC + DTaP) for the majority of serotypes for the subjects in the evaluable immunogenicity population (Table 3). The results were consistent for subjects in Subset A and in Subset B.

Table 3. Comparison of Pneumococcal IgG GMCs (µg/mL) 3 Years After the Last Vaccination – Group 1 vs Group 2

	Vaccine Group (as Enrolled)							
	Group 1 (7vPnC)			Group 2 (7vPnC + DTaP)			Vaccine Comparison	
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
4	123	0.98	(0.77, 1.23)	121	0.66	(0.52, 0.84)	0.68	(0.48, 0.94)
6B	123	11.35	(9.71, 13.27)	120	9.24	(7.66, 11.16)	0.81	(0.64, 1.04)
9V	123	1.35	(1.13, 1.62)	120	1.29	(1.08, 1.54)	0.95	(0.74, 1.23)
14	123	4.50	(3.38, 5.98)	121	3.02	(2.25, 4.05)	0.67	(0.45, 1.01)
18C	123	0.80	(0.66, 0.97)	121	0.77	(0.60, 0.98)	0.96	(0.70, 1.31)
19F	123	10.14	(8.06, 12.75)	121	5.67	(4.50, 7.14)	0.56	(0.40, 0.77)
23F	120	3.31	(2.80, 3.91)	121	2.71	(2.26, 3.25)	0.82	(0.64, 1.05)

7vPnC=7-valent pneumococcal conjugate vaccine; CI=confidence interval; DTaP= diphtheria, tetanus, and acellular pertussis vaccine; GMC=geometric mean concentrations.

a. n = Number of subjects with a determinate IgG antibody concentration to the given serotype.
b. GMCs were calculated using all subjects with available data for the specified blood draw.
c. CIs are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations.
d. Ratios of GMCs, Group 2 to Group 1, are calculated by back transforming the ratio difference between vaccine groups on the logarithmic scale.
e. CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the ratio difference of the logarithms of the measures (Group 2 – Group 1).

Program ID: Study B1841009 (6114A1-4001)/CP IMM_COMP_IGG_GMC_3Y.SAS. File ID: IMM_COMP_IGG_GMC_3Y_EVL.HTM. Runtime ID: 26SEP2011 14:49

* At 3 years after the last vaccination, for IgG GMCs, group 1 (7vPnC) and group 2 (7vPnC + DTaP) combined demonstrated significantly greater antibody concentrations compared to group 3 (DTaP) for 6 of 7 serotypes for the subjects of the evaluable immunogenicity population (Table4). In Subset A, for IgG GMCs there was a significant difference between groups 1 and 2 combined and group 3 for 4 of the 7 serotypes.

Table 4. Comparison of Pneumococcal IgG GMCs (µg/mL) 3 Years After the Last Vaccination – Groups 1 and 2 Combined vs Group 3

	Vaccine Group (as Enrolled)							
	Group 1 (7vPnC) and Group 2 (7vPnC + DTaP) Combined			Group 3 (DTaP)			Vaccine Comparison	
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
4	244	0.80	(0.68, 0.95)	84	0.41	(0.29, 0.58)	1.97	(1.39, 2.80)
6B	243	10.26	(9.08, 11.59)	91	3.37	(2.76, 4.13)	3.04	(2.41, 3.84)
9V	243	1.32	(1.16, 1.50)	91	1.05	(0.83, 1.32)	1.26	(0.98, 1.62)
14	244	3.65	(3.01, 4.53)	91	0.55	(0.40, 0.76)	6.66	(4.53, 9.79)
18C	244	0.78	(0.67, 0.92)	88	0.34	(0.24, 0.47)	2.34	(1.68, 3.24)
19F	243	7.60	(6.44, 8.97)	90	1.70	(1.35, 2.15)	4.47	(3.29, 6.07)
23F	243	2.99	(2.65, 3.39)	91	1.44	(1.17, 1.76)	2.08	(1.65, 2.63)

7vPnC=7-valent pneumococcal conjugate vaccine; CI=confidence interval; DTaP= diphtheria, tetanus, and acellular pertussis vaccine; GMC=geometric mean concentrations.

a. n = Number of subjects with a determinate IgG antibody concentration to the given serotype.
b. GMCs were calculated using all subjects with available data for the specified blood draw.
c. CIs are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations.
d. Ratios of GMCs, Groups 1 and 2 combined to Group 3, are calculated by back transforming the ratio difference between vaccine groups on the logarithmic scale.
e. CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the ratio difference of the logarithms of the measures (Groups 1 and 2 combined – Group 3).

Program ID: Study B1841009 (6114A1-4001)/CP IMM_COMP_IGG_GMC_GRP.SAS. File ID: IMM_COMP_IGG_GMC_GRP_EVL.HTM. Runtime ID: 26SEP2011 14:49

* At 3 years after the last vaccination, for the proportion of subjects with a pneumococcal IgG concentration ≥0.35 µg/mL, group 1 was similar to group 2 for the majority of serotypes for the

subjects in the evaluable immunogenicity population. The results were consistent for subjects in Subset A and Subset B.
* At 3 years after the last vaccination, for the proportion of subjects with a pneumococcal IgG concentration ≥0.35 µg/mL, group 1 and group 2 combined was significantly greater than group 3 for 6 of 7 of serotypes for the evaluable immunogenicity population. In contrast, group 1 and group 2 combined had a similar proportion of subjects with a pneumococcal IgG concentration ≥0.35 µg/mL compared to group 3 for 5 of 7 serotypes for the subjects in Subset A.
* In groups 1 and 2, the IgG GMCs at 3 years after the last vaccination were generally lower than after the infant series, and were also generally lower than after the toddler vaccination, but were higher than before vaccination 1 of the infant series.
* In group 3 the IgG GMCs at 3 years after the last vaccination were higher than after the infant series for all serotypes. However, serotype-specific IgG GMCs for all serotypes decreased from before vaccination 1 of the infant series to after the infant series.

In conclusion, at 3 years after the last vaccination, the circulating anti-pneumococcal antibody concentrations were similar for subjects who received 7vPnC alone compared with subjects who received 7vPnC and DTaP as measured by serotype-specific IgG concentrations. At 3 years after the last vaccination, the anti-pneumococcal antibody concentrations for subjects who received 7vPnC either alone or combined with DTaP were greater than for subjects who received DTaP alone.

- Safety results

For protocol-related AEs and SAEs, the reporting period to Pfizer or its designated representative was from the time of informed consent until the end of the visit at the clinic (Visit 1). Any SAE occurring any time after the reporting period was reported if a causal relationship to the protocol/procedures was suspected.

There were no protocol related AEs, SAEs, or AEs that led to withdrawal during the study. No subjects died during this study.

3. Discussion on clinical aspects

In conclusion, at 3 years after the last vaccination, the circulating anti-pneumococcal antibody concentrations were similar for subjects who received 7vPnC alone compared with subjects who received 7vPnC and DTaP as measured by serotype-specific IgG concentrations, except for the serotypes 4 and 19F. At 3 years after the last vaccination, the anti-pneumococcal antibody concentrations for subjects who received 7vPnC either alone or combined with DTaP were greater than for subjects who received DTaP alone except for serotype 9V.
No vaccine was administered in this study and there were no AEs of any kind reported.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

*Note: Please ensure that the **final** conclusion does not contain references to individual Member States. "If a type II variation is recommended, please specify the texts proposed for inclusion in the relevant SPC sections.*

➢ **Overall conclusion**

In 2005, a Phase 3 safety and immunogenicity study (Wyeth study 0887X-101518) was conducted, in which Chinese infants were assigned to 1 of 3 groups to receive either Prevenar alone (group 1), Prevenar given concomitantly with a diphtheria, tetanus and acellular pertussis (DTaP) vaccine (group 2), or DTaP alone (group 3). The Chinese State Food and Drug Administration (SFDA) has requested that an additional study be conducted as a postapproval commitment, to evaluate postvaccination antibody concentrations in children aged up to 5 years. This follow-up study (B1841009 [6114A1-3002-CN]) assessed the postvaccination pneumococcal antipolysaccharide antibody concentrations in children who previously completed Wyeth study 0887X-101518, at a time point at least 36 months after the last vaccination. It also compared antibody levels in subjects who received Prevenar in this study to those subjects who received DTaP alone (control group) at a single time point. The total number of subjects in the three groups participating in this study was 335. The serotype specific anti-pneumococcal IgG concentrations were not significantly different between subjects who received 7vPnC alone and those who received 7vPnC simultaneously with the DTaP vaccine, except for serotypes 4 and 19F. Antibody concentrations against the latter serotypes were significantly lower in the latter group. Anti-pneumococcal antibody concentrations for subjects who received 7vPnC either

alone or combined with DTaP were significantly higher than for subjects who received DTaP alone except for serotype 9V that showed antibody concentrations that were not significantly different.
No vaccine was administered in this study, and there were no AEs of any kind reported.

- **Recommendation**

No further action required.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

None