15 November 2012
EMA/89713/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Prevenar 13

International non-proprietary name: pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)

Procedure No. EMEA/H/C/001104/II/0055

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

1. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) [P/73/2011] on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP [P/73/2011] was not yet completed as some measures were deferred.

2. Scientific discussion

2.1. Introduction

Prevenar 13 is a 13-valent pneumococcal conjugate vaccine for use in infants and young children to prevent pneumococcal disease (IPD, pneumonia, and acute otitis media [AOM]) caused by the 13 pneumococcal serotypes (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) contained in the vaccine.

To overcome the limited immunogenicity of pneumococcal polysaccharide vaccines, the protein conjugation technology was applied to the development of 13vPnC. Each of the pneumococcal polysaccharides is covalently conjugated to the diphtheria cross-reactive material 197 (CRM197) protein, which acts as an immunologic carrier.

Children aged <5 years are particularly susceptible to pneumococcal disease, but older children may also be vulnerable. There are well-established at risk medical conditions such as asthma and diabetes mellitus, which predispose to IPD. The relative risk of children with these predisposing medical conditions is often 2 to 4 fold, when compared to the healthy population of the respective age group. There is also a smaller group of children with complex immune compromising conditions (often called high-risk conditions such as HIV infection and sickle cell disease), who also have an increased risk for pneumococcal infections.

The current application is based on results from clinical study 6096A1-3011 which was designed to evaluate the safety, tolerability, and immunogenicity of 13vPnC administered to healthy children in 4 age groups:

- >15 months to <2 years (group 1);
- ages ≥2 years to <5 years (group 2);
- ages ≥5 years to <10 years (group 3);
- ages ≥10 years to <18 years (group 4).

Children were offered 1 or 2 doses of the study vaccine depending on their age. The data for groups 1 and 2 have previously been submitted and assessed (FUM 18 and FU2 018.2). The data for groups 3 and 4 form the basis for extending the indication for 13vPnC to include children and adolescents 6 to 17 years of age.

2.2. Clinical Efficacy aspects

2.2.1. Methods – analysis of data submitted

Study Design

Study 6096A1-3011 was an open-label study, which evaluated the safety, tolerability, and immunogenicity of 13vPnC administered to healthy children in 4 age groups: ages >15 months to <2 years (group 1); ages ≥2 years to <5 years (group 2); ages ≥5 years to <10 years (group 3); and ages ≥10 years to <18 years (group 4). The results for groups 1 and 2 are not relevant to this application and will not be presented or discussed as these were already assessed as pots-approval measures.

Subjects in group 3 had been previously vaccinated with at least 1 dose of 7vPnC, and subjects in group 4 had never been vaccinated with 7vPnC or any other pneumococcal vaccine. In this study, subjects from groups 3 and 4 were to receive 1 dose of 13vPnC.

The study was conducted in USA between November 2008 and August 2010.

Study objectives

The primary objective of this study was to assess the pneumococcal immune responses induced by 13-valent pneumococcal conjugate vaccine (13vPnC) when measured 1 month after the last scheduled study vaccination in each of 4 age groups. The safety objective of this study was to evaluate the acceptability of the safety profile of 13vPnC as measured by the incidence of local reactions, systemic events, and adverse events (AEs). The exploratory objective was to assess the level of opsonophagocytic activity (OPA) induced by 13vPnC in a subset of subjects measured 1 month after the last scheduled dose of 13vPnC. Note that OPA assays were originally to be done for a randomly selected subset of subjects but were instead done for all subjects in the analysis population.

Number of Subjects

As of Amendment 3, the number of subjects planned for age groups 3 and 4 was 600, ie, 300 subjects in group 3 and 300 subjects in group 4. Per an addendum to the statistical analysis plan (SAP), groups 3 and 4 were divided into exploratory and confirmatory cohorts and data from previously completed study 6096A1-3005 was used for comparison purposes in certain specified immunogenicity analyses.

Study 6096A1-3005 was a parallel-group, randomized, active-controlled, double-blind, multicenter trial conducted to evaluate the safety, tolerability, and immunogenicity of 3 lots of 13vPnC in healthy infants (approximately 2 months of age at first vaccination) when co-administered with routine pediatric vaccinations. Subjects received 1 dose (0.5 mL) of either 13vPnC or 7vPnC at each of the 4 vaccination visits along with a concomitant dose of Pediarix and Hib vaccine at the 2-, 4-, and 6-month visits, and with MMR, varicella, and hepatitis A vaccines at the 12-month visit. A total of 1712 subjects were randomly assigned in the 4 groups (3 lots of 13vPnC and 1 lot of 7PnC). The mean age at which the subjects received the toddler dose was 12.4 months.

Diagnosis and Main Criteria for Inclusion

Eligible subjects for groups 3 and 4 were healthy children aged ≥5 years and <18 years at the time of enrollment who were available for the entire study period, and whose parent/legal guardian could be reached by telephone. Subjects in group 3 had to have received at least 1 previous dose of Prevenar. In group 4, female and male subjects who were biologically capable of having children agreed to

abstinence or committed to the use of a reliable method of hormonal and/or non hormonal contraception for 3 months after the vaccination.

Children were excluded if they had a major illness or condition that would have substantially increased the risk associated with study completion or precluded the evaluation of the child's response. Children were also excluded if previously vaccinated with 23-valent pneumococcal polysaccharide vaccine or if they were direct descendants of site study personnel. Children in group 4 were excluded if previously vaccinated with Prevenar or any other pneumococcal vaccine or were pregnant or breastfeeding adolescent females.

Duration of Treatment

Subjects in groups 3 and 4 received a single dose of 13vPnC. Subjects were evaluated for immunogenicity at approximately 1 month after vaccination and for safety through the 6-month telephone follow-up.

Immunogenicity assessment methods

Using enzyme-linked immunosorbent assay (ELISA), serum concentrations of anticapsular immunoglobulin G (IgG) for each of the 13 pneumococcal serotypes contained in 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) were determined in all subjects for each blood sample and expressed as micrograms per milliliter (µg/mL). Functional antibody titers for the 13 pneumococcal serotypes contained in 13vPnC were determined using serum OPA assays.

Endpoints

The primary comparison of IgG concentrations for group 3 confirmatory cohort was a non-inferiority comparison to anti-capsular IgG data from Wyeth study 6096A1- 3005. For each of the original 7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) included in Prevenar (7-valent pneumococcal conjugate vaccine [7vPnC]), the ratio of the geometric mean concentrations (GMCs) comparing group 3 confirmatory cohort to the 7vPnC data from study 6096A1-3005 was computed. For each of the additional serotypes included in 13vPnC (1, 3, 5, 6A, 7F and 19A), the ratio of the GMCs comparing group 3 confirmatory cohort to 13vPnC data from study 6096A1-3005 (combined across lots as lot consistency was verified) was computed.

An analysis similar to that described above for group 3 confirmatory cohort was performed to compare the IgG data from group 4 confirmatory cohort to data from Wyeth study 6096A1-3005.

Per the statistical analysis plan (SAP) addendum, this was designated a secondary analysis for group 4 confirmatory cohort. The primary comparison for group 4 was the comparison of OPA titers for the group 4 confirmatory cohort compared to the group 3 confirmatory cohort via their OPA geometric mean ratio (GMR) by serotype.

Within each age group, GMCs of pneumococcal IgG and geometric means of the OPA titers (GMTs) were calculated at each visit at which blood was drawn. The OPA antibody titers were logarithmically transformed for analysis. 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. The geometric mean fold rises (GMFRs) in antibody concentration and in OPA titers (post-vaccination/pre-vaccination) were summarized by geometric means and 95% CIs.

The proportion of subjects with pre-specified IgG concentrations for each of the 13 pneumococcal serotypes was calculated before and after vaccination in each age group. For each serotype, an exact, 2-sided 95% CI for the proportions was calculated. The CI for the single proportions was computed using the F distribution. Type I error was not adjusted for multiple comparisons within each age group. No formal statistical comparisons were made between the age groups.

The lower limit of quantitation (LLOQ) for OPA titers was used to compute the proportion of subjects with OPA titers ≥LLOQ for each serotype, along with exact, 2-sided 95% CI, for group 3 exploratory cohort, group 3 confirmatory cohort, group 4 exploratory cohort and group 4 confirmatory cohort. No formal statistical comparisons were made between the age groups.

Reverse cumulative distribution curves (RCDCs) were generated for each serotype-specific IgG concentration and for OPA titers before and after vaccination.

As a post hoc sensitivity analysis, comparison of OPA titers for the group 4 confirmatory cohort compared to the group 3 confirmatory cohort via their OPA GMR by serotype was repeated using the actual titer and ½LLOQ (0.5*LLOQ), ¾LLOQ (0.75*LLOQ), 4/5LLOQ (0.80*LLOQ) and LLOQ (1.0*LLOQ) for those titers that fell below the LLOQ.

Analysis Populations

Evaluable Immunogenicity Population This population included all subjects who were eligible for the study; met the age requirement (≥5 to <10 years of age for group 3 and ≥10 to <18 years of age for group 4); received the required study vaccination; had at least 1 valid and determinate assay result before and after the study vaccination; had blood drawn before and after the vaccination within the required time frame; and had no other major protocol violations.

All-Available Immunogenicity Population: Subjects who had at least 1 valid and determinate assay result were included in the all-available immunogenicity population for each age group.

2.2.2. Results

All of the 598 subjects who consented to be in the study were randomized: 299 in group 3 and 299 in group 4. The majority of the enrolled subjects in group 3 and group 4 were vaccinated (294, 98.3% and 298, 99.7%, respectively) and completed the study (277, 92.6% and 294, 98.3%).

In group 3, 22 subjects were withdrawn from the study for the following reasons: lost to follow up (6 subjects), failed to return (5 subjects), parent/legal guardian request (5 subjects), protocol violation (5 subjects), and for “other” reason (1 subject [“subject uncooperative”]). In group 4, 5 subjects were withdrawn for the following reasons: failed to return (2 subjects), lost to follow-up (1 subject), protocol violation (1 subject), and for “other” reason (1 subject [“unable to withdraw blood”]).

In groups 3 and 4, a total of 598 subjects were enrolled: 299 in group 3 and 299 in group 4. The majority of subjects were white (66.9% [group 3] and 77.9% [group 4]) and non-hispanic and non-latino (91.3% [group 3] and 91.3 [group 4]). The percentages of males were 48.2% (group 3) and 54.5% (group 4), and the percentages of females were 51.8% (group 3) and 45.5% (group 4). In group 3, age at enrollment ranged from 5 to 10 years, with the mean age at enrollment of 7.4 years. In group 4, age at enrollment ranged from 10 to 18 years, with the mean age at enrollment of 13.7 years.

Immunogenicity results

Primary comparison (Group 3 GMC)

The primary immunogenicity objective was to demonstrate non-inferiority, based on IgG concentrations 1 month after 13vPnC vaccination in the group 3 (subjects ≥5 years to <10 years) confirmatory cohort compared to the post-toddler responses in the 7vPnC group from study 6096A1-3005 for the 7 common serotypes and compared to the post-toddler responses in the combined 13vPnC groups from study 6096A1-3005 for the 6 additional serotypes. The criterion for non-inferiority for a given serotype was met if the lower limit of the 2-sided 95% CI for the ratio of GMCs (GMRs) (group 3 confirmatory cohort relative to study 6096A1-3005) was >0.5.

As shown in Table 1 for the evaluable immunogenicity population, this criterion was met for all 7 common serotypes. The serotype-specific GMCs were higher in group 3 in this study compared to the 7vPnC group from study 6096A1-3005 for all of the 7 common serotypes. The serotype-specific GMRs ranged from 2.51 for serotype 23F to 5.66 for serotype 6B.

Table 1. Comparison of Pneumococcal IgG GMCs (µg/mL) After Vaccination for Original 7 Serotypes, 13vPnC Group 3c in Study 3011 Relative to 7vPnC in Study 3005 (Post-toddler) – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled/Randomized)							
	13vPnC Group 3c (Study 3011)			7vPnC (Study 3005)				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	169	8.45	(7.24, 9.87)	173	2.79	(2.45, 3.18)	3.03	(2.48, 3.71)
6B	171	53.56	(45.48, 63.07)	173	9.47	(8.26, 10.86)	5.66	(4.57, 6.99)
9V	171	9.51	(8.38, 10.78)	172	1.97	(1.77, 2.19)	4.83	(4.10, 5.70)
14	169	29.36	(24.78, 34.78)	173	8.19	(7.31, 9.18)	3.58	(2.93, 4.39)
18C	171	8.23	(7.13, 9.51)	173	2.33	(2.05, 2.65)	3.53	(2.91, 4.29)
19F	171	17.58	(14.95, 20.67)	173	3.31	(2.87, 3.81)	5.31	(4.29, 6.58)
23F	169	11.26	(9.79, 12.95)	173	4.49	(3.86, 5.23)	2.51	(2.04, 3.08)

a. n = Number of subjects with a determinate antibody concentration for the specified serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw. GMC after toddler dose for 7vPnC (Study 3005).
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: 13vPnC Group 3c (Study 3011) to 7vPnC (Study 3005) reference.
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 (13vPnC Group 3c [Study 3011] – 7vPnC [Study 3005]).

As shown in Table 2, the criterion for non-inferiority (lower limit of the 2-sided 95% CI for GMR >0.5) was met for all 6 of the additional serotypes. The serotype-specific GMCs were higher for the group 3 confirmatory 13vPnC group in this study than for the combined 13vPnc groups from study 6096A1-3005 for all of the 6 additional serotypes. The serotype-specific GMRs ranged from 1.23 for serotype 1 to 3.17 for serotype 3.

Table 2. Comparison of Pneumococcal IgG GMCs (µg/mL) After Vaccination for Additional 6 Serotypes, 13vPnC Group 3c in Study 3011 Relative to Combined 13vPnC in Study 3005 (Post-toddler) – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled/Randomized)							
	13vPnC Group 3c (Study 3011)			13vPnC (Study 3005)				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
Additional								
1	171	3.57	(3.05, 4.18)	1068	2.90	(2.75, 3.05)	1.23	(1.07, 1.42)
3	171	2.38	(2.07, 2.74)	1065	0.75	(0.72, 0.79)	3.17	(2.78, 3.62)
5	171	5.52	(4.82, 6.32)	1068	2.85	(2.72, 2.98)	1.94	(1.71, 2.20)
6A	169	21.51	(18.15, 25.51)	1063	7.11	(6.78, 7.46)	3.03	(2.64, 3.47)
7F	170	6.24	(5.49, 7.08)	1067	4.39	(4.18, 4.61)	1.42	(1.24, 1.62)
19A	170	17.18	(15.01, 19.67)	1056	8.44	(8.05, 8.86)	2.03	(1.78, 2.32)

a. n = Number of subjects with a determinate antibody concentration for the specified serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw. GMC after toddler dose for 13vPnC (Study 3005).
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: 13vPnC Group 3c (Study 3011) to 13vPnC (Study 3005).
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 (13vPnC Group 3c [Study 3011] – 13vPnC [Study 3005]).

Primary comparison group 4 OPA GMTs

For group 4, the primary immunogenicity objective was to demonstrate non-inferiority of the immune responses to the 13 serotypes in 13vPnC in the group 4 (subjects ≥10 years to <18 years) confirmatory cohort compared to the group 3 (subjects ≥5 years to <10 years) confirmatory cohort, as measured by OPA titers 1 month after vaccination. OPA titers for group 4 were to be declared non-inferior to those for group 3 if the lower limit of the 2-sided, 95% CI for the GMR (group 4 confirmatory GMT/group 3 confirmatory GMT) was >0.5 (2-fold criterion). As shown in Table 3, this criterion was met for all 7 common serotypes and for all of the 6 additional serotypes except serotype 3. The serotype-specific GMRs ranged from 0.7 (serotype 18C) to 1.5 (serotypes 4 and 19F) for the 7 common serotypes and from 0.6 (serotypes 3 and 7F) to 1.7 (serotype 1) for the 6 additional serotypes.

Table 3. Comparison of Pneumococcal OPA GMTs After Vaccination, 13vPnC Group 4c Relative to 13vPnC Group 3c – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled)							
	13vPnC Group 4c			13vPnC Group 3c				
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	188	6912	(6101.2, 7831.4)	181	4629	(4017.2, 5334.3)	1.5	(1.24, 1.80)
6B	183	14224	(12316.4, 16427.3)	178	14996	(13164.1, 17083.1)	0.9	(0.78, 1.15)
9V	186	4485	(4001.1, 5027.5)	180	4733	(4203.3, 5328.4)	0.9	(0.80, 1.12)
14	187	6894	(6028.3, 7884.0)	176	4759	(4120.4, 5497.0)	1.4	(1.19, 1.76)
18C	182	6263	(5436.4, 7215.1)	175	8815	(7738.2, 10041.0)	0.7	(0.59, 0.86)
19F	184	2280	(1949.4, 2667.6)	178	1559	(1293.3, 1878.9)	1.5	(1.15, 1.86)
23F	187	3808	(3354.7, 4322.6)	176	3245	(2818.8, 3735.5)	1.2	(0.97, 1.42)
Additional								
1	189	319	(271.2, 376.0)	179	187	(160.4, 218.6)	1.7	(1.36, 2.13)
3	181	114	(100.4, 129.4)	178	202	(180.9, 226.3)	0.6	(0.48, 0.67)
5	183	336	(270.3, 417.6)	178	491	(426.3, 565.3)	0.7	(0.53, 0.89)
6A	182	9928	(8457.0, 11654.8)	178	7514	(6350.8, 8890.7)	1.3	(1.05, 1.67)
7F	185	6584	(5829.4, 7435.5)	178	10334	(9099.0, 11736.8)	0.6	(0.53, 0.76)
19A	187	1276	(1131.7, 1439.0)	180	1180	(1047.5, 1329.4)	1.1	(0.91, 1.28)

a. n = Number of subjects with a determinate antibody titer for the specified serotype.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t-distribution for the mean logarithm of the titers.
d. Ratio of GMTs: 13vPnC Group 4c to 13vPnC Group 3c.
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 (13vPnC Group 4c – 13vPnC Group 3c)

Secondary analysis (group 4)

The secondary immunogenicity objective was to demonstrate, based on IgG concentrations 1 month after vaccination, non-inferiority of the immune responses induced by 13vPnC received by the group 4 confirmatory cohort compared (lower limit of the 2-sided 95% CI for the GMR >0.5) to the posttoddler responses in the 7vPnC group from study 6096A1-3005 for the 7 common serotypes and compared to the post-toddler responses in the combined 13vPnC groups from study 6096A1-3005 for the 6 additional serotypes.

The criterion for non-inferiority was met for all 7 common serotypes (Table 4) and all 6 additional serotypes (Table 5).

Table 4. Comparison of Pneumococcal IgG GMCs (µg/mL) After Vaccination for Original 7 Serotypes, 13vPnC Group 4c in Study 3011 Relative to 7vPnC in Study 3005 (Posttoddler) – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled/Randomized)							
	13vPnC Group 4c (Study 3011)			7vPnC (Study 3005)				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	189	4.47	(3.80, 5.25)	173	2.79	(2.45, 3.18)	1.60	(1.30, 1.97)
6B	187	26.48	(21.77, 32.20)	173	9.47	(8.26, 10.86)	2.80	(2.20, 3.56)
9V	188	5.35	(4.68, 6.11)	172	1.97	(1.77, 2.19)	2.72	(2.29, 3.23)
14	188	18.53	(14.43, 23.78)	173	8.19	(7.31, 9.18)	2.26	(1.71, 3.00)
18C	187	6.57	(5.51, 7.84)	173	2.33	(2.05, 2.65)	2.82	(2.26, 3.52)
19F	185	13.91	(11.67, 16.58)	173	3.31	(2.87, 3.81)	4.20	(3.35, 5.27)
23F	184	15.41	(12.57, 18.89)	173	4.49	(3.86, 5.23)	3.43	(2.66, 4.43)

Abbreviations: 7vPnC = 7-valent pneumococcal conjugate vaccine; 13vPnC = 13-valent pneumococcal conjugate vaccine; CI = confidence interval; GMC = geometric mean concentration; Group 4c = confirmatory cohort of group 4; IgG = immunoglobulin G.
a. n = Number of subjects with a determinate antibody concentration for the specified serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw. GMC after toddler dose for 7vPnC (Study 3005).
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: 13vPnC Group 4c (Study 3011) to 7vPnC (Study 3005) reference.
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 (13vPnC Group 4c (Study 3011) – 7vPnC (Study 3005)).

Table 5. Comparison of Pneumococcal IgG GMCs (µg/mL) After Vaccination for Additional 6 Serotypes, 13vPnC Group 4c in Study 3011 Relative to Combined 13vPnC in Study 3005 (Posttoddler) – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled/Randomized)							
	13vPnC Group 4c (Study 3011)			13vPnC (Study 3005)				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
Additional								
1	188	6.28	(5.28, 7.47)	1068	2.90	(2.75, 3.05)	2.17	(1.88, 2.50)
3	187	1.88	(1.66, 2.12)	1065	0.75	(0.72, 0.79)	2.50	(2.20, 2.83)
5	188	7.06	(6.14, 8.13)	1068	2.85	(2.72, 2.98)	2.48	(2.19, 2.81)
6A	188	16.87	(14.06, 20.23)	1063	7.11	(6.78, 7.46)	2.37	(2.07, 2.72)
7F	188	6.36	(5.59, 7.25)	1067	4.39	(4.18, 4.61)	1.45	(1.27, 1.65)
19A	188	17.68	(15.52, 20.14)	1056	8.44	(8.05, 8.86)	2.09	(1.85, 2.38)

Abbreviations: 13vPnC = 13-valent pneumococcal conjugate vaccine; CI = confidence interval; GMC = geometric mean concentration; Group 4c = confirmatory cohort of group 4; IgG = immunoglobulin G.
a. n = Number of subjects with a determinate antibody concentration for the specified serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw. GMC after toddler dose for 13vPnC (Study 3005).
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: 13vPnC Group 4c (Study 3011) to 13vPnC (Study 3005).
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 (13vPnC Group 4c (Study 3011) – 13vPnC (Study 3005)).

Additional analyses

Proportion of Subjects Achieving Prespecified IgG Concentrations

The proportion of subjects (ie, responders) in group 3 who had IgG concentrations ≥0.35 µg/mL 1 month after vaccination with 13vPnC is summarized in Table 6 for the evaluable immunogenicity

population. After vaccination, the proportion of subjects who achieved IgG concentrations ≥0.35 µg/mL was 100% for the 7 common serotypes, and ranged from 98.2% to 100% for the 6 additional serotypes in group 3. Before vaccination, the percentage of subjects with IgG concentrations ≥0.35 µg/mL ranged from 54.0% to 100% (lowest for serotype 4; highest for serotype 6B) for the 7 common serotypes, and from 58.9% to 100% (lowest for serotype 1; highest for serotype 19A) for the 6 additional serotypes in group 3.

After vaccination, the proportion of subjects who had IgG concentrations ≥1.0 µg/mL ranged from 98.8% to 100% for the 7 common serotypes, and ranged from 82.5% to 100% for the 6 additional serotypes in group 3. Before vaccination, the percentage of subjects with IgG concentrations ≥1.0 µg/mL ranged from 23.3% to 97.1% (lowest for serotype 4; highest for serotype 6B) for the 7 common serotypes, and from 38.4% to 97.1% (lowest for serotype 1; highest for serotype 19A) for the 6 additional serotypes in group 3.

Table 6. Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After Vaccination – Group 3 – Evaluable Immunogenicity Population

	Vaccine Group (as Enrolled)											
	13vPnC Group 3e+3c				13vPnC Group 3e				13vPnC Group 3c			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
7vPnC												
4	259	259	100.0	(98.6, 100.0)	90	90	100.0	(96.0, 100.0)	169	169	100.0	(97.8, 100.0)
6B	261	261	100.0	(98.6, 100.0)	90	90	100.0	(96.0, 100.0)	171	171	100.0	(97.9, 100.0)
9V	261	261	100.0	(98.6, 100.0)	90	90	100.0	(96.0, 100.0)	171	171	100.0	(97.9, 100.0)
14	259	259	100.0	(98.6, 100.0)	90	90	100.0	(96.0, 100.0)	169	169	100.0	(97.8, 100.0)
18C	261	261	100.0	(98.6, 100.0)	90	90	100.0	(96.0, 100.0)	171	171	100.0	(97.9, 100.0)
19F	260	260	100.0	(98.6, 100.0)	89	89	100.0	(95.9, 100.0)	171	171	100.0	(97.9, 100.0)
23F	258	258	100.0	(98.6, 100.0)	89	89	100.0	(95.9, 100.0)	169	169	100.0	(97.8, 100.0)
Additional												
1	261	259	99.2	(97.3, 99.9)	90	90	100.0	(96.0, 100.0)	171	169	98.8	(95.8, 99.9)
3	261	258	98.9	(96.7, 99.8)	90	90	100.0	(96.0, 100.0)	171	168	98.2	(95.0, 99.6)
5	261	261	100.0	(98.6, 100.0)	90	90	100.0	(96.0, 100.0)	171	171	100.0	(97.9, 100.0)
6A	259	259	100.0	(98.6, 100.0)	90	90	100.0	(96.0, 100.0)	169	169	100.0	(97.8, 100.0)
7F	259	259	100.0	(98.6, 100.0)	89	89	100.0	(95.9, 100.0)	170	170	100.0	(97.9, 100.0)
19A	260	260	100.0	(98.6, 100.0)	90	90	100.0	(96.0, 100.0)	170	170	100.0	(97.9, 100.0)

a. N = number of subjects with a determinate IgG antibody concentration to the given serotype.
b. n = Number of subjects with an antibody concentration ≥0.35 µg/mL for the given serotype. Assay result from blood sample obtained after vaccination.
c. Exact 2-sided confidence interval based on the observed proportion of subjects.

Proportion of Subjects Achieving an OPA Titer ≥LLOQ group 3

The proportion of subjects in group 3 achieving an OPA titer ≥LLOQ after vaccination is presented in Table 7 for the evaluable immunogenicity population. The majority of subjects in group 3 achieved an OPA titer ≥LLOQ for the 7 common serotypes (98.9% to 100%) and the 6 additional serotypes (97.8% to 100%).

Table 7. Subjects Achieving a Pneumococcal OPA Antibody Titer ≥ LLOQ After Vaccination – Group 3 – Evaluable Immunogenicity Population

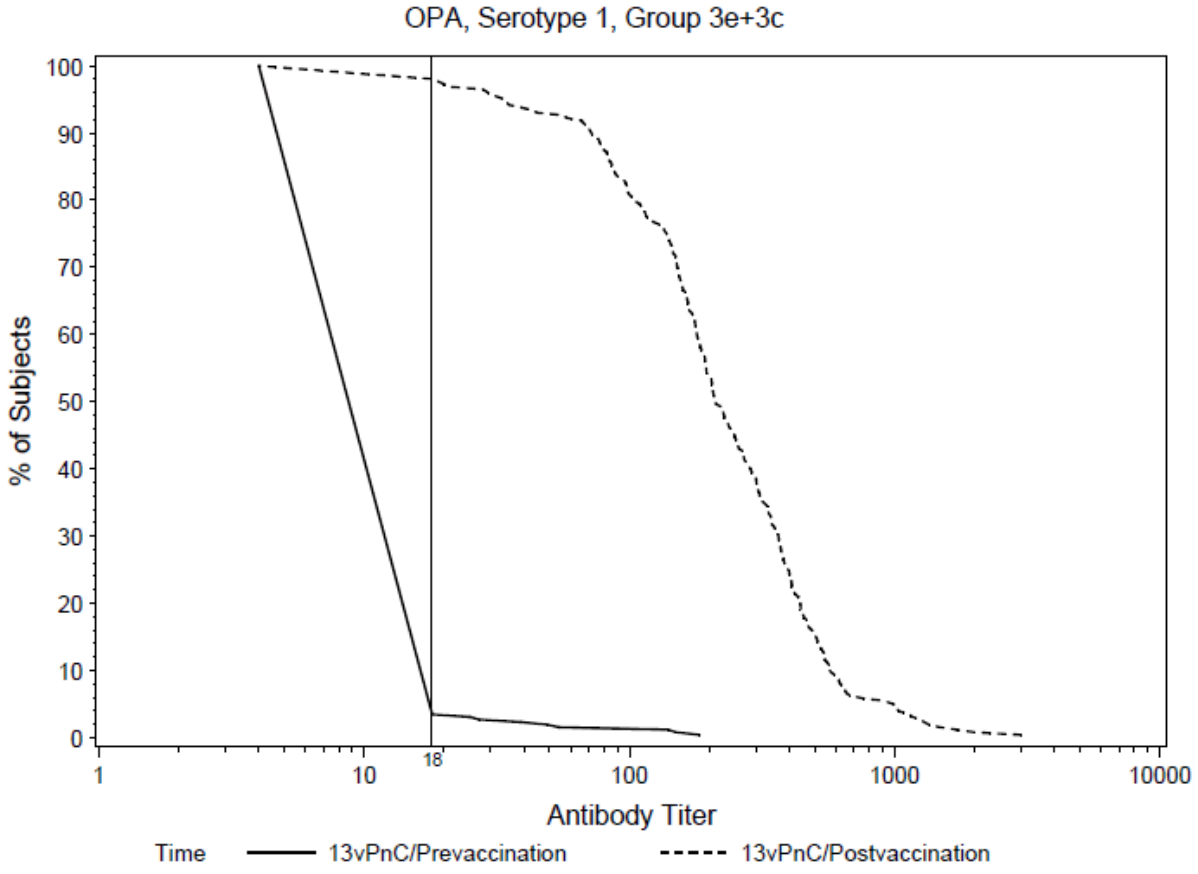
	Vaccine Group (as Enrolled)											
	13vPnC Group 3e+3c				13vPnC Group 3e				13vPnC Group 3c			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
7vPnC												
4	259	259	100.0	(98.6, 100.0)	78	78	100.0	(95.4, 100.0)	181	181	100.0	(98.0, 100.0)
6B	257	257	100.0	(98.6, 100.0)	79	79	100.0	(95.4, 100.0)	178	178	100.0	(97.9, 100.0)
9V	249	249	100.0	(98.5, 100.0)	69	69	100.0	(94.8, 100.0)	180	180	100.0	(98.0, 100.0)
14	257	257	100.0	(98.6, 100.0)	81	81	100.0	(95.5, 100.0)	176	176	100.0	(97.9, 100.0)
18C	250	250	100.0	(98.5, 100.0)	75	75	100.0	(95.2, 100.0)	175	175	100.0	(97.9, 100.0)
19F	253	248	98.0	(95.4, 99.4)	75	72	96.0	(88.8, 99.2)	178	176	98.9	(96.0, 99.9)
23F	254	254	100.0	(98.6, 100.0)	78	78	100.0	(95.4, 100.0)	176	176	100.0	(97.9, 100.0)
Additional												
1	258	253	98.1	(95.5, 99.4)	79	78	98.7	(93.1, 100.0)	179	175	97.8	(94.4, 99.4)
3	255	253	99.2	(97.2, 99.9)	77	76	98.7	(93.0, 100.0)	178	177	99.4	(96.9, 100.0)
5	257	254	98.8	(96.6, 99.8)	79	78	98.7	(93.1, 100.0)	178	176	98.9	(96.0, 99.9)
6A	260	260	100.0	(98.6, 100.0)	82	82	100.0	(95.6, 100.0)	178	178	100.0	(97.9, 100.0)
7F	255	255	100.0	(98.6, 100.0)	77	77	100.0	(95.3, 100.0)	178	178	100.0	(97.9, 100.0)
19A	256	256	100.0	(98.6, 100.0)	76	76	100.0	(95.3, 100.0)	180	180	100.0	(98.0, 100.0)

Abbreviation: LLOQ = Lower limit of quantitation.
a. N = number of subjects with a determinate OPA antibody titer to the given serotype.
b. n = Number of subjects with an antibody titer who meet the comparison level for the given serotype.
c. Exact 2-sided confidence interval based on the observed proportion of subjects

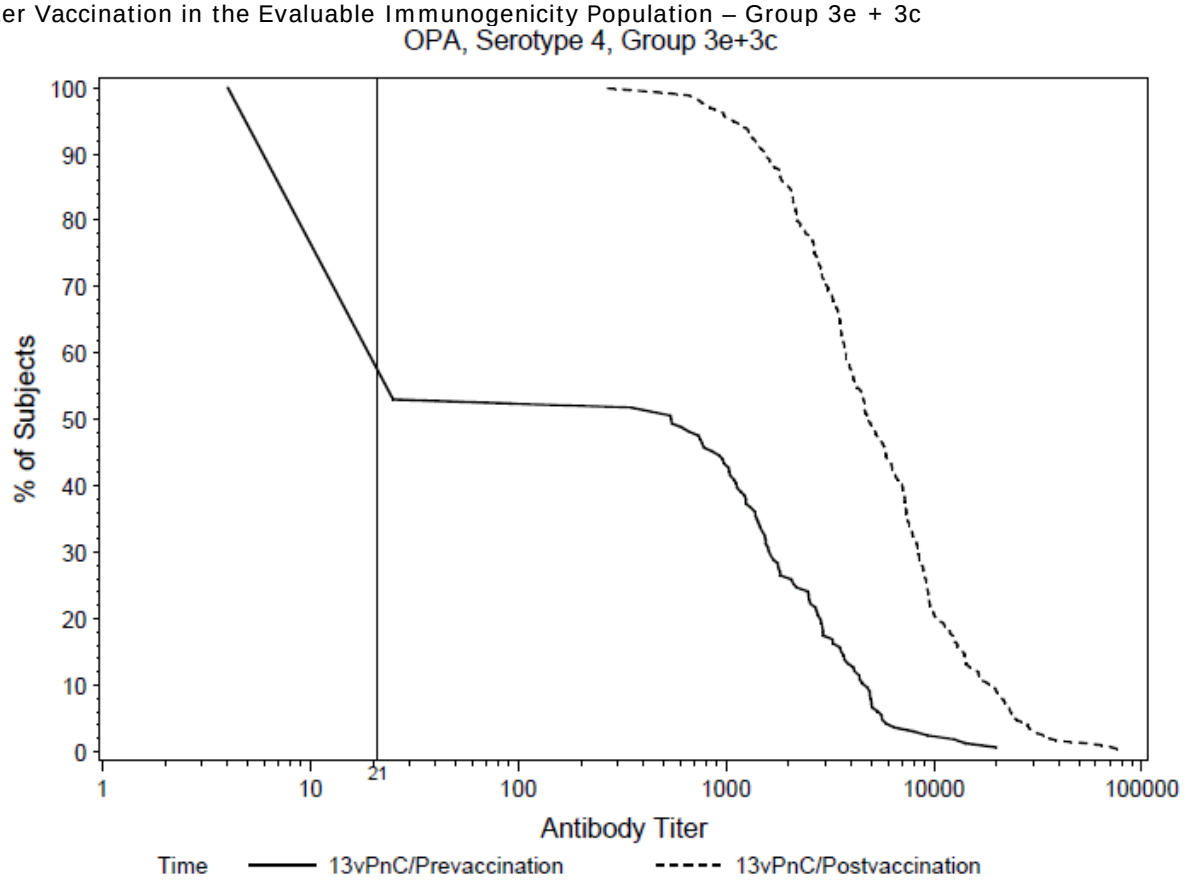
OPA Reverse Cumulative Distribution Curves group 3

RCDCs were plotted for both pre- and post- vaccination OPA titers for each of the 13 pneumococcal serotypes for group 3, group 3 exploratory cohort, and group 3 confirmatory cohort (serotypes 1 and 4 shown as examples below). The curves show an increase in each of the serotype-specific OPA titers after vaccination.

Reverse Cumulative Distribution Curves, Pneumococcal Serotype 1, OPA Titers Before Vaccination and After Vaccination in the Evaluable Immunogenicity Population – Group 3e + 3c



Reverse Cumulative Distribution Curves, Pneumococcal Serotype 4, OPA Titers Before Vaccination and After Vaccination in the Evaluable Immunogenicity Population – Group 3e + 3c



Proportion of Subjects Achieving an OPA Titer ≥LLOQ (group 4)

The proportion of subjects in group 4 that achieved an OPA titer ≥LLOQ after vaccination is presented in Table 8 for the evaluable immunogenicity population. The majority of subjects in group 4 achieved an OPA titer ≥LLOQ for the 7 common serotypes (100%) and the 6 additional serotypes (94.5% to 100%).

Table 8. Subjects Achieving a Pneumococcal OPA Antibody Titer ≥ LLOQ After Vaccination – Group 4 – Evaluable Immunogenicity Population

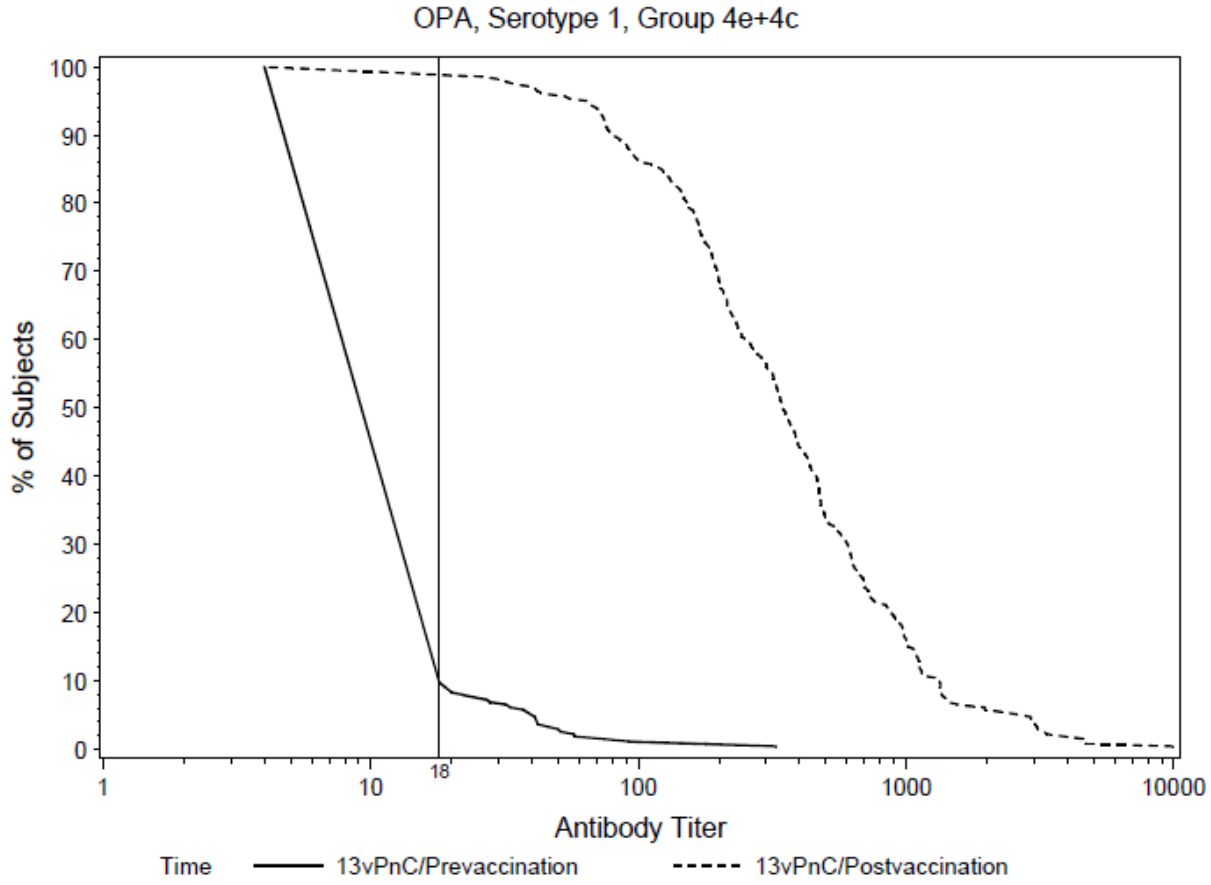
	Vaccine Group (as Enrolled)											
	13vPnC Group 4e+4c				13vPnC Group 4e				13vPnC Group 4c			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
7vPnC												
4	268	268	100.0	(98.6, 100.0)	80	80	100.0	(95.5, 100.0)	188	188	100.0	(98.1, 100.0)
6B	270	270	100.0	(98.6, 100.0)	87	87	100.0	(95.8, 100.0)	183	183	100.0	(98.0, 100.0)
9V	259	259	100.0	(98.6, 100.0)	73	73	100.0	(95.1, 100.0)	186	186	100.0	(98.0, 100.0)
14	270	270	100.0	(98.6, 100.0)	83	83	100.0	(95.7, 100.0)	187	187	100.0	(98.0, 100.0)
18C	263	262	99.6	(97.9, 100.0)	81	80	98.8	(93.3, 100.0)	182	182	100.0	(98.0, 100.0)
19F	259	258	99.6	(97.9, 100.0)	75	74	98.7	(92.8, 100.0)	184	184	100.0	(98.0, 100.0)
23F	273	273	100.0	(98.7, 100.0)	86	86	100.0	(95.8, 100.0)	187	187	100.0	(98.0, 100.0)
Additional												
1	280	276	98.6	(96.4, 99.6)	91	89	97.8	(92.3, 99.7)	189	187	98.9	(96.2, 99.9)
3	267	266	99.6	(97.9, 100.0)	86	86	100.0	(95.8, 100.0)	181	180	99.4	(97.0, 100.0)
5	266	254	95.5	(92.3, 97.6)	83	81	97.6	(91.6, 99.7)	183	173	94.5	(90.2, 97.3)
6A	269	269	100.0	(98.6, 100.0)	87	87	100.0	(95.8, 100.0)	182	182	100.0	(98.0, 100.0)
7F	268	267	99.6	(97.9, 100.0)	83	82	98.8	(93.5, 100.0)	185	185	100.0	(98.0, 100.0)
19A	264	264	100.0	(98.6, 100.0)	77	77	100.0	(95.3, 100.0)	187	187	100.0	(98.0, 100.0)

Abbreviation: LLOQ = Lower limit of quantitation.
a. N = number of subjects with a determinate OPA antibody titer to the given serotype.
b. n = Number of subjects with an antibody titer who meet the comparison level for the given serotype.
c. Exact 2-sided confidence interval based on the observed proportion of subjects.

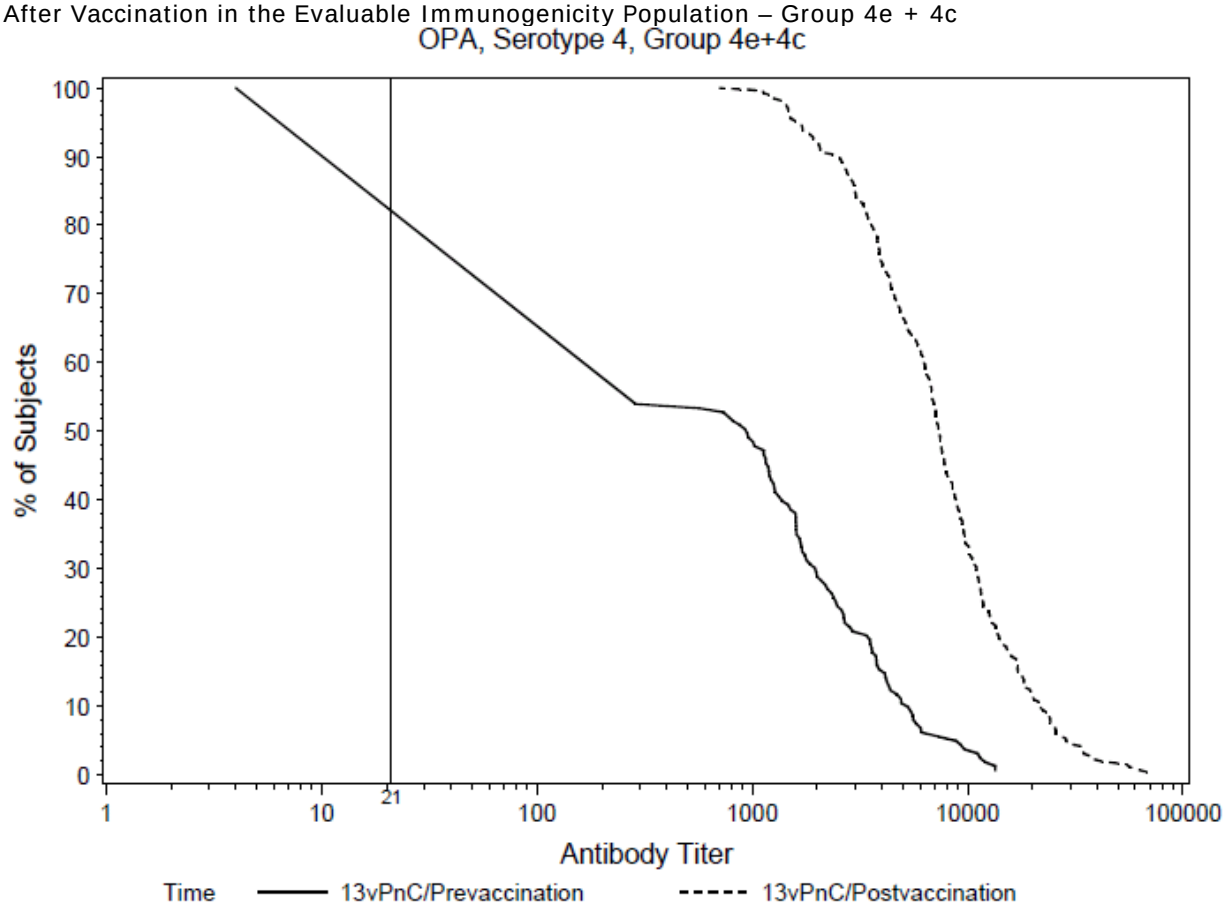
OPA Reverse Cumulative Distribution Curves (group 4)

RCDCs were plotted for both pre- and post- vaccination OPA titers for each of the 13 pneumococcal serotypes for group 4, group 4 exploratory cohort, and group 4 confirmatory cohort (serogroup 1 and 4 shown as examples below). The curves show an increase in the each of the serotype-specific OPA titers after the study vaccine was administered.

Reverse Cumulative Distribution Curves, Pneumococcal Serotype 1, OPA Titers Before Vaccination and After Vaccination in the Evaluable Immunogenicity Population – Group 4e + 4c



Reverse Cumulative Distribution Curves, Pneumococcal Serotype 4, OPA Titers Before Vaccination and After Vaccination in the Evaluable Immunogenicity Population – Group 4e + 4c



2.2.3. Discussion

There is no established serological correlate of protection in the age groups 5-10 and 10-18 years. The company has compared the IgG responses in the 5-10 year old children who were previously primed with at least one dose of Prevenar (group 3), to the IgG responses in toddlers (booster dose) vaccinated with Prevenar 13 in study 3005. The comparison provides a bridge to a population where efficacy has been demonstrated. The IgG responses in group 3 were clearly non-inferior, even superior to the responses in toddlers, both against the 7 Prevenar serotypes and the 6 additional serotypes.

In group 4, the unprimed children 10-18 years of age the primary comparison was OPA GMT vs group 3. This comparison is also considered acceptable as protection is mediated by opsonophagocytic antibodies, and the same approach was used to extend the indication to adults >50 years of age. Also for the 10-18 year old children non-inferiority was demonstrated.

Fort both age groups the secondary and exploratory analyses support substantial immune responses that are very likely to be protective. These results are not unexpected, as immune responses in older children generally are stronger than in the youngest children (below 2 years of age). In addition, many of the older children have encountered pneumococci of various serotypes, and can thus be considered primed. This is also supported by the presence of antibodies to some serotypes before vaccination, in many but not all subjects.

The MAH rationale for extending the use of 13vPnC in children and adolescents up to 17 years of age was based on:

1. Burden of disease: While there has been a significant reduction in invasive pneumococcal disease (IPD) since the introduction of 7-valent pneumococcal conjugate vaccine (7vPnC, Prevenar) in young children up to 5 years of age, there remains a significant burden of disease in children and adolescents 6 to 17 years of age. According to Eurostat 5.4 million children were born in the European Union (EU27) in 2008. Conservatively generalizing from population based data presented below an incidence of IPD of about 2 per 100,000 population, among the 70.2 million children age 5 to <18 years in EU27, there are about 1,404 IPD cases annually. Based on current 13vPnC IPD-coverage data (39.4% and 86% for bacteraemia and meningitis in France, respectively, 65% in Germany, 59% for England and Wales), approximately half to two-thirds of the cases could be vaccine preventable.

   Similar calculations based on Center for Disease Control (CDC) Active Bacterial Core (ABC) surveillance in the United States of America (USA), estimate that, as of 2007, 1300 cases of IPD occur annually in this age group (population 54 million; www.census.gov, intercensal estimate for 2010, incidence 2.4 per 100,000 population according to ABC data) and between 52.4% and 61.3% (based on ABC surveillance data for 2007 to 2009) are caused by 13vPnC serotypes.

2. Risk subjects: Certain patients have a significantly elevated risk of pneumococcal diseases including those with chronic heart or lung disease, diabetes, or asthma. Moreover, some underlying diseases like human immunodeficiency virus (HIV) or sickle cell disease have a very high risk for IPD (high-risk subjects) and for those 13vPnC is recommended in case they are 5 to 17 years of age (eg, in Ireland).

3. Limited benefits of 23vPPV: Vaccination with the 23-valent pneumococcal polysaccharides vaccine (23vPPV) of at risk and high-risk children and young adults is recommended in some countries. Although a number of randomized clinical trials and case-control studies have been published, the degree of protection afforded by 23vPPV remains much debated. While it appears that 23vPPV offers some protection against IPD in the general elderly population, it has an only moderate effect in the high-risk elderly and the vaccine has little or no effect against pneumonia. In contrast, for serotypes in the vaccine, 7vPnC has demonstrated a high degree of efficacy against IPD in infants and young children and efficacy against acute otitis media (AOM); published studies have reported efficacy and effectiveness against pneumonia. 13vPnC has been licensed subsequently for children up to 5 years of age of age based on a favorable immunogenicity profile compared to 7vPnC, with an expectation of effectiveness for all serotypes.

Of these arguments, the CHMP considered that the number of vaccine preventable cases in the proposed age group is considerably lower than in younger children (pre-vaccination era).

Initially, the CHMP was of the opinion that the expected benefit of vaccination in healthy children 5-17 years of age is considered limited, while the benefit in risk groups is expected to be larger, but no efficacy or safety data in such subjects have been submitted. This was considered a major shortcoming; therefore the MAH was requested to provide a justification of the adequacy of extrapolating efficacy and safety data from healthy children to high risk groups. The MAH provided an overview of the published literature supporting the benefit of Prevenar (7-valent) in risk groups, i.e. significant immune responses were demonstrated. In healthy children it has been shown that immune responses to Prevenar13 were non-inferior to those of Prevenar for the 7 common serotypes, and that the immune responses were of similar magnitude to the 6 additional serotypes. It can be concluded that this will be the case also in risk groups. The MAH is conducting studies (6096A1-3014, 6115A1-

3002 as part of the Paediatric Investigation Plan and 6115A1-3003 as a pharmacovigilance activity) that will provide immunogenicity data in various risk groups and these results will be submitted as supporting evidence. Regarding safety in risk groups the ongoing studies are not likely to detect rare events, and post-marketing surveillance will be in placed.

Risk group children are considered a very important group to protect against pneumococcal infections. Some countries (i.e. USA and Ireland) are already recommending the use of Prevenar 13 to older risk group children. There is clearly a medical need for effective vaccines for risk groups up to 18 years.

Currently the 23-valent polysaccharide vaccine is used in risk groups from 2 years of age in many countries. The data to support this use is considered limited.

2.3. Clinical Safety aspects

The data relevant to the current age expansion submission are from Study 6096A1-3011 group 3 (ages ≥5 years to <10 years) and group 4 (ages ≥10 years to <18 years). Group 3 enrolled subjects in the specified age range who had received at least 1 dose of marketed 7-valent pneumococcal conjugate vaccine (7vPnC, Prevenar), while group 4 enrolled subjects in the specified age range who had not received any doses of 7vPnC or any other pneumococcal vaccine. At study entry, all subjects received 1 dose of open-label 13vPnC administered intramuscularly in the left arm.

Safety was evaluated based on information regarding solicited AEs and unsolicited AEs. Solicited AEs included local reactions and systemic events, which were to be evaluated and recorded by the parent/legal guardian in an electronic diary (e-diary) for 7 days after vaccination. In addition, information was to be reported regarding unsolicited AEs that occurred from the day of vaccination through the 1-month post-vaccination visit. At the 6-month telephone contact, the parent/legal guardian was asked to report any newly diagnosed medical conditions, as well as any hospitalisations or serious adverse events (SAEs) that had occurred since the 1-month follow-up visit.

2.3.1. Methods – analysis of data submitted

Safety assessment methods:

Local reactions (tenderness, redness, and swelling at the vaccine injection site): Tenderness was recorded as no discernible tenderness, tenderness present, or tenderness interfered with limb movement. For redness and swelling, the parent/legal guardian measured the actual size of the reaction with a caliper. For analysis purposes, measurements recorded for redness and swelling were categorized as absent (no redness or swelling present), mild (1 to 4 caliper units), moderate (5 to 14 caliper units), or severe (>14 caliper units).

Systemic events (fever, decreased appetite, irritability, increased sleep, decreased sleep, hives [urticaria], and the use of antipyretic medications to prevent or treat symptoms):

Temperature was measured at bedtime using an age-appropriate method. Severity of fever was categorized as absent, mild (≥100.4°F to ≤102.2°F), moderate (≥102.2°F to ≤104.0°F), or severe (≥104.0°F) for analysis. Other systemic events were reported as present or absent.

Adverse events: AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA). The relation between an AE and study vaccine was categorized as related or not related. AE severity was categorized as mild, moderate, severe, or life threatening.

Endpoints

The safety endpoints were local reactions, systemic events, and AEs. No formal statistical comparisons were made. The percentage of subjects with local reactions and systemic events reported within the 7-day post-vaccination period was summarized for each age group. Only subjects actually reporting the reaction/event were included in the summary statistics. AEs were summarized by age group for each vaccine dose. All summaries showed the number and percentage of subjects reporting at least 1 event and the number of such events. Summaries of severe or life-threatening AEs and AEs by relationship to vaccine were prepared.

For exploratory subgroup analyses of AEs and reactogenicity, subjects were categorized by the number of Prevnar doses they had received before study enrollment, provided that more than 20% of subjects in an age group had received the same number of Prevnar doses. Because the number of doses was not controlled, no formal statistical within-group comparisons were made.

Analysis Population

The safety population included all subjects who received at least 1 dose of 13vPnC.

2.3.2. Results

Overall exposure

A total of 294 subjects were vaccinated in group 3, and 298 subjects were vaccinated in group 4. All vaccinated subjects were within the protocol-specified age range at the time of vaccination.

The most common medical history by system organ class (SOC) in both age groups were respiratory, thoracic and mediastinal disorders, and infections and infestations. In each group, 17.4% of subjects had a medical history of asthma.

Local Reactions

At least 1 local reaction was reported within 7 days of vaccine administration for 89.6% of subjects in group 3 and for 90.5% of subjects in group 4 (Table 9). The most frequent local reaction was tenderness, which occurred in 86.8% of subjects in group 3 and 89.0% of subjects in group 4. The percentage of subjects reporting significant tenderness was higher in group 4 (43.8%) than in group 3 (19.5%). Most reports of redness or swelling were of mild or moderate severity. Severe redness and severe swelling were each reported in $\leq$ 3.3% of subjects in either group. The severity of redness or swelling categorised by maximum diameter is shown in the Table below.

Severity of Redness and Swelling Categorised by Maximum Diameter – Study 3011, Group 3 and 4

Local Reaction/ Vaccine Group	N[b]	Subjects Reporting a Maximum Diameter[a] (cm) of: 0[c]	>0 – 2.4	2.5 – 5.0	5.1 – 7.0	> 7.0
Redness						
13vPnC Group 3	233	133	50	28	15	7
13vPnC Group 4	232	162	38	16	12	4
Swelling						
13vPnC Group 3	226	141	35	33	10	7
13vPnC Group 4	233	147	35	34	13	4

a. Includes only the largest measurement reported for each subject. Diameters were measured in caliper units of whole numbers from 1 to 14 or 14+. One (1) caliper unit = 0.5 cm.
b. N = number of subjects reporting yes for at least 1 day or no for all days.
c. Includes reports of no reaction that are not included in the category ">0 – 2.4".

The mean duration for each type of local reaction ranged from 1.9 days to 2.4 days in Group 3 and from 1.3 days to 2.2 days in group 4. In both groups, the highest incidences of tenderness occurred on days 1 and 2, and the highest incidences of redness and of swelling occurred on days 2 and 3 (data not shown). Thereafter, the percentages of subjects reporting tenderness, redness, and swelling diminished over time.

Table 9. Number (%) of Subjects Reporting Local Reactions Within 7 Days After Vaccination – Study 3011, Group 3 and Group 4

	Group 3 (≥5 years to <10 years)			Group 4 (≥10 years to <18 years)		
Local Reaction	N[a]	n[b]	%	N[a]	n[b]	%
Tenderness						
Any	265	230	86.8	283	252	89.0
Significant[c]	221	43	19.5	242	106	43.8
Swelling						
Any	226	85	37.6	233	86	36.9
Mild[d]	220	48	21.8	221	50	22.6
Moderate[d]	219	48	21.9	226	48	21.2
Severe[d]	211	7	3.3	214	4	1.9
Redness						
Any	233	100	42.9	232	70	30.2
Mild[d]	226	63	27.9	226	48	21.2
Moderate[d]	218	48	22.0	221	31	14.0
Severe[d]	212	7	3.3	213	4	1.9
Any of the above	270	242	89.6	285	258	90.5

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

Systemic Events

The percentage of subjects with any systemic event was similar in group 3 (47.2%) and group 4 (51.4%), see Table 10. In both groups, the most frequently reported types of systemic events were irritability, increased sleep, and decreased appetite, all reported for between 21.2% and 31.2% of subjects in each group. Decreased sleep was reported for a higher percentage of subjects in group 4 (18.8%) than in group 3 (5.7%). Hives were reported for 4 (1.9%) subjects in group 3 and 3 (1.4%) subjects in group 4.

Most cases of fever were mild (≥38.0°C but <39.0°C), with 4.2% of subjects in group 3 and 5.1% of subjects in group 4 reporting mild fever. Severe fever (>40°C) was reported for 1 subject (0.5%) in each group. The use of antipyretic medications to treat or prevent symptoms was reported for 45.1% of subjects in group 3 and for 33.1% of subjects in group 4.

The incidence of systemic events and use of antipyretic medications was generally highest on day 1, day 2 or day 3 in both age groups (data not shown). The mean durations of the systemic events were similar in the 2 age groups and did not exceed 3.0 days in either age group.

Table 10. Number (%) of Subjects Reporting Systemic Events and Antipyretic Medication Use Within 7 Days After Vaccination – Study 3011, Group 3 and Group 4

	Group 3 (≥5 years to <10 years)			Group 4 (≥10 years to <18 years)		
Systemic Event	N[a]	n[b]	%	N[a]	n[b]	%
Fever ≥38°C but ≤39°C	212	9	4.2	214	11	5.1
Fever >39°C but ≤40°C	212	5	2.4	212	1	0.5
Fever >40°C	210	1	0.5	212	1	0.5
Decreased appetite	227	52	22.9	223	51	22.9
Irritability	234	73	31.2	234	59	25.2
Increased sleep	226	48	21.2	229	61	26.6
Decreased sleep	212	12	5.7	224	42	18.8
Hives (urticaria)	213	4	1.9	214	3	1.4
Use of medication to treat symptoms	232	88	37.9	232	66	28.4
Use of medication to prevent symptoms	225	58	25.8	225	47	20.9
Use of medication to treat or to prevent symptoms	237	107	45.1	236	78	33.1
Use of medication to treat and to prevent symptoms	220	35	15.9	221	29	13.1
Any systemic event[c]	250	118	47.2	253	130	51.4

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

Unsolicited Adverse Events

The incidence of unsolicited AEs occurring through approximately 1 month after vaccination was similar in group 3 (19.4%) and in group 4 (24.2%). In both vaccine groups, the most frequently reported types of AEs were infections and infestations (10.2% in group 3 and 10.4% in group 4). Nervous system disorders were reported for more subjects in group 4 (14, 4.7%) than in group 3 (5, 1.7%). The most frequently reported AEs in group 3 were cough (10 subjects, 3.4%), vomiting (8 subjects, 2.7%), pyrexia (7 subjects, 2.4%), and streptococcal pharyngitis (6 subjects, 2.0%). The most frequently reported individual AEs in group 4 were headache (10 subjects, 3.4%), and cough, oropharyngeal pain, pharyngitis, influenza, and sinusitis (each in 5 subjects, 1.7%). AEs after vaccination were generally consistent with childhood illnesses common in the respective age groups. At the 6-month follow-up telephone contact, AE reports were to include only newly diagnosed chronic medical conditions and SAEs. At this time point, AEs were reported for 2.4% of subjects in group 3 and 1.7% in group 4. In group 3, 7 subjects reported 7 AEs: bronchial hyperreactivity (2 patients), asthma (2 patients), and myopia, irritable bowel syndrome, and allergic rhinitis, in 1 subject each. In group 4, 5 subjects reported 5 AEs: diarrhoea, migraine, depression, asthma, and allergic rhinitis. AEs that the investigator considered related to study vaccination were reported for 3 subjects (1.0%) in each group. In group 3, 3 subjects reported a total of 6 related AEs: headache (in 2 subjects), and diarrhoea, nausea, vomiting, and pyrexia (in 1 subject each). In group 4, 3 subjects reported a total of 7 related AEs: headache (in 2 subjects), and nausea, injection site pain, injection site pruritis, back pain, and dizziness (in 1 subject each). No AEs considered related to study vaccine were reported at the 6-month follow-up telephone contact.

Deaths and other serious adverse events

No subjects died during the study. Two SAEs were reported during the study. One subject in group 3 experienced appendicitis on the day of vaccination. One subject in group 4 experienced moderate asthma on day 161 after vaccination. Neither of these events was considered related to study vaccine, and both resolved.

Post-marketing experience

This section is not applicable, as 13vPnC is not currently approved for use in children over 5 years of age.

2.3.3. Discussion

The safety data base in children 5-17 years of age consisted of close to 300 subjects in each age cohort (5-9 and 10-18 years respectively) and is considered acceptable. This allows detection of adverse events occurring up to a frequency of 1/100, i.e. common adverse events. The presented data did not reveal any new safety signal, and the overall data suggested that Prevenar 13 was well tolerated in these age groups.

The MAH has stated that the use of Prevenar 13 is recommended off-licence in the USA and Ireland in children up to 18 years of age at increased risk for pneumococcal infections. Therefore the statement that post-marketing data are not relevant as the product is not currently licensed in this age group is not acceptable.

2.4. Risk management plan

Based on the safety conclusions, the CHMP requested the submission of an updated Risk Management Plan within this procedure (see the summary Table below).

Table 11. Summary of the risk management plan (including the changes related to the application presented highlighted)

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Important identified risks:		
Increased fever rates when coadministered Infanrix hexa	Routine pharmacovigilance to monitor the safety profile of 13vPnC.	Routine: The MAH proposes to amend Section 4.4 and Section 4.8 of the SmPC to reflect this interaction.
Important potential risks:		
Unanticipated safety signals (including the onset of rare events) not seen in clinical trials of 13vPnC.	Post-approval observational safety study of all medically attended events following 13vPnC compared to control periods.	None
Vaccine failure in subjects who are fully immunized according to local recommendations	Post-approval adverse event reports of vaccine failure. Follow-up questionnaire of vaccine failure reports to ascertain whether serotype information was collected.	Routine: SmPC (section 4.4) Special warnings and precautions for use. As with any vaccine, 13vPnC may not protect all individuals receiving the vaccine from pneumococcal disease.
AEs which were not associated with 13vPnC in clinical trials or with 7vPnC in post-authorisation observational safety studies, but are included in the Prevenar SmPC:		
Wheezing diagnoses Apnea Convulsions/seizures Anaphylaxis/hypersensitivity (infants/children).	Wheezing diagnoses, apnea, convulsions, seizures, anaphylaxis and hypersensitivity are prespecified endpoints in the post-authorisation observational safety study and will be tracked as prespecified topics in PSURs.	Routine: SmPC (section 4.4) Special warnings and precautions for use Antipyretic treatment should be initiated according to local treatment guidelines for children with seizure disorders or with a prior history of febrile seizures and for all children receiving Prevenar 13 simultaneously with vaccines containing whole cell pertussis
Important missing information:		
Effectiveness of 13vPnC consistent with the high effectiveness of 7vPnC (infants/children).	Population-based surveillance of the incidence rates of IPD in Canada (Quebec), USA, and 5 European countries for 5 years using national surveillance systems (in France, Germany, Denmark, Norway, and the UK), pneumonia rates in the UK and Netherlands, and AOM rates in the UK for 5 years.	None
Effectiveness of 13vPnC (adults).	Population-based surveillance in Canada (Quebec), USA, and 5 European countries for 5 years using national surveillance systems. A clinical trial to assess efficacy of 13vPnC in preventing CAP and IPD in the Netherlands (adults).	None
Long-term vaccine effectiveness.	Assessment of long-term effectiveness of 7vPnC and 13vPnC through population-based national surveillance systems for pneumococcal disease in 5 European countries, Canada (Quebec), and the USA.	None
Potential changes in the	The same 5 European	None

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
epidemiology of non-vaccine *S pneumoniae* serotypes associated with the reduction in disease and nasopharyngeal carriage of serotypes contained in 13vPnC (infants/children).	population-based surveillance systems used for effectiveness evaluation will be used to monitor potential changes in non-13vPnC serotypes for 5 years after 13vPnC introduction.	
Safety and immunogenicity in high risk populations: HIV-infected subjects. Premature infants <37 weeks of gestational age. Immunocompromised subjects including those with bone marrow transplant and sickle cell disease.	Clinical trials of safety and immunogenicity in HIV-positive subjects, premature infants, subjects with sickle cell disease previously immunized with 23-valent pneumococcal polysaccharide vaccine, and subjects with bone marrow transplant.	Routine: SmPC (section 4.4) Special warnings and precautions for use Individuals with impaired immune responsiveness, whether due to the use of immune-suppressive therapy, a genetic defect, human immunodeficiency virus (HIV) infection, or other causes, may have reduced antibody response to active immunization. Safety and immunogenicity data for Prevenar 13 are not available for individuals in specific immunocompromised groups (eg, congenital or acquired splenic dysfunction, HIV infected, malignancy, hematopoietic stem cell transplant, nephrotic syndrome) and vaccination should be considered on an individual basis. Limited data have demonstrated that Prevenar 7 valent (three-dose primary series) induces an acceptable immune response in infants with sickle cell disease with a safety profile similar to that observed in non-high-risk groups (see section 5.1). The potential risk of apnoea and the need for respiratory monitoring for 48-72 h should be considered when administering the primary immunisation series to very premature infants (born $\leq$ 28 weeks of gestation), and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed. SmPC (section 5.1) Pharmacodynamic properties The immunogenicity of Prevenar has been investigated in an openlabel, multicentre study in 49 infants with sickle cell disease. Children were vaccinated with Prevenar (3 doses one month apart from the age of 2 months), and 46 of these children also received a 23-valent pneumococcal polysaccharide vaccine at the age of 15-18 months. After primary immunization, 95.6% of the subjects had antibody levels of at least 0.35 µg/mL for all seven

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		serotypes found in Prevenar. A significant increase was seen in the concentrations of antibodies against the seven serotypes after the polysaccharide vaccination, suggesting that immunological memory was well established.
Age group (>5 to <50 years).	Ongoing clinical trials of safety and immunogenicity in healthy subjects 15 months to 17 years of age, in HIV-positive subjects aged 6 years and older, in subjects with sickle cell disease aged 6 years to less than 18 years, in recipients of hematopoietic stem cell transplant aged 2 years and older, and in healthy subjects 18 to 49 years of age.	None
Impact of 13vPnC on nasopharyngeal carriage (infants/children).	Ongoing surveillance of nasopharyngeal carriage in France through the ACTIV surveillance program comparing nasopharyngeal carriage of *S pneumoniae* and other key commensal bacteria among vaccinated and unvaccinated children Monitoring for replacement of *S pneumoniae* with non-pneumococcal bacteria in the nasopharyngeal flora of children will be conducted in the ACTIV study.	
Pediatric transition plan	Vaccine failures occurring during the 2-3 month Transition period will also be evaluated by the UK, French, German, Dutch and Norwegian national surveillance programs. Vaccine failure reported to the Company via routine pharmacovigilance activities will be reviewed. PSUR analysis will identify all reports of vaccination failure occurring in patients who are transitioning from Prevenar to 13vPnC.	The MAH is informing the health care professionals about a) the differentiating characteristics of 13vPnC and 7vPnC, ie, difference in packaging, the product label and different color of syringe and tip cap and b) how to transition to 13vPnC for children who started a vaccination schedule with 7vPnC. In order to ensure that potential adverse event reports can be unambiguously linked to the type of vaccine administered, the two vaccines have different batch numbers, different color of the plunger and tip cap of the syringe, and different carton packaging and label.
Effect of antipyretics on immune response to vaccination (infants/children).	Planned clinical trial will assess the effect of prophylactic antipyretic medication on the immunogenicity of 13vPnC in healthy infants.	None
Safety of more than 1 dose of 13vPnC in adults administered at >1 year apart.	An ongoing clinical trial will evaluate the safety of a second dose of 13vPnC administered 5 years after the initial dose. The safety of a second dose after 3.5 to 4 years has been confirmed in study 004 extension, now complete.	
Vaccine exposure in pregnancy and lactation (adults).	Routine pharmacovigilance to monitor safety profile of 13vPnC.	SmPC (section 4.6): Fertility, pregnancy, and lactation

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		There are no data from the use of pneumococcal 13-valent conjugate in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. It is unknown whether pneumococcal 13-valent conjugate is excreted in human milk.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

2.5. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

4.1 Therapeutic indications

Active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by Streptococcus pneumoniae in infants and children from 6 weeks to ~~5~~ 17 years of age.

4.2 Posology and method of administration
Unvaccinated infants and children ≥ 7 months of age
Children aged 2-~~5~~ 17 years
One single dose of 0.5 ml.

Children 5 –17 years
Children 5 to 17 years of age may receive a single dose of Prevenar 13 if they have been previously vaccinated with one or more doses of Prevenar. This dose of Prevenar 13 should be administered at least 8 weeks after the final dose of Prevenar (7-valent) (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction
Children 6 to 17 years of age
No data are currently available regarding concomitant use with other vaccines.

4.8 Undesirable effects
The most commonly reported adverse reactions in children 6 weeks to 5 years of age were vaccination-site reactions, fever, irritability, decreased appetite, and increased and/or decreased sleep.

Children and adolescents aged 6 to 17 years of age
Safety was evaluated in 592 children aged 6 to 17 years of age 294 children aged 5 to 10 years previously immunised with at least one dose of Prevenar and 298 children aged 10 to 17 years who had not received a pneumococcal vaccine.

The most common adverse events in children and adolescents 6 to 17 years of age were:

Nervous system disorders:

Common: Headaches

Gastrointestinal disorders:

Very common: Decreased appetite
Common: Vomiting; diarrhoea

Skin and subcutaneous tissue disorders:

Common: Rash; urticaria or urticaria-like rash

General disorders and administration site conditions:

Very common: Irritability; any vaccination-site erythema; induration/swelling or pain/tenderness; somnolence; poor quality sleep; vaccination-site tenderness (including impaired movement)

Common: Pyrexia

Other adverse events previously observed in infants and children 6 weeks to 5 years of age may also be applicable to this age group but were not seen in this study possibly due to the small sample size.

5.1 Pharmacodynamic properties

Burden of disease in children and adolescents aged 6 to 17 years

In children and adolescents aged 6 to 17 years, the incidence of pneumococcal disease is low, however, there is an increased risk of morbidity and mortality in those with underlying co-morbidities.

Children and Adolescents 5 to 17 years of age

In an open-label study in 592 healthy children and adolescents including those with asthma (17.4%) who may be predisposed to pneumococcal infection, Prevenar 13 elicited immune responses to all 13 serotypes. A single dose of Prevenar 13 was given to children 5 to 10 years of age previously vaccinated with at least 1 dose of Prevenar, and children and adolescents 10 to 17 years of age who had never received a pneumococcal vaccine.

In both the children 5 to 10 years of age and children and adolescents aged 10 to 17 years, the immune response to Prevenar 13 was non inferior to Prevenar for the 7 common serotypes and to Prevenar 13 for the 6 additional serotypes compared to the immune response after the fourth dose in infants vaccinated at 2, 4, 6 and 12-15 months of age as measured by serum IgG.

In children and adolescents aged 10 to 17 years of age OPA GMTs 1 month after vaccination were noninferior to OPA GMTs in the 5 to 10 year old age group for 12 of the 1 serotypes (except serotype 3).

Package Leaflet

Section 1

Prevenar 13 is a pneumococcal vaccine given to:

- *children from 6 weeks to ~~5~~ 17 years to help protect against diseases such as: meningitis (inflammation around the brain), sepsis or bacteraemia (bacteria in the blood stream), pneumonia (lung infection) and ear infections,*

Section 3

Unvaccinated infants, children, and adolescents over 7 months of age
Children aged 2 to ~~5~~ 17 years should receive one injection.

Infants, children, and adolescents previously vaccinated with Prevenar

Children and adolescents 6 to 17 years of age should receive one injection

Section 4

The following side effects include those reported for Prevenar 13 in infants and children (6 weeks to 5 years of age):
Common side effects (these may occur with up to 1 in 10 doses of the vaccine) are:

- *Fever of more than 39°C; tenderness at the vaccination site interfering with movement, redness, hardness, swelling at the vaccination site of 2.5 cm -7.0 cm*

The following side effects include those reported for Prevenar 13 in children and adolescents (6 to 17 years of age):

The most common side effects (these may occur with more than 1 in 10 doses of the vaccine) are:
- *Decreased appetite*
- *Irritability; any vaccination-site erythema; induration/swelling or pain/tenderness; somnolence; poor quality sleep; vaccination-site tenderness (including impaired movement)*

Common side effects (these may occur with up to 1 in 10 doses of the vaccine) are:
- *Headaches*
- *Vomiting; diarrhea*
- *Rash; urticaria or urticaria-like rash*
- *Pyrexia*

The following additional side effects have been seen with Prevenar in infants and children up to 5 years of age because it has been available for a longer period of time. These side effects may be reported in the future with Prevenar 13:

The CHMP accepted the revision of the local representative details for Cyprus listed in the Package Leaflet.

During the procedure, the CHMP requested the following additional amendments to the Product Information:

5.1 Pharmacodynamic properties

Children and Adolescents 5 to 17 years of age

The CHMP recommend the revision of the first sentence as follows and it was accepted by the MAH.

In an open-label study in 592 healthy children and adolescents including those with asthma (17.4%) who may be ~~are considered~~ predisposed to pneumococcal infection, Prevenar 13 elicited immune responses to all 13 serotypes.

3. Overall conclusion and impact on the benefit/risk balance

The MAH has provided data from one clinical study in children >5 and ≤17 years of age. Overall the results of this study support substantial immune responses that are very likely to be protective in children 5-17 years of age, and the safety profile was considered acceptable. The expected benefit of Prevenar 13 in healthy children >5 and ≤17 years of age is considered limited as the incidence of disease is much lower than in younger children. The proposed SPC includes a section on burden of disease in this age group in section 5.1, which was considered adequate. The CHMP requested to emphasise by adding this information to section 4.1 as well.

The benefit of Prevenar 13 in children belonging to risk groups, e.g. immunocompromised or with other underlying conditions is expected to be greater, as the risk of pneumococcal infections is higher as well as the morbidity and mortality. Currently the recommendations for these children often include the 23-valent pneumococcal polysaccharide vaccines. There are no data comparing immune responses in children>5 and ≤17 years of age between Prevenar 13 and 23v polysaccharide vaccines. In adults the immune responses to all 12 of the common serotypes were non-inferior, and for 9 serotypes superior for Prevenar 13 compared to 23v polysaccharide vaccines, but it is unknown if this is the case also for children >5 and ≤17 years of age.

The provided overview of the published literature supports the benefit of Prevenar (7-valent) in risk groups, i.e. significant immune responses are demonstrated. In healthy children it has been shown that immune responses to Prevenar13 were non-inferior to Prevenar. Therefore, the CHMP concluded that Prevenar 13 offers a benefit to risk groups based on extrapolation of immunogenicity and effectiveness data for Prevenar. In addition, the MAH is conducting studies that will provide immunogenicity data in various risk groups as supporting evidence.

The safety data obtained in the published studies is considered limited both because many of the studies were small and because safety was not always reported in the publications. However, no specific safety signals were identified in the currently available data. In healthy children the same type and frequency of adverse reactions was observed after administration of Prevenar and Prevenar 13, and it is therefore reasonable to extrapolate safety data from Prevenar to Prevenar 13. Safety data from the ongoing studies in risk groups are not likely to detect rare events.

In conclusion, the sought indication is considered approvable, and the data on risk groups from ongoing studies will be provided as post-authorisation measures.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation(s) accepted		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC to include information related to the extension of the indication to include children from 6 to 17 years of age. The MAH took the opportunity to revise the local representative details for Cyprus that are listed in the Package Leaflet.

The Package Leaflet was updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Conditions and requirements of the marketing authorisation

Risk management system and PSUR cycle

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

The PSUR cycle for the product will follow a half-yearly cycle until otherwise agreed by the CHMP.

Paediatric Data

It should be noted that the submitted study 6096A1-3011 has been submitted as a post-approval measure requested by the CHMP. It is not included in the PIP and has not been assessed by the PDCO.

5. EPAR changes

The EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Update of sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC to include information related to the extension of the indication to include children from 6 to 17 years of age. The MAH took the opportunity to revise the local representative details for Cyprus that are listed in the Package Leaflet.

The Package Leaflet was updated accordingly.

Summary

Please refer to Assessment Report EMEA/H/C/1104/II/55.