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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/0071

Note

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

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1. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) [P/0161/2012] on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP [P/0161/2012] was not yet completed as some measures were deferred.

2. Scientific discussion

2.1. Introduction

Prevenar 13 was developed as a successor to 7vPnC 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. 13vPnC has also been licensed to prevent pneumococcal disease in adults 50 years and older. Starting at about age 50 years, adults are recognised to be at increased risk for developing pneumococcal disease.

The incidence of IPD is greatest at the extremes of life; however, the incidence of pneumococcal disease and associated hospitalisation rates and mortality in younger adults, especially those with risk conditions, are substantial.

Currently, recommendations in most European countries advise vaccination of younger adults, 18 to 64 years of age, who are at higher risk of IPD with one dose of 23vPS. In some countries smokers and subjects with alcohol abuse were added to the high-risk group recently and are also recommended to receive 1 dose of 23vPS, as stated for example by the immunisation guidelines from Ireland.

However, effective protection of 23vPS has not been confirmed in immunocompromised subjects with conditions such as solid or hematologic malignancy, organ or bone marrow transplant or on immunosuppressive therapy. In the only large, randomised placebo controlled efficacy trial of 23vPS in immunocompromised young Ugandan adults suffering from HIV infection, 23vPS was not protective against first-event IPD or all cause pneumonia (ACP).

To overcome the limited immunogenicity of pneumococcal polysaccharide vaccines, the protein conjugation technology was applied to the development of 7vPnC and 13vPnC. In these conjugate vaccines, each pneumococcal polysaccharide is covalently conjugated to the diphtheria cross-reactive material 197 (CRM197) protein, which acts as an immunologic carrier. Thus, 13vPnC would provide an alternative vaccine to the currently recommended pneumococcal free polysaccharide vaccine to protect adults 18 to 49 years of age who are at increased risk for pneumococcal disease.

Results from cohort 3 of study 6115A1-004 (B1851019) in 18 to 49-year-old adults support the use of 13vPnC in this age group. The rationale to extend the use of 13vPnC for adults beginning at 18 years of age is based on the burden of disease, risk groups and the limited benefits of 23vPS.

Evaluation of serotype-specific immune responses after administration of 13vPnC to young adults 18 to 49 years of age in cohort 3 of study 6115A1-004 (B1851019) indicates that 13vPnC elicits similar or greater functional antibody responses compared to those observed in the 60 to 64-year-old group (cohort 1) and, therefore, is expected to confer similar benefits for the younger population.

2.2. Clinical Pharmacology aspects

No dose response studies were conducted for this extension indication. Considering that the same dose is recommended for adults 50 years and older as well as adolescents, the choice of dose is considered adequate.

2.3. Clinical Efficacy aspects

Study 6115A1-004 compared the immunogenicity, tolerability, and safety of 13vPnC and 23vPS in adults 60 to 64 years of age (cohort 1) who had not previously been vaccinated with 23vPS, using a randomised, double-blind design. The study also included a cohort of subjects 50 to 59 years of age (cohort 2), and a cohort of subjects 18 to 49 years of age (cohort 3). Data for cohort 2 (aged 50 to 59 years) were included in the submission for licensure of13vPnC in adults aged 50 years and older, while data for cohort 3 (aged 18 to 49 years) were submitted to support the extension of the adult indication to include individuals aged 18 to 49 years. As 23vPS is not generally recommended in the younger adult age groups, 13vPnC antibody responses in cohorts 2 and 3 were not directly compared to responses after 23vPS, but were compared to antibody responses elicited by 13vPnC in the 60 to 64 year age group (cohort 1). As cohort 1 included a direct comparison to 23vPS, this design allowed for indirect comparison of antibody responses in cohorts 2 and 3 to 23vPS.

2.3.1. Methods – analysis of data submitted

Study Participants

Subjects eligible for the study were healthy (as determined by medical history, physical examination, and clinical judgment of the investigator) male or female adults 60 to 64 years of age (cohort 1), 50 to 59 years of age (cohort 2), or 18 to 49 years of age (cohort 3). Subjects with pre-existing stable disease (as specified in the protocol) were eligible. Subjects had to be able to complete an electronic diary (e-diary) and follow study procedures, and were expected to be available for the duration of the trial.

Subjects were excluded if they had previously been vaccinated with any licensed or experimental pneumococcal vaccine, had a documented Streptococcus pneumoniae infection within the past 5 years, had any other disorder that in the investigator's opinion precluded them from participating in the study, or had any of the other exclusion criteria specified in the protocol.

Treatments

13vPnC contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to a nontoxic mutant form of diphtheria toxin cross-reactive material 197 (CRM197). The vaccine is formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B, per 0.5-mL dose1 Each dose is formulated in 5.0 mM succinate and 0.85% sodium chloride (NaCl) at pH 5.8 with 0.125 mg aluminum as aluminum phosphate (AlPO4) and 0.02% polysorbate 80. The vaccine was to be prefilled into single-dose syringes without preservatives. Study vaccine was administered by intramuscular injection into the deltoid muscle.

Objectives

The primary objective of this study with respect to cohort 3 was:

- To demonstrate that the immune response to the 13 serotypes in the 13vPnC in the 18 to 49 year-old age group is noninferior to the immune response to 13vPnC in the 60 to 64 year-old age group as measured by serotype specific opsonophagocytic assay (OPA) titers 1 month after vaccination.

The secondary objectives of this study with respect to cohort 3 were:

- To demonstrate that the proportion of subjects achieving an OPA titer ≥ lower limit of quantitation (LLOQ) in the 18 to 49 year-old age group is noninferior to the proportion of subjects achieving an OPA titer ≥ LLOQ in the 60 to 64 year-old age group measured 1 month after vaccination.
- To demonstrate that the immune response to the 13 serotypes in the 13vPnC in each subgroup (18-29 years, 30-39 years and 40-49 years) is noninferior to the immune response to 13vPnC in the 60 to 64 year-old age group as measured by serotype-specific OPA titers 1 month after vaccination.
- To evaluate the immune responses 1 month after vaccination with 13vPnC in the 18 to 49 year-old age group compared to the immune responses 1 month after vaccination with 13vPnC in the 60 to 64 year-old age group as measured by serotypespecific fold rise OPA geometric mean titers (GMTs).
- To evaluate the immune responses 1 month after vaccination with 13vPnC in each subgroup (18-29 years, 30-39 years and 40-49 years) compared to the immune responses 1 month after vaccination with 13vPnC in the 60 to 64 year-old age group as measured by serotype-specific fold rise OPA GMTs.

The exploratory objectives of this study with respect to cohort 3 were:

- To demonstrate that 13vPnC in the 18 to 49 year-old age group is as immunogenic as 13vPnC in the 60 to 64 year-old age group as measured by serotype-specific immunoglobulin G (IgG) antibody concentrations 1 month after vaccination in a subset of 100 subjects.
- To demonstrate that 13vPnC in each subgroup (18-29 years, 30-39 years, and 40-49 years) is as immunogenic as 13vPnC in the 60 to 64 year-old age group as measured by serotype-specific IgG antibody concentrations 1 month after vaccination in a subset of 100 subjects in each (sub)group.
- To evaluate the immune responses 1 month after vaccination with 13vPnC in the 18 to 49 year-old age group compared to the immune responses 1 month after vaccination with 13vPnC in the 60 to 64 year-old age group as measured by serotype-specific fold rise IgG GMCs in a subset of 100 subjects in each group.
- To evaluate the immune responses 1 month after vaccination with 13vPnC in each subgroup (18-29 years, 30-39 years, and 40-49 years) compared to the immune responses 1 month after vaccination with 13vPnC in the 60 to 64 year-old age group as measured by serotype-specific fold rise IgG GMCs in a subset of 100 subjects in each (sub)group.
- To assess persistence of antibody by IgG and OPA in the 18-49 year old age group and each of the subgroups (18-29 years, 30-39 years, and 40-49 years) 1 year after vaccination in a subset of 100 subjects per subgroup.

Outcomes / endpoints

Blood samples were collected before study vaccine administration at visit 1 and approximately 1 month after study vaccine administration for cohort 3, with blood samples also collected approximately 1 year after study vaccine administration for subjects in cohort 3 who enrolled under protocol amendment 4.

Functional antibody titers for the 13 pneumococcal serotypes contained in 13vPnC were determined for all subjects for blood samples collected at baseline and 1-month after vaccination using OPA assays. In addition, OPA titers were determined for blood samples collected at 1 year after vaccination for randomly selected subsets of 100 subjects in cohort 1 (100 in each vaccine group) and cohort 3 (100 in each of the 3 age subgroups).

The serotype-specific OPA assays do not use an external reference standard and therefore OPA titers cannot be compared across serotypes. An OPA titer is defined as the interpolated reciprocal serum

dilution that results in complement mediated killing of 50% of the bacteria in each OPA assay. The lowest titer that can be determined in OPA assays is a titer of 1:8 (limit of detection, LOD) and is the same for each serotype-specific OPA assay. However, to quantify functional antibodies in the OPA assays with appropriate precision and accuracy, the LLOQ was determined for each serotype-specific OPA assay during assay validation. The LLOQ for each serotype-specific OPA assay was used as a cut-off to determine serum response for the immunogenicity subjects. OPA titers above the LLOQ were considered accurate and their quantitated values were reported. Titers below the LLOQ or denoted below the level of quantitation were set to 0.5*LOD for analysis. Previously, an OPA serum response was determined using an OPA titer cut-off of 1:8 for all serotype-specific OPA assays in exploratory analyses for the 13vPnC vaccine assessments in support of an infant/young children indication. However, additional more stringent qualification and validation of the improved microcolony OPA (mcOPA) assays used in this study did not support a universal LLOQ of 1:8 for the quantitation of a serum response and thus the following cut-offs (LLOQs) were used for the mcOPA: serotype 1, 1:18; serotype 3, 1:12; serotype 4, 1:21; serotype 5, 1:29; serotype 6A, 1:37; serotype 6B, 1:43; serotype 7F, 1:210; serotype 9V, 1:345; serotype 14, 1:35; serotype 18, 1:31; serotype 19A, 1:18; serotype 19F, 1:48; and serotype 23F, 1:13.

Serum concentrations of serotype-specific polysaccharide IgG binding antibodies were determined for each of the 13 pneumococcal serotypes contained in 13vPnC using a standardized enzyme-linked immunosorbent assay (ELISA). Serotype-specific polysaccharide IgG concentrations were determined for all 3 blood samples (baseline, 1 month after vaccination, and 1 year after vaccination) for the same subsets of 100 subjects selected for the 1-year postvaccination OPA analyses.

Sample size

Sample sizes of 350 evaluable subjects in cohort 3 and cohort 1 would provide at least 90% overall power to declare noninferiority of the response in cohort 3 (based on OPA GMTs) relative to cohort 1 for all 13 pneumococcal antigens using a 2-fold noninferiority criterion (cohort 3/cohort 1). Assuming a dropout rate of no more than 5%, 370 subjects per group should achieve 350 evaluable subjects per group. As part of Amendment 4 to the protocol, the sample size in cohort 3 was increased in order to provide sufficient power for comparisons of age subgroups (18 to 29, 30 to 39, and 40 to 49 years of age) to the 60-64 year age group. A total of 274 evaluable subjects in each of the subgroups would provide approximately 80% power to declare noninferiority between each subgroup and cohort 1 (60 to 64 years of age). Assuming a dropout rate of approximately 9% in each of the subgroups, a total of 900 subjects (300 subjects in each subgroup) were to be enrolled in cohort 3.

Randomisation

Not applicable.

Blinding (masking)

Not applicable.

Statistical methods

For cohort 3, the primary immunologic comparisons were the serotype specific OPA responses to the 13 pneumococcal serotypes contained in 13vPnC measured 1 month after study vaccine administration in cohort 3 (subjects 18 to 49 years of age) relative to the responses among subjects vaccinated with 13vPnC in cohort 1 (subjects 60 to 64 years of age). The primary endpoint for the cohort 3 and cohort 1 comparison was the serotype specific OPA GMTs 1 month after vaccination. The secondary endpoint for the cohort 3 and cohort 1 comparison was the proportion of subjects achieving an OPA titer $\geq$ LLOQ for each serotype 1 month after vaccination.

The serotype specific OPA GMTs and fold rise OPA GMTs for each serotype 1 month after vaccination were the endpoints for the secondary immunologic comparisons between age subgroups of cohort 3 (18 to 29, 30 to 39, and 40 to 49 groups) and cohort 1. Exploratory comparison endpoints were the serotype-specific IgG concentrations measured 1 month after vaccination, as well as the serotype-specific IgG concentrations and OPA titres measured 1 year after vaccination.

2.3.2. Results

Participant flow

Disposition of subjects through the 6-month follow-up contact is summarized for cohort 3 in Table 1. There were 67 subjects that were screened but not assigned to receive vaccine; 64 of these subjects provided written informed consent and 3 of these subjects had not provided written informed consent. In cohort 3, 900 subjects provided written informed consent to participate in the study. One of these subjects gave consent, was assigned to cohort 3, and then withdrew consent prior to vaccination. This subject was then withdrawn from the study.

The majority of subjects assigned to cohort 3 completed the 1-month blood draw (98.1%) and the 6-month contact (94.9%) as shown in Table 1. Similar results were seen for each of the 18 to 29, 30 to 39, and 40 to 49 year-old age subgroups in cohort 3.

Table 1 Disposition of Subjects through 6-Month Follow-up Telephone Contact, Age 18-49 Years (Cohort 3)

	Screened Only		Vaccine Group (as Assigned) Cohort 3 13vPnC		Total	
	n[a]	%	n[a]	%	n[a]	%
Consented[b]	64	100.0	900	100.0	964	107.1
Vaccine assigned[c]	N/A		900	100.0	900	100.0
Vaccine not assigned	67	104.7	0	0.0	67	7.4
Vaccinated	0	0.0	899	99.9	899	99.9
Completed 1-month blood draw	0	0.0	883	98.1	883	98.1
Withdrawn before 1-month blood draw	0	0.0	16	1.8	16	1.8
Reasons for withdrawal						
Lost to follow-up	0	0.0	10	1.1	10	1.1
Subject request	0	0.0	3	0.3	3	0.3
Failed to return	0	0.0	2	0.2	2	0.2
Protocol violation	0	0.0	1	0.1	1	0.1
Completed 6-month contact	0	0.0	854	94.9	854	94.9
Withdrawn after 1-month blood draw visit and before 6-month contact	0	0.0	29	3.2	29	3.2
Reasons for withdrawal						
Lost to follow-up	0	0.0	22	2.4	22	2.4
Subject request	0	0.0	4	0.4	4	0.4
Other	0	0.0	2	0.2	2	0.2
Protocol violation	0	0.0	1	0.1	1	0.1

Subjects 004-002-000142, 004-009-000985 and 004-030-003133 had no consent and no randomization information. Subject 004-004-003366 consented and was assigned to Cohort 3, but not vaccinated.
a. n = Number of subjects in the specified category.
b. The values in this row are used as the denominators for percentages for screened only.
c. The values in this row are used as the denominators for percentages for 13vPnC.

Disposition of subjects at 1 year after vaccination is summarized for cohort 3 in Table 2. Cohort 3 subjects enrolled under protocol amendments 2 and 3 were not scheduled to have a 1-year visit. Of the 854 subjects (94.9% of the subjects assigned to cohort 3) who completed the 6-month contact, 352 subjects (39.1% of the subjects assigned to cohort 3) were not scheduled to have a 1-year visit and 502 subjects (55.8% of the subjects assigned to cohort 3) were scheduled to have a 1-year visit. There were 469 subjects who completed the 1-year blood draw in cohort 3 (52.1% of the 900 subjects assigned to cohort 3, 93.4% of the 502 subjects who completed the 6-month contact and were scheduled to have a 1-year visit) (Table 2). Similar results were seen for the cohort 3 age subgroups.

Table 2 Disposition of Subjects at Year 1, Age 18-49 Years (Cohort 3)

	Vaccine Group (as Assigned) Cohort 3 13vPnC	
	n[a]	%
Vaccine assigned[b]	900	100.0
Completed 6-month contact	854	94.9
Amendment 3 subjects[c]	352	39.1
Withdrawn after 6-month contact and before 1-year blood draw	33	3.7
Reason for withdrawal		
Lost to follow-up	21	2.3
Failed to return	5	0.6
Subject Request	4	0.4
Other	2	0.2
Protocol violation	1	0.1
Completed 1-year blood draw	469	52.1

a. n = Number of subjects in the specified category.
b. The value in this row is used as the denominator for percentages for 13vPnC.
c. Patients in Amendment 3 were not scheduled to have a blood draw at 1 year post vaccination.

Baseline data

The demographic characteristics of the evaluable immunogenicity population are summarized for cohort 3 in Table 3. The demographic characteristics of the evaluable population were similar to those of the safety population for cohort 3.

Table 3 Evaluable Immunogenicity Population - Demographic Characteristics in Subjects Aged 18-49 Years (Cohort 3)

Characteristic	Vaccine Group (as Assigned) Cohort 3 13vPnC N[a]=874 n[b]	%
Sex		
Female	509	58.2
Male	365	41.8
Race		
White	753	86.2
Black or African American	92	10.5
Asian	13	1.5
Other	11	1.3
American Indian or Alaska Native	3	0.3
Native Hawaiian or Other Pacific Islander	2	0.2
Ethnicity		
Non-Hispanic and Non-Latino	798	91.3
Hispanic or Latino	76	8.7
Age groups		
18–29 years	293	33.5
30–39 years	288	33.0
40–49 years	293	33.5
Age at vaccination (in years)		
Mean (SD)	34.0 (9.3)	
Median	34.5	
Min, max	18, 49	

a. N = number of subjects in the vaccine group.
b. n = Number of subjects in the specified category.

Numbers analysed

The evaluable immunogenicity population was the primary immunogenicity analysis population for cohort 1 and cohort 3. The evaluable immunogenicity populations comprised subjects who were eligible for the study, adhered to protocol requirements, had valid and determinate assay results, and had no major protocol violations. Analyses were also performed on data for the all-available immunogenicity population, which included all subjects with at least 1 valid and determinate assay result related to the proposed analysis. The majority of the randomized subjects in cohort 1 (99.8%) met the criterion for inclusion in the all-available immunogenicity population; 1 subject in cohort 1 was excluded for having no assay result, before or after vaccination, for any serotype. All of the subjects assigned to cohort 3 were included in the all-available immunogenicity population.

Summary of Main immunogenicity Results

For cohort 3, the primary immunologic comparisons were the serotype specific OPA responses to the 13 pneumococcal serotypes contained in 13vPnC measured 1 month after study vaccine administration in cohort 3 (subjects 18 to 49 years of age) relative to the responses among subjects vaccinated with 13vPnC in cohort 1 (subjects 60 to 64 years of age). Noninferiority was declared if the lower limit of the 2-sided, 95% CI for the ratio of GMTs (GMT for cohort 3/GMT for cohort 1) was greater than 0.5 (2-fold

criterion). As shown in Table 4, for the evaluable immunogenicity population, this criterion was met for all 13 serotypes.

Table 4 Comparison of Pneumococcal OPA Titer GMTs 1 Month After Vaccination With 13vPnC in Subjects Aged 18-49 Years (Cohort 3) and 60-64 Years (Cohort 1) – Evaluable Immunogenicity Population

	18-49 Years Old (Cohort 3)		60-64 Years Old (Cohort 1)		Group Comparison (Cohort 3/Cohort 1)	
Serotype	n[a]	GMT[b]	n[a]	GMT[b]	Ratio[c]	(95% CI[d])
1	866	353	404	146	2.4	(2.03, 2.87)
3	860	91	394	93	1.0	(0.84, 1.13)
4	849	4747	359	2062	2.3	(1.92, 2.76)
5	836	386	392	199	1.9	(1.55, 2.42)
6A	855	5746	401	2593	2.2	(1.84, 2.67)
6B	865	9813	371	1984	4.9	(4.13, 5.93)
7F	859	3249	394	1120	2.9	(2.41, 3.49)
9V	844	3339	367	1164	2.9	(2.34, 3.52)
14	860	2983	375	612	4.9	(4.01, 5.93)
18C	850	3989	379	1726	2.3	(1.91, 2.79)
19A	855	1580	392	682	2.3	(2.02, 2.66)
19F	841	1533	377	517	3.0	(2.44, 3.60)
23F	851	1570	375	375	4.2	(3.31, 5.31)

a. n = Number of subjects with a determinate OPA titer to the given serotype.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
c. Ratio of GMTs, Cohort 3 to Cohort 1, is calculated by back transforming the mean difference between cohorts on the logarithmic scale.
d. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Cohort 3 – Cohort 1).

The primary comparison demonstrated that the OPA titres after vaccination were non-inferior in subjects 18-49 compared to subjects 60-64, as expected.

Secondary comparisons

For cohort 3, the secondary immunologic comparisons were of the serotype-specific OPA GMTs measured 1 month after vaccination in subjects in age subgroups of cohort 3 (18 to 29, 30 to 39, and 40 to 49 year-old groups) with those in subjects vaccinated with 13vPnC in cohort 1. For all 3 age subgroups of cohort 3, the immune response was noninferior to that for cohort 1 for all 13 serotypes. In addition, the immune response in each of the 3 age subgroups in cohort 3 was statistically significantly higher than the response among subjects receiving 13vPnC in cohort 1 for all serotypes except serotype 3.

OPA GMTs before vaccination, 1 month after vaccination and 1 year after vaccination for cohort 3 and the 13vPnC group in cohort 1 are presented in Table 5 for the evaluable immunogenicity population. Except for serotype 3, the OPA GMTs were higher for cohort 3 than for cohort 1 at 1 month after vaccination and 1 year after vaccination. Among the age subgroups, in general the OPA GMTs were highest for the subjects in the 18 to 29 year-old age subgroup and lowest in the 40 to 49 year-old age subgroup.

Table 5 Pneumococcal OPA GMTs for 13vPnC in Subjects Aged 60-64 Years (Cohort 1) and 18-49 Years (Cohort 3) – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized) Cohort 1 13vPnC			Vaccine Group (as Assigned) Cohort 3 13vPnC		
Serotype	Time Point[a]	n[b]	GMT[c]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])
1	Before vaccination	411	5	(4.9, 5.7)	872	6	(5.2, 5.9)
	1 month after vaccination	404	146	(124.0, 172.9)	866	353	(322.8, 386.9)
	1 year after vaccination	99	38	(27.2, 53.1)	277	82	(68.7, 97.5)
3	Before vaccination	400	7	(6.1, 7.6)	863	7	(6.8, 7.9)
	1 month after vaccination	394	93	(81.1, 106.6)	860	91	(84.2, 98.4)
	1 year after vaccination	97	19	(13.9, 25.3)	277	23	(19.9, 27.1)
4	Before vaccination	354	15	(11.5, 19.9)	730	34	(27.8, 42.2)
	1 month after vaccination	359	2062	(1693.6, 2510.5)	849	4747	(4370.2, 5155.5)
	1 year after vaccination	90	248	(148.9, 414.4)	272	1275	(1068.0, 1521.0)
5	Before vaccination	405	6	(5.3, 6.4)	853	5	(4.4, 4.8)
	1 month after vaccination	392	199	(164.0, 242.3)	836	386	(342.6, 435.8)
	1 year after vaccination	100	35	(23.0, 52.1)	264	73	(57.4, 92.2)
6A	Before vaccination	383	14	(11.0, 17.1)	820	14	(11.8, 15.9)
	1 month after vaccination	401	2593	(2146.7, 3131.1)	855	5746	(5240.7, 6300.4)
	1 year after vaccination	95	733	(480.0, 1120.3)	274	1043	(835.0, 1303.0)
6B	Before vaccination	354	37	(27.4, 49.6)	725	186	(148.5, 234.1)
	1 month after vaccination	371	1984	(1604.0, 2453.6)	865	9813	(9097.8, 10583.5)
	1 year after vaccination	98	445	(267.5, 739.4)	277	2948	(2517.2, 3453.5)
7F	Before vaccination	399	7	(6.2, 8.6)	821	22	(18.8, 26.7)
	1 month after vaccination	394	1120	(907.6, 1382.9)	859	3249	(2994.8, 3523.9)
	1 year after vaccination	98	125	(72.6, 216.9)	276	1179	(1006.7, 1380.2)
9V	Before vaccination	356	22	(16.4, 28.3)	766	70	(56.8, 86.0)
	1 month after vaccination	367	1164	(934.8, 1448.3)	844	3339	(3037.4, 3670.4)
	1 year after vaccination	93	193	(109.0, 340.5)	273	1697	(1436.3, 2005.1)
14	Before vaccination	372	28	(21.6, 36.0)	813	111	(92.4, 134.1)
	1 month after vaccination	375	612	(489.6, 764.2)	860	2983	(2740.5, 3246.6)
	1 year after vaccination	99	240	(149.7, 385.0)	278	1557	(1366.8, 1773.8)
18C	Before vaccination	393	25	(19.5, 31.5)	824	34	(28.2, 40.8)
	1 month after vaccination	379	1726	(1429.7, 2082.9)	850	3989	(3629.4, 4383.8)
	1 year after vaccination	93	477	(304.4, 748.5)	270	1367	(1142.1, 1635.4)
19A	Before vaccination	385	21	(17.9, 25.4)	840	49	(42.4, 56.1)
	1 month after vaccination	392	682	(596.5, 779.9)	855	1580	(1471.4, 1696.3)
	1 year after vaccination	92	138	(101.1, 189.7)	274	596	(521.5, 682.2)
19F	Before vaccination	383	17	(13.7, 20.7)	822	30	(25.6, 35.2)
	1 month after vaccination	377	517	(420.8, 635.3)	841	1533	(1397.3, 1680.9)
	1 year after vaccination	94	102	(67.2, 153.6)	269	616	(525.8, 721.3)
23F	Before vaccination	382	8	(7.2, 9.9)	829	9	(7.8, 9.9)
	1 month after vaccination	375	375	(297.2, 472.6)	851	1570	(1392.8, 1770.2)
	1 year after vaccination	94	79	(47.7, 132.2)	271	394	(304.0, 511.9)

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

In the evaluable population, GMFRs from before vaccination to 1 month after vaccination ranged from 12.3 (serotype 3) to 407.6 (serotype 6A) in cohort 3, and from 13.5 (serotype 3) to 184.7 (serotype 6A) in cohort 1. Comparisons of OPA GMFRs at 1 month after vaccination between cohort 3 and cohort 1 were presented. Although not pre-specified, the same criterion that was used for the demonstration of a statistically significantly higher response of other geometric mean comparisons (lower limit of the 2-sided, 95% CI for the ratio >1) was used for the comparisons of OPA GMFRs. The OPA GMFRs in cohort 3 were statistically significantly higher than the OPA GMFRs among subjects receiving 13vPnC in cohort 1 for 6 of 13 serotypes (serotypes 1,5, 6A, 18C, 19F, and 23F) in the evaluable population. In the evaluable population, GMFRs from before vaccination to 1 year after vaccination ranged from 3.3 (serotype 3) to 86.5 (serotype 6A) in cohort 3, and from 3.1 (serotype 3) to 39.9 (serotype 6A) in cohort 1.

The proportion of subjects in cohort 3 and cohort 1 achieving an OPA titer ≥ LLOQ after vaccination are presented in Table 6 for the evaluable immunogenicity population. Although the statistical analysis plan (SAP) and the clinical study protocol did not specify criteria for statistical significance, using the same criterion as in other 13vPnC studies, the immune response in the cohort 3 was statistically significantly higher (lower limit of the 95% CI for the difference in proportions >0) than in cohort 1 for all serotypes except serotype 3.

Table 6 Comparison of Subjects Aged 18-49 Years (Cohort 3) and 60-64 Years (Cohort 1) Achieving an OPA Titer ≥ LLOQ 1 Month After Vaccination With 13vPnC – Evaluable Immunogenicity Population

	Vaccine Group (as Assigned/Randomized) – 13vPnC									
	18-49 Years Old (Cohort 3)				60-64 Years Old (Cohort 1)					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
1	866	845	97.6	(96.3, 98.5)	404	365	90.3	(87.0, 93.0)	7.2	(4.3, 10.6)
3	860	815	94.8	(93.1, 96.2)	394	363	92.1	(89.0, 94.6)	2.6	(-0.3, 5.9)
4	849	842	99.2	(98.3, 99.7)	359	341	95.0	(92.2, 97.0)	4.2	(2.1, 6.9)
5	836	770	92.1	(90.1, 93.8)	392	341	87.0	(83.3, 90.2)	5.1	(1.4, 9.1)
6A	855	850	99.4	(98.6, 99.8)	401	384	95.8	(93.3, 97.5)	3.7	(1.7, 6.1)
6B	865	864	99.9	(99.4, 100.0)	371	347	93.5	(90.5, 95.8)	6.4	(4.1, 9.3)
7F	859	847	98.6	(97.6, 99.3)	394	356	90.4	(87.0, 93.1)	8.2	(5.4, 11.6)
9V	844	825	97.7	(96.5, 98.6)	367	330	89.9	(86.4, 92.8)	7.8	(4.8, 11.4)
14	860	851	99.0	(98.0, 99.5)	375	329	87.7	(84.0, 90.9)	11.2	(8.0, 14.9)
18C	850	838	98.6	(97.5, 99.3)	379	362	95.5	(92.9, 97.4)	3.1	(0.9, 5.7)
19A	855	854	99.9	(99.4, 100.0)	392	386	98.5	(96.7, 99.4)	1.4	(0.3, 3.1)
19F	841	825	98.1	(96.9, 98.9)	377	338	89.7	(86.1, 92.5)	8.4	(5.4, 12.0)
23F	851	809	95.1	(93.4, 96.4)	375	317	84.5	(80.5, 88.0)	10.5	(6.8, 14.7)

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 (Clopper and Pearson) based upon the observed proportion of subjects.
d. Difference (Cohort 3 – Cohort 1) in proportions, expressed as a percentage.
e. Exact 2-sided confidence interval (based on Chan and Zhang) for the difference in proportions, Cohort 3 –Cohort 1, expressed as a percentage.

IgG responses

Pneumococcal serotype-specific IgG GMCs measured 1 month after vaccination were compared between the 13vPnC group in cohort 1 and cohort 3. For the evaluable immunogenicity population, cohort 3 was noninferior (lower limit of the 2-sided, 95% CI for the ratio of GMTs >0.5) to cohort 1 for all 13 serotypes (Table 7). Although a superiority analysis comparing the immune responses in cohorts 1 and 3 was not pre-specified, applying the superiority criterion that was used in the analyses comparing responses between the vaccine groups in cohort 1 (lower limit of the 2-sided, 95% CI for the ratio of GMTs >1) demonstrates that the immune response to 13vPnC in cohort 3 was significantly higher than the response to 13vPnC in cohort 1 for 8 serotypes: 1, 4, 6A, 6B, 14, 19A, 19F, and 23F.

Table 7 Comparison of Pneumococcal IgG GMCs (µg/mL) 1 Month After Vaccination With 13vPnC in a Subset of Subjects Aged 18-49 Years (Cohort 3) and 60-64 Years (Cohort 1) – Evaluable Immunogenicity Population

	18-49 Years Old (Cohort 3)		60-64 Years Old (Cohort 1)		Group Comparison (Cohort 3/Cohort 1)	
Serotype	n[a]	GMC[b]	n[a]	GMC[b]	Ratio[c]	(95% CI[d])
1	296	6.30	99	4.42	1.43	(1.04, 1.96)
3	296	1.77	98	1.65	1.08	(0.84, 1.37)
4	295	4.05	98	2.64	1.53	(1.15, 2.05)
5	296	6.86	99	6.04	1.14	(0.85, 1.52)
6A	293	11.28	99	7.16	1.57	(1.20, 2.06)
6B	293	16.78	98	7.87	2.13	(1.57, 2.90)
7F	296	8.92	99	10.07	0.89	(0.68, 1.16)
9V	293	6.36	98	6.32	1.01	(0.78, 1.30)
14	294	20.05	99	7.09	2.83	(2.04, 3.92)
18C	295	9.74	97	12.04	0.81	(0.60, 1.08)
19A	296	18.93	99	12.30	1.54	(1.21, 1.96)
19F	296	10.92	99	4.57	2.39	(1.75, 3.26)
23F	295	14.10	98	6.98	2.02	(1.48, 2.75)

a. n = Number of subjects with a determinate IgG concentration to the given serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Ratio of GMCs, Cohort 3 to Cohort 1, is calculated by back transforming the mean difference between cohorts on the logarithmic scale.
d. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Cohort 3 – Cohort 1).

IgG GMCs before vaccination, 1 month after vaccination and 1 year after vaccination for cohort 3 and the 13vPnC group in cohort 1 are presented in Table 8 for the evaluable immunogenicity population. In general, the IgG GMCs for cohort 3 were similar to or higher than those for cohort 1 at 1 month after vaccination and 1 year after vaccination. Among the age subgroups, in general the IgG GMCs were highest for the subjects in the 18 to 29 year-old age subgroup and lowest in the 40 to 49 year-old age subgroup.

Table 8 Pneumococcal IgG Antibody GMCs (µg/mL) for 13vPnC in Subjects Aged 60-64 Years (Cohort 1) and 18-49 Years (Cohort 3) – Evaluable Immunogenicity Population

		Vaccine Group (as Randomized) Cohort 1 13vPnC			Vaccine Group (as Assigned) Cohort 3 13vPnC		
Serotype	Time Point[a]	n[b]	GMC[c]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])
1	Before vaccination	93	0.39	(0.30, 0.50)	287	0.62	(0.54, 0.71)
	1 month after vaccination	99	4.42	(3.24, 6.02)	296	6.30	(5.41, 7.33)
	1 year after vaccination	100	2.08	(1.57, 2.77)	272	2.29	(1.94, 2.71)
3	Before vaccination	97	0.40	(0.31, 0.52)	284	0.65	(0.57, 0.75)
	1 month after vaccination	98	1.65	(1.28, 2.12)	296	1.77	(1.58, 1.99)
	1 year after vaccination	100	0.74	(0.57, 0.96)	272	0.95	(0.84, 1.08)
4	Before vaccination	96	0.20	(0.15, 0.27)	273	0.29	(0.25, 0.33)
	1 month after vaccination	98	2.64	(1.95, 3.58)	295	4.05	(3.54, 4.63)
	1 year after vaccination	100	1.12	(0.83, 1.50)	273	1.40	(1.22, 1.61)
5	Before vaccination	97	1.80	(1.51, 2.14)	296	2.16	(1.96, 2.37)
	1 month after vaccination	99	6.04	(4.54, 8.05)	296	6.86	(5.97, 7.88)
	1 year after vaccination	100	3.23	(2.55, 4.11)	274	4.12	(3.68, 4.62)
6A	Before vaccination	97	1.72	(1.45, 2.04)	296	2.37	(2.15, 2.62)
	1 month after vaccination	99	7.16	(5.80, 8.84)	293	11.28	(9.79, 12.98)
	1 year after vaccination	100	3.95	(3.20, 4.87)	273	5.47	(4.81, 6.23)
6B	Before vaccination	96	1.80	(1.47, 2.21)	295	2.49	(2.22, 2.78)
	1 month after vaccination	98	7.87	(6.06, 10.21)	293	16.78	(14.37, 19.60)
	1 year after vaccination	100	4.13	(3.27, 5.23)	273	7.63	(6.62, 8.79)
7F	Before vaccination	96	0.77	(0.61, 0.98)	293	0.85	(0.74, 0.97)
	1 month after vaccination	99	10.07	(7.59, 13.35)	296	8.92	(7.90, 10.08)
	1 year after vaccination	100	3.71	(2.82, 4.88)	274	3.62	(3.19, 4.10)
9V	Before vaccination	97	0.95	(0.79, 1.14)	295	1.26	(1.14, 1.39)
	1 month after vaccination	98	6.32	(5.00, 7.99)	293	6.36	(5.60, 7.22)
	1 year after vaccination	100	2.80	(2.27, 3.47)	272	3.02	(2.70, 3.39)
14	Before vaccination	96	1.68	(1.25, 2.26)	295	1.54	(1.28, 1.84)
	1 month after vaccination	99	7.09	(5.24, 9.59)	294	20.05	(17.08, 23.53)
	1 year after vaccination	100	4.48	(3.40, 5.89)	273	10.88	(9.15, 12.93)
18C	Before vaccination	95	0.89	(0.71, 1.13)	295	0.69	(0.60, 0.79)
	1 month after vaccination	97	12.04	(8.91, 16.28)	295	9.74	(8.50, 11.16)
	1 year after vaccination	99	4.90	(3.73, 6.45)	273	3.98	(3.43, 4.61)
19A	Before vaccination	96	2.77	(2.29, 3.35)	296	4.12	(3.73, 4.55)
	1 month after vaccination	99	12.30	(9.93, 15.22)	296	18.93	(16.78, 21.37)
	1 year after vaccination	100	6.02	(4.88, 7.44)	274	9.36	(8.29, 10.57)
19F	Before vaccination	94	1.17	(0.95, 1.45)	289	1.81	(1.59, 2.07)
	1 month after vaccination	99	4.57	(3.44, 6.06)	296	10.92	(9.36, 12.74)
	1 year after vaccination	100	2.48	(1.96, 3.13)	274	5.38	(4.62, 6.27)
23F	Before vaccination	94	1.05	(0.82, 1.33)	296	1.55	(1.38, 1.73)
	1 month after vaccination	98	6.98	(5.19, 9.39)	295	14.10	(12.15, 16.35)
	1 year after vaccination	100	2.80	(2.14, 3.67)	274	5.42	(4.66, 6.31)

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

Immunogenicity Conclusions

The immune response to the 13 serotypes in 13vPnC in the 18 to 49 year-old age group (cohort 3) was noninferior to the immune response to 13vPnC in the 60 to 64 year-old age group (cohort 1) as measured by serotype-specific OPA GMTs 1 month after vaccination (primary objective) for the evaluable immunogenicity population. In addition, the immune response to the 13 serotypes in the 13vPnC in each age subgroup (18-29 years, 30-39 years and 40-49 years) in cohort 3 was noninferior to the immune response to 13vPnC in cohort 1 as measured by serotype-specific OPA GMTs 1 month after vaccination (secondary objective).

In cohort 3, and each of the age subgroups in cohort 3, the immune response as measured by serotype-specific OPA GMTs 1 month after vaccination was statistically significantly higher than the response among subjects receiving 13vPnC in cohort 1 for all serotypes except serotype 3.

The MAH has provided an updated discussion on serotype 3 risk of vaccine failures. This issue is also part of a follow-up measure (MEA47) as well as under continuous surveillance in the PSURs. The CHMP considered that the available data are not sufficient to conclude on a lack of efficacy or effectiveness of serotype 3, although some concerning results are available. Taking into account that this issue is not age specific, it was considered appropriate to continue its monitoring and assessment within the ongoing procedures.

Among the age subgroups, in general the OPA GMTs were highest for the subjects in the 18 to 29 year-old age subgroup and lowest in the 40 to 49 year-old age subgroup at 1 month after vaccination and 1 year after vaccination, indicating a lower immune response with increasing age.

The proportion of subjects achieving a serotype-specific OPA titer ≥ LLOQ in cohort 3 was noninferior to the proportion of subjects achieving an OPA titer ≥ LLOQ in cohort 1 for all 13 serotypes at 1 month after vaccination (secondary objective).

The immune response to the 13 serotypes in 13vPnC in cohort 3 was noninferior to the immune response to 13vPnC in cohort 1 as measured by serotype-specific IgG GMCs 1 month after vaccination (exploratory objective) for the evaluable immunogenicity population. Among the age subgroups, in general the IgG GMCs were highest for the subjects in the 18 to 29 year-old age subgroup and lowest in the 40 to 49 year-old age subgroup, indicating a lower immune response with increasing age.

OPA GMTs and IgG GMCs increased from prevaccination to 1 month after vaccination and then decreased from 1 month to 1 year after vaccination but remained higher 1 year after vaccination than at prevaccination for cohort 3, for each of the cohort 3 age subgroups (18-29 years, 30-39 years, and 40-49 years) and cohort 1.

In conclusion, the immune responses to vaccination with Prevenar 13 in younger adults have been convincingly shown to be superior to those of elderly subjects, as expected. There is no serological correlate to protection for pneumococcal vaccines in adults, but opsonising antibodies are considered to mediate protection against invasive disease. Therefore a high opsonising antibody titre is thought to be protective. The OPA GMTs indicated a higher level of protection in the younger adults compared to 60-64 year old subjects.

2.3.3. Discussion

Design and conduct of clinical studies

In an earlier procedure, OPA responses to Prevenar 13 were compared to OPA responses to 23vPS vaccine in subjects 60 years of age and older, which was considered relevant as the 23vPS vaccine was

considered efficacious in this population. The immune responses to Prevenar 13 were clearly non-inferior to the responses to 23vPS vaccine in 60-64 year old subjects, and superior responses were seen for 8 serotypes. Based on the outcome of that comparison Prevenar 13 was approved for use in adults 50 years of age and older. Therefore, the comparison of immune responses to the age group 60-64 years (cohort 1) is considered relevant.

The choice of primary endpoint is also considered relevant, i.e. OPA GMTs, while the secondary comparisons, OPA response rate (% of subjects with titres above LLOQ) and ELISA IgG are also considered important.

Efficacy data and additional analyses

The immune responses seen after vaccination with Prevenar 13 in adults 18-49 years of age are very likely to be protective against IPD, and possibly also against non-invasive disease.

There are no specific recommendations to vaccinate healthy adults with pneumococcal vaccines, and the medical need is considered small. However, for adults belonging to risk groups for pneumococcal infection Prevenar 13 could provide benefit as a complement to the 23vPS vaccine.

The responses to the LoQ have clarified that the use in adults 18-49 years is intended primarily for risk groups. There are no data on specific risk groups included in the current variation, but another ongoing variation aims at including data on risk groups in section 4.8 and 5.1 of the SPC, i.e. premature children, children with sickle cell disease and HIV infected adults. Thus, some data are available, although it is currently unknown to what extent the SmPC will be updated as the variation is still ongoing.

Conclusions on clinical efficacy

The immune responses seen after vaccination with Prevenar 13 are likely to be protective, and the pre-vaccination data indicate that more than half of the subjects could be unprotected from 9-10 of the 13 Prevenar 13 serotypes. Overall, the benefit of vaccinating healthy adults 18-49 years of age is considered limited, but the benefit is considered potentially greater in subjects belonging to risk groups in this age group.

2.4. Clinical Safety aspects

2.4.1. Methods – analysis of data submitted

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.

At study entry, all subjects received 1 dose of open-label 13vPnC administered intramuscularly into the deltoid muscle of either arm. Subjects attended a follow-up visit approximately 1 month after vaccination and were contacted by telephone for collection of additional follow-up safety information approximately 6 months after vaccination.

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 in an electronic diary for 14 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.

Although this variation application is focussed only on cohort 3 from this study, safety results from cohorts 1 and 2 are shown below for the sake of comparison.

2.4.2. Results

Patient exposure

A total of 899 subjects (300 in the 18- to 29-year age group, 298 in the 30- to 39-year age group, and 301 in the 40- to 49-year age group) in cohort 3 were vaccinated. All vaccinated subjects were within the protocol-specified age range at the time of vaccination.

Demographic characteristics for all subjects who received at least 1 dose of study vaccine (safety population) are summarised for cohort 3 in Table 9.

Table 9 Demographic Characteristics in Subjects Aged 18-49 Years (Cohort 3) – Study 6115A1-004 Safety Population

	Vaccine Group (as Administered) Cohort 3 13vPnC N[a]=899	
Characteristic	n[b]	%
Sex		
Female	523	58.2
Male	376	41.8
Race		
White	772	85.9
Black or African American	96	10.7
Asian	13	1.4
Other	13	1.4
American Indian or Alaska Native	3	0.3
Native Hawaiian or Other Pacific Islander	2	0.2
Ethnicity		
Non-Hispanic and Non-Latino	820	91.2
Hispanic or Latino	79	8.8
Age groups		
18–29 years	300	33.4
30–39 years	298	33.1
40–49 years	301	33.5
Age at vaccination (in years)		
Mean (SD)	34.0 (9.3)	
Median	34.0	
Min, max	18, 49	

a. N = number of subjects in the vaccine group.
b. n = Number of subjects in the specified category

Adverse events

Local Reactions

At least 1 local reaction was reported within 14 days after vaccine administration for 82.2% of subjects in cohort 1, 89.6% of subjects in cohort 2, and 97.3% of subjects in cohort 3 (Table 10). The most frequent local reaction was pain, which occurred in 80.1% of subjects in cohort 1, 88.8% of subjects in cohort 2, and 96.7% of subjects in cohort 3. The percentage of subjects reporting severe pain was higher in cohort 3 (16.0%) than in cohort 1 (1.7%) and cohort 2 (3.6%). Most reports of redness, swelling, or limitation of arm movement were of mild or moderate severity. Severe redness and severe swelling were each reported in <2.8% of subjects in cohorts 1, 2, and 3. The percentage of subjects reporting severe limitation of arm movement was much higher in cohort 3 (15.6%) than in cohort 1 (1.7%) and cohort 2 (2.9%).

Table 10 Subjects Reporting Local Reactions Within 14 Days After Vaccination With 13vPnC, Ages 60-64 Years (Cohort 1), 50-59 Years (Cohort 2), and 18-49 Years (Cohort 3) – Study 6115A1-004 Safety Population

	Vaccine Group (as Administered) 13vPnC											
	60-64 Years Old (Cohort 1)				50-59 Years Old (Cohort 2)				18-49 Years Old (Cohort 3)			
Local Reaction	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
Redness[d]												
Any	193	39	20.2	(14.8, 26.6)	152	24	15.8	(10.4, 22.6)	266	81	30.5	(25.0, 36.4)
Mild	189	30	15.9	(11.0, 21.9)	151	23	15.2	(9.9, 22.0)	258	68	26.4	(21.1, 32.2)
Moderate	185	16	8.6	(5.0, 13.7)	140	7	5.0	(2.0, 10.0)	227	27	11.9	(8.0, 16.8)
Severe	178	3	1.7	(0.3, 4.8)	137	1	0.7	(0.0, 4.0)	211	6	2.8	(1.1, 6.1)
Swelling[d]												
Any	197	38	19.3	(14.0, 25.5)	161	35	21.7	(15.6, 28.9)	302	119	39.4	(33.9, 45.2)
Mild	192	30	15.6	(10.8, 21.5)	160	33	20.6	(14.6, 27.7)	293	109	37.2	(31.7, 43.0)
Moderate	184	15	8.2	(4.6, 13.1)	138	6	4.3	(1.6, 9.2)	238	36	15.1	(10.8, 20.3)
Severe	178	1	0.6	(0.0, 3.1)	136	0	0.0	(0.0, 2.7)	209	3	1.4	(0.3, 4.1)
Pain[e]												
Any	331	265	80.1	(75.3, 84.2)	322	286	88.8	(84.9, 92.0)	787	761	96.7	(95.2, 97.8)
Mild	323	254	78.6	(73.8, 83.0)	306	263	85.9	(81.5, 89.6)	721	672	93.2	(91.1, 94.9)
Moderate	206	48	23.3	(17.7, 29.7)	190	75	39.5	(32.5, 46.8)	467	360	77.1	(73.0, 80.8)
Severe	178	3	1.7	(0.3, 4.8)	139	5	3.6	(1.2, 8.2)	238	38	16.0	(11.6, 21.3)
Limitation of arm movement[f]												
Any	214	61	28.5	(22.6, 35.1)	194	79	40.7	(33.7, 48.0)	499	375	75.2	(71.1, 78.9)
Mild	212	57	26.9	(21.0, 33.4)	189	73	38.6	(31.6, 46.0)	466	333	71.5	(67.1, 75.5)
Moderate	179	4	2.2	(0.6, 5.6)	140	4	2.9	(0.8, 7.2)	238	44	18.5	(13.8, 24.0)
Severe	180	3	1.7	(0.3, 4.8)	139	4	2.9	(0.8, 7.2)	237	37	15.6	(11.2, 20.9)
Any local reaction[g]	337	277	82.2	(77.7, 86.1)	327	293	89.6	(85.8, 92.7)	801	779	97.3	(95.9, 98.3)

a. N = number of subjects with known values.
b. n = Number of subjects with the given characteristic.
c. Exact 2-sided confidence interval (Clopper & Pearson) based upon the observed proportion of subjects.
d. Mild is 2.5 to 5.0 cm, moderate is 5.1 to 10.0 cm, and severe is >10.0 cm. e. Mild = awareness of symptom but easily tolerated, moderate = discomfort enough to cause interference with usual activity, and severe = incapacitating with inability to do usual activity.
f. Mild = some limitation of arm movement, moderate = unable to move arm above head but able to move arm above shoulder, and severe = unable to move arm above shoulder.
g. Any local reaction = any pain, any swelling, any redness, or any limitation of arm movement.

For cohort 3, at least 1 local reaction was reported within 14 days after vaccine administration for 99.6% of 18- to 29-year-old subjects, 97.4% of 30- to 39-year-old subjects, and 94.6% of 40- to 49-year-old subjects (Table 11). The percentages of subjects with any redness, any swelling, and any limitation of arm movement were highest in 18- to 29-year-old subjects and lowest in 40- to 49-year-old subjects. High, and similar, percentages of subjects reported any pain in the 3 age subgroups. However, the percentage of subjects with severe pain was highest in 18- to 29-year-old subjects and lowest in 40- to 49-year-old subjects. Although the frequency of severe pain and limitation of arm movement was

significantly higher in younger adults in cohort 3 than in older adults in the other 2 cohorts, only 4 younger adults had unscheduled doctor visits due to pain at the injection site and/or limitation of arm movement. In all 4 cases the symptoms were mild or moderate. There was no unscheduled doctor visit for severe pain or limitation of arm movement.

Table 11 Subjects Reporting Local Reactions Within 14 Days After Vaccination With 13vPnC by Age Groups, Ages 18-29 Years, 30-39 Years, and 40-49 Years (Cohort 3) – Study 6115A1-004 Safety Population

	Age Group (Years)											
	18-29 Years Old				30-39 Years Old				40-49 Years Old			
Local Reaction	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
Redness[d]												
Any	62	31	50.0	(37.0, 63.0)	104	29	27.9	(19.5, 37.5)	100	21	21.0	(13.5, 30.3)
Mild	60	29	48.3	(35.2, 61.6)	101	24	23.8	(15.9, 33.3)	97	15	15.5	(8.9, 24.2)
Moderate	41	5	12.2	(4.1, 26.2)	90	12	13.3	(7.1, 22.1)	96	10	10.4	(5.1, 18.3)
Severe	38	1	2.6	(0.1, 13.8)	82	3	3.7	(0.8, 10.3)	91	2	2.2	(0.3, 7.7)
Swelling[d]												
Any	73	41	56.2	(44.1, 67.8)	118	48	40.7	(31.7, 50.1)	111	30	27.0	(19.0, 36.3)
Mild	68	36	52.9	(40.4, 65.2)	116	46	39.7	(30.7, 49.2)	109	27	24.8	(17.0, 34.0)
Moderate	51	15	29.4	(17.5, 43.8)	92	14	15.2	(8.6, 24.2)	95	7	7.4	(3.0, 14.6)
Severe	38	1	2.6	(0.1, 13.8)	81	1	1.2	(0.0, 6.7)	90	1	1.1	(0.0, 6.0)
Pain[e]												
Any	268	267	99.6	(97.9, 100.0)	265	257	97.0	(94.1, 98.7)	254	237	93.3	(89.5, 96.1)
Mild	242	238	98.3	(95.8, 99.5)	245	226	92.2	(88.2, 95.3)	234	208	88.9	(84.1, 92.6)
Moderate	150	135	90.0	(84.0, 94.3)	164	126	76.8	(69.6, 83.1)	153	99	64.7	(56.6, 72.3)
Severe	48	12	25.0	(13.6, 39.6)	93	17	18.3	(11.0, 27.6)	97	9	9.3	(4.3, 16.9)
Limitation of arm movement[f]												
Any	187	170	90.9	(85.8, 94.6)	165	119	72.1	(64.6, 78.8)	147	86	58.5	(50.1, 66.6)
Mild	173	153	88.4	(82.7, 92.8)	151	103	68.2	(60.1, 75.5)	142	77	54.2	(45.7, 62.6)
Moderate	56	23	41.1	(28.1, 55.0)	89	14	15.7	(8.9, 25.0)	93	7	7.5	(3.1, 14.9)
Severe	50	15	30.0	(17.9, 44.6)	93	17	18.3	(11.0, 27.6)	94	5	5.3	(1.7, 12.0)
Any local reaction[g]	274	273	99.6	(98.0, 100.0)	269	262	97.4	(94.7, 98.9)	258	244	94.6	(91.1, 97.0)

a. N = number of subjects with known values.
b. n = Number of subjects with the given characteristic.
c. Exact 2-sided confidence interval (Clopper & Pearson) based upon the observed proportion of subjects.
d. Mild is 2.5 to 5.0 cm, moderate is 5.1 to 10.0 cm, and severe is >10.0 cm.
e. Mild = awareness of symptom but easily tolerated, moderate = discomfort enough to cause interference with usual activity, and severe = incapacitating with inability to do usual activity.
f. Mild = some limitation of arm movement, moderate = unable to move arm above head but able to move arm above shoulder, and severe = unable to move arm above shoulder.
g. Any local reaction = any pain, any swelling, any redness, or any limitation of arm movement

The mean durations of local reactions were similar for cohorts 1, 2, and 3, and did not exceed 3.0 days. The mean durations of local reactions were similar for the age subgroups in cohort 3, and did not exceed 2.8 days. Most local reactions occurred during the first 4 days after vaccination and then tapered off in cohorts 1, 2, and 3. In cohort 3, the highest values for any local reaction, any pain, any limitation of arm movement, and any swelling occurred on day 2. The percentages of subjects with any local reaction, any pain, any limitation of arm movement, any redness and any swelling were higher in cohort 3 than in cohort 1 or cohort 2 during the first 4 days after vaccination.

Most local reactions occurred during the first 4 days after vaccination and then tapered off in each of the 3 age subgroups in cohort 3. Beginning on day 2, the percentages of subjects with any local reaction, any pain, any limitation of arm movement, any redness and any swelling were lower in 40- to 49-year-old subjects than in 18- to 29-year-old subjects or 30- to 39-year-old subjects.

Systemic reactions

At least one systemic event occurring within 14 days after vaccine administration was reported by the majority of subjects who received 13vPnC in cohort 3 (approximately 96%), cohort 2 (approximately

84%), and cohort 1 (approximately 83%; Table 12). The 3 most frequently reported systemic events in cohort 3 (new generalized muscle pain, headache, and fatigue) were reported by higher percentages of subjects in cohort 3 (82.0%, 81.4%, and 80.5%) than in cohort 1 (56.2%, 54.0%, and 63.2%) or cohort 2 (61.8%, 65.9%, and 63.3%). In general, the percentages of subjects with individual systemic events were reported by higher percentages of subjects in cohort 3 than in cohort 1 or cohort 2.

Table 12 Subjects Reporting Systemic Events Within 14 Days After Vaccination With 13vPnC, Ages 60-64 Years (Cohort 1), 50-59 Years (Cohort 2), and 18-49 Years (Cohort 3) – Study 6115A1-004 Safety Population

	Vaccine Group (as Administered) 13vPnC											
	60-64 Years Old (Cohort 1)				50-59 Years Old (Cohort 2)				18-49 Years Old (Cohort 3)			
Systemic Event	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
Fever												
Any (≥38°C)	181	14	7.7	(4.3, 12.6)	137	2	1.5	(0.2, 5.2)	221	16	7.2	(4.2, 11.5)
Mild (≥38°C but <38.5°C)	179	7	3.9	(1.6, 7.9)	137	2	1.5	(0.2, 5.2)	214	9	4.2	(1.9, 7.8)
Moderate (≥38.5°C but <39°C)	178	1	0.6	(0.0, 3.1)	136	0	0.0	(0.0, 2.7)	211	4	1.9	(0.5, 4.8)
Severe (≥39°C but ≤40°C)	177	0	0.0	(0.0, 2.1)	136	0	0.0	(0.0, 2.7)	210	3	1.4	(0.3, 4.1)
Potentially life threatening (>40°C)	180	8	4.4	(1.9, 8.6)	136	0	0.0	(0.0, 2.7)	208	1	0.5	(0.0, 2.6)
Fatigue	277	175	63.2	(57.2, 68.9)	248	157	63.3	(57.0, 69.3)	554	446	80.5	(77.0, 83.7)
Headache	252	136	54.0	(47.6, 60.2)	246	162	65.9	(59.6, 71.8)	527	429	81.4	(77.8, 84.6)
Chills	204	48	23.5	(17.9, 30.0)	158	31	19.6	(13.7, 26.7)	286	109	38.1	(32.5, 44.0)
Rash	194	32	16.5	(11.6, 22.5)	148	21	14.2	(9.0, 20.9)	249	53	21.3	(16.4, 26.9)
Vomiting	180	7	3.9	(1.6, 7.8)	144	10	6.9	(3.4, 12.4)	240	36	15.0	(10.7, 20.2)
Decreased appetite	202	43	21.3	(15.9, 27.6)	166	42	25.3	(18.9, 32.6)	363	202	55.6	(50.4, 60.8)
New generalized muscle pain	249	140	56.2	(49.8, 62.5)	238	147	61.8	(55.3, 68.0)	561	460	82.0	(78.6, 85.1)
Aggravated generalized muscle pain	215	70	32.6	(26.3, 39.3)	188	75	39.9	(32.8, 47.3)	370	207	55.9	(50.7, 61.1)
New generalized joint pain	197	48	24.4	(18.5, 31.0)	165	52	31.5	(24.5, 39.2)	307	128	41.7	(36.1, 47.4)
Aggravated generalized joint pain	205	51	24.9	(19.1, 31.4)	168	43	25.6	(19.2, 32.9)	269	77	28.6	(23.3, 34.4)
Any systemic event[d]	327	270	82.6	(78.0, 86.5)	314	265	84.4	(79.9, 88.2)	752	718	95.5	(93.7, 96.8)

a. N = number of subjects with known values.
b. n = Number of subjects with the given characteristic.
c. Exact 2-sided confidence interval (Clopper & Pearson) based upon the observed proportion of subjects.
d. Any systemic event = any fever ≥38°C, any fatigue, any headache, any chills, any rash, any vomiting, any decreased appetite, any new or aggravated generalized muscle pain, and any new or aggravated joint pain.

At least one systemic event occurring within 14 days after vaccine administration was reported by the majority of subjects in the 18- to 29-year-old (approximately 99%), 30- to 39- year-old (approximately 94%), and 40- to 49-year-old (approximately 93%) age subgroups in cohort 3 (Table 13). In general, the percentages of subjects with individual systemic events were highest in the 18- to 29-year-old age subgroup.

Table 13 Subjects Reporting Systemic Events Within 14 Days After Vaccination With 13vPnC by Age Groups, Ages 18-29 Years, 30-39 Years, and 40-49 Years (Cohort 3) – Study 6115A1-004 Safety Population

	Age Group (Years)											
	18-29 Years Old				30-39 Years Old				40-49 Years Old			
Systemic Event	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
Fever												
Any (≥38°C)	43	6	14.0	(5.3, 27.9)	87	8	9.2	(4.1, 17.3)	91	2	2.2	(0.3, 7.7)
Mild (≥38°C but <38.5°C)	41	4	9.8	(2.7, 23.1)	82	3	3.7	(0.8, 10.3)	91	2	2.2	(0.3, 7.7)
Moderate (≥38.5°C but <39°C)	38	1	2.6	(0.1, 13.8)	83	3	3.6	(0.8, 10.2)	90	0	0.0	(0.0, 4.0)
Severe (≥39°C but ≤40°C)	38	1	2.6	(0.1, 13.8)	82	2	2.4	(0.3, 8.5)	90	0	0.0	(0.0, 4.0)
Potentially life threatening (>40°C)	37	0	0.0	(0.0, 9.5)	81	1	1.2	(0.0, 6.7)	90	0	0.0	(0.0, 4.0)
Fatigue	177	161	91.0	(85.7, 94.7)	186	150	80.6	(74.2, 86.1)	191	135	70.7	(63.7, 77.0)
Headache	162	146	90.1	(84.5, 94.2)	174	139	79.9	(73.2, 85.6)	191	144	75.4	(68.7, 81.3)
Chills	73	40	54.8	(42.7, 66.5)	104	43	41.3	(31.8, 51.4)	109	26	23.9	(16.2, 33.0)
Rash	47	10	21.3	(10.7, 35.7)	98	25	25.5	(17.2, 35.3)	104	18	17.3	(10.6, 26.0)
Vomiting	54	17	31.5	(19.5, 45.6)	88	8	9.1	(4.0, 17.1)	98	11	11.2	(5.7, 19.2)
Decreased appetite	104	78	75.0	(65.6, 83.0)	124	64	51.6	(42.5, 60.7)	135	60	44.4	(35.9, 53.2)
New generalized muscle pain	190	179	94.2	(89.9, 97.1)	181	142	78.5	(71.7, 84.2)	190	139	73.2	(66.3, 79.3)
Aggravated generalized muscle pain	107	84	78.5	(69.5, 85.9)	131	68	51.9	(43.0, 60.7)	132	55	41.7	(33.2, 50.6)
New generalized joint pain	72	39	54.2	(42.0, 66.0)	114	45	39.5	(30.4, 49.1)	121	44	36.4	(27.8, 45.6)
Aggravated generalized joint pain	57	23	40.4	(27.6, 54.2)	103	28	27.2	(18.9, 36.8)	109	26	23.9	(16.2, 33.0)
Any systemic event[d]	258	255	98.8	(96.6, 99.8)	246	232	94.3	(90.6, 96.9)	248	231	93.1	(89.3, 96.0)

a. N = number of subjects with known values.
b. n = Number of subjects with the given characteristic.
c. Exact 2-sided confidence interval (Clopper & Pearson) based upon the observed proportion of subjects.
d. Any systemic event = any fever ≥38°C, any fatigue, any headache, any chills, any rash, any vomiting, any decreased appetite, any new or aggravated generalized muscle pain, and any new or aggravated joint pain.

The mean durations of systemic events were generally similar and did not exceed 5.9 days for cohorts 1, 2, and 3, and 5.8 days for the age subgroups. The mean durations of systemic events were similar for the age subgroups in cohort 3, and did not exceed 5.9 days. Systemic events that extended beyond 14 days after vaccination were reported by 108 subjects in cohort 3.

Unsolicited adverse events

The percentage of subjects reporting any AEs within approximately 1 month after vaccination was similar in cohort 3 (14.3%), in cohort 2 (11.4%) and in the 13vPnC group in cohort 1 (17.0%). Most AEs were the types of diseases and conditions commonly observed among adults in these age groups.

In cohort 3, the most frequently occurring types of AEs were infections and infestations (4.4% of subjects) and gastrointestinal disorders (2.6%). The most frequently reported individual AEs in cohort 3 were nausea (12 subjects, 1.3%), upper respiratory tract infection (11 subjects, 1.2%), nasopharyngitis (7 subjects, 0.8%), and diarrhoea (6 subjects, 0.7%).

In cohort 2, the most frequently occurring types of AEs were infections and infestations (4.2% of subjects), general disorders and administration site conditions (2.5%), and musculoskeletal and connective tissue disorders (2.0%). Sinusitis was reported for 4 subjects (1.0%) and arthralgia was reported for 3 subjects (0.7%). All other AEs were reported for ≤ 2 subjects each.

In cohort 1, the most frequently occurring types of AEs were infections and infestations (7.7% of subjects) and musculoskeletal and connective tissue disorders (4.1%). The most frequently reported individual AEs in cohort 1 were nasopharyngitis (7 subjects, 1.7%), sinusitis (6 subjects, 1.4%); myalgia (5 subjects, 1.2%); and upper respiratory tract infection, cough, and gastroenteritis (each in 4 subjects, 1.0%).

The percentage of subjects reporting any AEs within approximately 1 month after vaccination was similar in the 18- to 29-year-old (13.0%), the 30- to 39-year-old (14.4%), and the 40- to 49-year-old (15.6%) age subgroups in cohort 3 (table not recreated in the interest of space). The percentages of subjects reporting individual AEs were also similar among the age subgroups.

Serious adverse events

SAEs occurring within approximately 1 month after vaccination were reported for 2 subjects (migraine, basal cell carcinoma) in cohort 3, for 2 subjects (cellulitis, ovarian cancer) in cohort 2 and for 1 subject (hemangioma) in cohort 1. In cohort 3, the migraine was reported by a subject in the 30- to 39-year-old age group and the basal cell carcinoma was reported by a subject in the 40- to 49-year-old age group. Except for the SAE of migraine reported by the subject in cohort 3, none of the serious AEs reported within 1 month after vaccination in cohorts 1, 2, and 3 were considered by the investigator to be related to study vaccine, and all of the SAEs were considered to have resolved.

SAEs were reported at the 6-month follow-up contact for 2 subjects (0.2%) in cohort 3, for 5 subjects (1.2%) in cohort 2, and for 12 subjects (2.9%) in cohort 1. In cohort 3, the types of SAEs reported at the 6-month follow-up contact included reproductive system and breast disorders and injury, poisoning and procedural complications. An SAE in the category of injury, poisoning and procedural complications was also reported in cohort 2. With that exception, the types of SAEs seen in the older cohorts were not reported in cohort 3 at the 6-month follow-up contact.

In cohort 3, the SAE of hip fracture was reported by 1 subject in the 30- to 39-year-old subgroup and the SAE of ovarian cyst ruptured was reported by 1 subject in the 18- to 29-year-old subgroup (CSR Table 49). Both SAEs were severe in intensity, neither was considered by the investigator to be related to study vaccine, and both of the SAEs were considered to have resolved.

Deaths

No deaths were reported for subjects in cohort 3, or in cohort 2. One (1) subject in cohort 1 died due to pancreatic cancer and liver cancer. These events were considered unrelated to study vaccine.

Laboratory findings

This section is not applicable because, with the exception of immunogencity testing, laboratory evaluations were not performed in Study 6115A1-004.

Safety in special populations

This section is not applicable because the submission comprises only data from Study 6115A1-004, cohort 3.

Discontinuation due to AES

No AEs that led to withdrawal were reported for cohort 3, cohort 2, or for subjects who received 13vPnC in cohort 1.

Post marketing experience

This section is not applicable because 13vPnC is not currently approved for use in adults 18 to 49 years of age.

2.4.3. Discussion

The safety of 13vPnC administered to the 18- to 49-year-old subjects in cohort 3 was compared with the safety of the 13vPnC vaccine administered to the older subjects (60 to 64 years old and 50 to 59 years old) in cohorts 1 and 2, respectively. The safety of 13vPnC administered to subjects in each of the age subgroups in cohort 3 was also assessed.

Local reactions and systemic events occurring within 14 days after vaccine administration were, in general, reported by higher percentages of subjects in cohort 3 compared with the older subjects in cohorts 1 and 2. In the age subgroups in cohort 3, in general, the percentages of subjects with local reactions and systemic events were generally highest in the youngest (18- to 29-year-old) age subgroup. In cohort 3, 62.9% of the subjects in the evaluable population reported they had never smoked. Overall, medical histories for subjects in cohort 3 were consistent with those of healthy adults in these age groups in the general population. The most common diagnoses by category were immune system disorders, surgical and medical procedures, nervous system disorders, eye disorders, and psychiatric disorders. The most common individual diagnoses were seasonal allergy, myopia, drug hypersensitivity, migraine, and depression.

However, with regard to the percentages of subjects who reported AEs within approximately 1 month after vaccination, there were no differences between cohort 3 and the older cohorts, or within the age subgroups in cohort 3. The percentage of subjects reporting any AEs at the 6-month follow-up contact was slightly lower in cohort 3 (0.3%) than in cohort 2 (1.5%) and cohort 1 (2.9%). Most AEs were the types of diseases and conditions commonly observed among adults in these age groups. There were few related AEs, severe or life threatening AEs, or SAEs reported and the incidences were similar in cohort 3

compared with cohort 1 and cohort 2. There were no deaths or AEs that led to withdrawal from the study in cohort 3.

These data demonstrate an acceptable safety profile for the administration of 13vPnC to subjects 18 to 49 years old.

Conclusions on clinical safety

As noted above, there were increased proportions of subjects from cohort 3 which experienced both local and systemic reactions. Furthermore, the youngest age sub group of cohort 3 also experienced a higher proportion of local and systemic reactions. However, the percentages of subjects reporting AEs (including SAEs) were not different between cohorts (or age groups) at 1 month after vaccination and, in fact, lower for cohort 3 at 6 months after vaccination.

While the local and systemic reactions are well characterised and generally well tolerated manifestations of immunogenicity, these safety data must be assessed in the context that there are no specific recommendations to vaccinate healthy adults with pneumococcal vaccines, and the medical need is considered small. Rates of at least one local reaction of 97.3% and at least one systemic reaction of 96% could be considered unacceptable if there is no foreseen benefit of vaccination in this population. In contrast, for adults belonging to risk groups for pneumococcal infection, the benefit of vaccination Prevenar 13 would outweigh these risks. Safety data in such populations will be provided as post-authorisation measures, as described in the pharmacovigilance activities.

2.4.4. PSUR cycle

The PSUR cycle remains unchanged. The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.5. Risk management plan

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

2.5.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 6, the PRAC considers by consensus that the risk management system for pneumococcal polysaccharide conjugate vaccine 13-valent, absorbed

(Prevenar 13) in the prophylaxis of invasive pneumococcal disease (IPD) in infants and children 6 weeks to 5 years of age and in adults 50 years of age and older (approved indication), and in adults 18-49 years (proposed indication) is acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Summary of safety concerns	
Important identified risks	Increased fever rates when 13vPnC is co-administered Infanrix hexa
Important potential risks	a) Unanticipated safety signals (including the onset of rare events) not seen in clinical trials of 13vPnC. b) Vaccine failure in subjects who are fully vaccinated according to local recommendations.
Important missing information	a) Effectiveness of 13vPnC consistent with the high effectiveness of 7vPnC vaccine (infants/children). b) Effectiveness of 13vPnC (adults). c) Long-term vaccine effectiveness. d) Potential changes in the epidemiology of non vaccine *S pneumoniae* serotypes that may occur (infants/children). e) Safety and immunogenicity in high risk populations: i) HIV-infected subjects ii) Premature infants born at <37 weeks of gestational age. iii) Immunocompromised subjects including those with bone marrow transplant and sickle cell disease f) Age group (18 to <50 years). g) Impact of 13vPnC on nasopharyngeal carriage, including monitoring replacement with non-vaccine serotypes and non-pneumococcal bacteria in the nasopharyngeal flora of children. h) No evidence of an association between wheezing diagnoses and vaccination was noted in post-marketing trials with 7vPnC or in clinical trials with 13vPnC; however, wheezing diagnoses will be monitored post-authorisation (infants/children). i) Paediatric transition plan. j) Effect of antipyretics on immune response to vaccination (infants/children). k) Safety of more than 1 dose of 13vPnC in adults administered >1 year apart. l) Vaccine exposure during pregnancy and lactation.

The PRAC agreed.

Pharmacovigilance plans

Table of ongoing and planned studies in the Pharmacovigilance development plan:

Actions	Milestones/Exposure	Milestones/Calendar Time	Study Status
Post-approval observational safety study of all medically attended events after 13vPnC administration compared to control periods. Wheezing diagnoses, apnea, convulsions/seizures and anaphylaxis/hypersensitivity are included as pre-specified endpoints in the safety	The study (6096A1-4002) began with product launch in the study population, subject to formulary committee approvals, and will take up to 4 years for completion depending on the rate of enrolment, which is in turn dependent on the size of the birth cohort of the study population. A final cleaned and locked dataset, data analysis, chart review, and	Interim report at 18 months after study start and at approximately 6 months after follow-up is completed for 43,000 children who have received 3 doses of the infant series. Study updates will also be provided with PSURs.	Start: 2Q 2010 - Ongoing

Actions	Milestones/Exposure	Milestones/Calendar Time	Study Status
assessment.	interpretation is expected to be available by approximately the 4th year.		
Adverse event reporting for vaccine failure reports following vaccination with 13vPnC.	The MAH's internal forecast for 13vPnC uptake is approximately 20 million doses per year in the EU. Every 6 months, approximately 10 million doses will be distributed.	PSURs every 6 months for the first 2 years after approval and annually thereafter.	Pharmacovigilance began with product launch
Effectiveness evaluation using population-based surveillance of the incidence rates of IPD, pneumonia and AOM-related outcomes in 5 European countries.	National surveillance systems in 5 countries will be used to monitor effectiveness - France (InVS and ACTIV), Germany (ESPED), Denmark, Norway (NIPH), and the UK (HPA).	Annual reports for 5 years from ESPED, HPA and ACTIV surveillance systems. Data from other surveillance systems will be obtained from their website & journal publications as they become available.	The national surveillance systems are ongoing to monitor pneumococcal conjugate vaccine effects.
Monitor potential changes in non-13vPnC serotypes after 13vPnC introduction.	The same 5 European population-based surveillance systems are being used to monitor potential changes in non-13vPnC serotypes	Annual reports for 5 years from ESPED, HPA and ACTIV surveillance systems. Data from other surveillance systems will be obtained from their websites & journal publications as they become available.	Surveillance is ongoing to monitor serotype-specific changes in *S pneumoniae* incidence rates
Assessment of long-term effectiveness	National surveillance systems in France, Germany, Denmark, Norway, the UK, Canada (Quebec), and the USA are being used to monitor long-term vaccine effectiveness.	Annual reports for 5 years from ESPED, HPA and ACTIV surveillance systems. Data from other surveillance systems will be obtained from their website & journal publications as they become available.	Surveillance is ongoing to monitor serotype-specific vaccine effectiveness
Clinical trials of safety and immunogenicity in HIV-positive children, premature infants <37 weeks gestational age, and children with sickle cell disease previously immunized with 23-valent pneumococcal polysaccharide vaccine. Monitor the effects of 13vPnC on nasopharyngeal carriage (NPC) of vaccine and non vaccine *S pneumoniae* serotypes and other key commensal bacteria, as well as antibiotic resistance. The French ACTIV surveillance program is ongoing.	Final study reports are expected to be available 6 months after the individual study is completed.	HIV (6115A1-3002) Report 31 December 2013 Premature (6096A1-4001) Final report 31 December 2012 Sickle cell (6096A1-3014) CSR due 31 Dec 2013 Annual reports from the ACTIV study in France.	HIV Start: 2Q 2009 Ongoing Premature Start: 2Q 2010 Ongoing Sickle cell Start: 4Q 2009 Ongoing Ongoing
Study 6096A1-4005: A postmarketing observational study that will estimate the impact of 13vPnC on IPD caused by vaccine serotypes of Streptococcus pneumoniae.	A final study report is expected to be available 6 months after study completion.	Final Report to be completed: March 2016	Start: May 2010 Ongoing
Study 6096A1-4010: A postmarketing study that will evaluate the impact of 13vPnC in reducing acute otitis media and nasopharyngeal colonization caused by Streptococcus pneumoniae in healthy children.	A final study report is expected to be available 6 months after study completion.	Final Report to be completed: June 2016	Start: September 2010 Ongoing
Study 6096A1-4018: National trends in ambulatory care visits for otitis media in children under the age of five in the	A final study report is expected to be available 6 months after study completion	Final report to be completed: March 2016	Start: July 2010 Ongoing

Actions	Milestones/Exposure	Milestones/Calendar Time	Study Status
United States.			
Study 6096A1-4024: Postmarketing observational study of the impact of 13vPnC on otitis media in children.	A final study report is expected to be available 6 months after study completion	Final Report to be completed: August 2013	Start: January 2010 Ongoing
Study 6115A1-3017: A phase 3 study that will evaluate the safety, tolerability, and immunogenicity of 3 doses of 13vPnC in HIV–infected subjects 18 years of age or older who have been previously immunized with 23vPS.	A final study report is expected to be available 1 year after study completion	Final Report to be completed: August 2012	Start: 4Q 2009 Ongoing
Study 6115A1-3006: A phase 4 study to evaluate the efficacy of 13vPnC in preventing vaccine-serotype pneumococcal CAP and IPD.	A final study report is expected to be available 1 year after study completion	Final Report to be completed: This is an event driven trial. Results will be available after the case count is complete.	Start: September 2008 Ongoing

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation Pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Summary table of Risk Minimisation Measures

Safety Concern	Proposed Risk Minimisation Activities (Routine and Additional)
A. Important identified risks: Increased rate of fever when coadministered with Infanrix hexa.	The SmPC revisions approved 22 November 2012 in procedure II/56 are as follows: Routine SmPC (Section 4.4) Special warnings and precautions for use When Prevenar 13 is administered concomitantly with Infanrix hexa (DTPa-HBV-IPV/Hib), the rates of febrile reactions are similar to those seen with concomitant administration of Prevenar (7-valent) and Infanrix hexa (see section 4.8). (Section 4.8) Undesirable effects In a clinical study in infants vaccinated at 2, 3, and 4 months of age, fever ≥ 38°C was reported at higher rates among infants who received Prevenar (7-valent) concomitantly with Infanrix hexa (28.3% to 42.3%) than in infants receiving Infanrix hexa alone (15.6% to 23.1%). After a booster dose at 12 to 15 months of age, the rate of fever ≥ 38°C was 50.0% in infants who received Prevenar (7-valent) and Infanrix hexa at the same time as compared to 33.6% in infants receiving Infanrix hexa alone. These reactions were mostly moderate (less than or equal to 39 °C) and transient.
B. Important potential risks: Unanticipated safety signals (including the onset of rare events) not seen in clinical trials of 13vPnC.	None
Vaccine failure in subjects who are fully immunized according to local recommendations.	Routine: SmPC (section 4.4) Special warnings and precautions As with any vaccine, Prevenar 13 may not protect all individuals receiving the vaccine from pneumococcal disease.
C. 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:	None

Safety Concern	Proposed Risk Minimisation Activities (Routine and Additional)
1. Wheezing diagnoses 2. Apnea 3. Convulsions/seizures 4. Anaphylaxis/hypersensitivity	
D. Important missing information: Effectiveness of 13vPnC consistent with the high effectiveness of 7vPnC (infants/children). Effectiveness of 13vPnC (adults). Long-term vaccine effectiveness. Potential changes in the epidemiology of non-vaccine S pneumoniae serotypes associated with the reduction in disease and nasopharyngeal carriage of serotypes contained in the 13vPnC (infants/children). 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.	None None None None Routine: SmPC (section 4.4) Special warnings and precautions 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). SmPC (section 5.1) Pharmacodynamic properties. The immunogenicity of Prevenar has been investigated in an open-label, multicenter trial 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 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.
Impact of 13vPnC on nasopharyngeal carriage. Safety of more than 4 doses of CRM-based pneumococcal conjugate vaccine when 13vPnC is administered for protection against the 6 additional serotypes in children previously vaccinated with a primary series of 7vPnC.	None None
Immunogenicity of 1 booster dose of 13vPnC against the 6 additional serotypes after a primary series of 7vPnC.	SmPC (section 4.2): Posology and method of administration - Prevenar 13 vaccine schedule for infants and children previously vaccinated with Prevenar (7-valent) (Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F). Prevenar 13 contains the same 7 serotypes included in Prevenar, using the same carrier protein CRM197. Infants and children who have begun immunisation with Prevenar may switch to Prevenar 13 at any point in the schedule.
Paediatric transition plan	The MAH is informing the health care professionals about the differentiating characteristics of 13vPnC and 7vPnC, ie, difference in packaging, the product label and different color of syringe and tip cap and 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 MAH is ensuring that the two vaccines have different batch numbers, different color of the plunger and tip cap of the syringe, and different carton packaging and label. None

Safety Concern	Proposed Risk Minimisation Activities (Routine and Additional)
Safety of more than 1 dose of 13vPnC in adults administered at >1 year apart Effect of antipyretics on immune response to vaccination (infants/children) Vaccine exposure in pregnancy and lactation in adults	None SmPC (section 4.6): Fertility, pregnancy, and lactation 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 PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed and accepted by the CHMP.

Section 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 and adolescents from 6 weeks to 17 years of age.

Active immunisation for the prevention of invasive disease caused by Streptococcus pneumoniae in adults ≥ 18 years of age and the elderly~~aged 50 years and older~~

The use of Prevenar 13 should be determined on the basis of official recommendations taking into consideration the risk~~impact~~ of invasive disease in different age groups, underlying comorbidities as well as the variability of serotype epidemiology in different geographical areas

4.2 Posology and method of administration

Children and adolescents aged 2 17 years

Adults ≥ 18 years of age, and the elderly ~~aged 50 years and older~~

4.4 Special warnings and precautions for use

Prevenar 13 will only protect against Streptococcus pneumoniae serotypes included in the vaccine, and will not protect against other microorganisms that cause invasive disease, pneumonia, or otitis media. As with any vaccine, Prevenar 13 may not protect all individuals receiving the vaccine from pneumococcal disease. For the most recent epidemiological information in your country you should consult with the relevant national organisation.

4.5 Interaction with other medicinal products and other forms of interaction

Children and adolescents 6 to 17 years of age

Adults 18 to 49 years of age

No data are available regarding concomitant use with other vaccines.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of pneumococcal 13-valent conjugate vaccine in pregnant women. Therefore the use of Prevenar 13 should be avoided during pregnancy.

Breast-feeding

It is unknown whether pneumococcal 13-valent conjugate vaccine is excreted in human milk.

4.8 Undesirable effects

A typographical error has been corrected for the definition for "very rare". It has been corrected to state very rare is defined as "<1/10,000" and not "≤ 1/10,000"

Adults ≥ 18 years and the elderly ~~aged 50 years and older~~

Safety was assessed in 6 clinical studies including 7,097~~6,198~~ adults ranging in age from 18~~50~~ to 95 years. Prevenar 13 was administered to 5,667 adults; 2,616 (46.2 %) aged 50 to 64 years, and 3,051 (53.8 %) aged 65 years and older. Of the Prevenar 13 recipients 1,916 adults were previously vaccinated with the 23 valent pneumococcal polysaccharide vaccine at least 3 years prior to study vaccination, and 3,751 were 23-valent pneumococcal polysaccharide vaccine unvaccinated. One of the six studies included a group of adults (n=899) ranging from 18 to 49 years who received Prevenar 13 and who were not previously vaccinated with 23-valent pneumococcal polysaccharide vaccine.

~~Subjects older than 65 years of age reported fewer adverse reactions than younger adults, regardless of prior pneumococcal vaccination status~~.A trend to lower frequency of adverse reactions was associated with greater age; adults >65 years of age (regardless of prior pneumococcal vaccination status) reported fewer adverse reactions than younger adults, with adverse reactions generally most common in the youngest adults, 18 to 29 years of age.

Overall, the frequency categories were similar for all ~~both~~ age groups, with the exception of vomiting which was very common (≥ 1/10) in adults aged 18 to 49 years and common (≥ 1/100 to < 1/10) in all other age groups, and pyrexia was very common in adults aged 18 to 29 years and common in all other age groups. Severe vaccination-site pain/tenderness and severe limitation of arm movement was very common in adults 18 to 39 years and common in all other age groups.

Gastrointestinal disorders:

Very common: Diarrhoea; vomiting (in adults aged 18 to 49 years)

Common: Vomiting (in adults aged 50 years and over)

Uncommon: Nausea

Very common: Chills; fatigue; vaccination-site erythema; vaccination-site induration/swelling; vaccination-site pain/tenderness (severe vaccination-site pain/tenderness very common in adults aged 18 to 39 years); limitation of arm movement (severe limitation of arm movements very common in adults aged 18 to 39 years)

Common: Pyrexia (very common in adults aged 18 to 29 years)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

Burden of disease in adults ≥ 18 years and the elderly ~~aged 50 years and older~~

~~The incidence of invasive pneumococcal disease (IPD) in adults increases with age from 50 years, risk factors (smoking status or alcohol use), and underlying co-morbidities (chronic cardiovascular disease, chronic pulmonary disease including asthma, renal disorders, diabetes mellitus, and chronic liver disease including alcoholic liver disease). Bacteraemic pneumonia, bacteraemia without a focus, and meningitis are the most common manifestations of IPD in adults aged 50 years or older. Based on surveillance data, the pneumococcal serotypes in Prevenar 13 may be responsible for at least 50 – 76% (depending on country) of IPD in adults aged over 50 years. Approximately 80% of IPD in adults is bacteraemic pneumonia.~~

Adults with underlying comorbidities are at an increased risk of invasive pneumococcal disease (IPD). Additionally the incidence of invasive pneumococcal disease (IPD) in adults increases with age from 50 years. Based on surveillance data following the introduction of Prevenar but before the introduction of Prevenar 13 in childhood vaccination programmes, the pneumococcal serotypes in Prevenar 13 may be responsible for at least 50 – 76% (depending on country) of IPD in adults aged over 50 years.

Bacteraemic pneumonia, bacteraemia without a focus, and meningitis are the most common manifestations of IPD in adults with approximately 80% of IPD in adults is bacteraemic pneumonia.

Prevenar 13 immunogenicity clinical studies in infants, ~~and~~ children and adolescents

Section 5.1

Immunogenicity studies in adults ≥ 18 years and the elderly ~~50 years and older~~

Five clinical studies were conducted in Europe and the USA evaluating the immunogenicity of Prevenar 13 in different age groups ranging from 18~~50~~-95 years of age. Clinical studies with Prevenar 13 currently provide immunogenicity data in adults aged 18~~50~~ years and older, including adults aged 65 and older previously vaccinated with one or more doses of 23-valent pneumococcal polysaccharide vaccine, 5 years prior to enrollment. Each study included healthy adults and immuno-competent adults with stable underlying conditions known to predispose individuals to pneumococcal infection (i.e., chronic cardiovascular disease, chronic pulmonary disease including asthma, renal disorders and diabetes mellitus, chronic liver disease including alcoholic liver disease), and adults with risk factors such as smoking and alcohol abuse.

Immunogenicity and safety of Prevenar 13 has been demonstrated in adults aged 18~~50~~ years and older including those previously vaccinated with a pneumococcal polysaccharide vaccine.

Adults not previously vaccinated with 23 valent pneumococcal polysaccharide vaccine

In a head-to-head, comparative trial conducted in adults aged 60-64 years, subjects received a single dose of either Prevenar 13 or 23-valent pneumococcal polysaccharide vaccine. In the same study another group of adults aged 50-59 years and another group of adults aged 18-49 years received a single dose of Prevenar 13.

Table 4 compares the OPA GMTs, 1-month post-dose, in 60-64 year olds given either a single dose of Prevenar 13 or 23-valent pneumococcal polysaccharide vaccine, and in 50-59 year olds given a single dose of Prevenar 13.

Table 5 shows OPA GMTs 1-month after a single dose of Prevenar 13 in 18-49 year olds compared to 60-64 year olds.

Table 5: OPA GMTs in adults aged 18-49 years and 60-64 years given Prevenar 13[a,b]				
	18-49 Years N=836-866	***60-64 Years N=359-404***	***18-49 Years Relative to 60-64 Years***	
Serotype	*GMT*[b]	*GMT*[b]	*GMR*	*(95% CI*[c]*)*
1	*353*	*146*	*2.4*	*(2.03, 2.87)*
3	*91*	*93*	*1.0*	*(0.84, 1.13)*
4	*4747*	*2062*	*2.3*	*(1.92, 2.76)*
5	*386*	*199*	*1.9*	*(1.55, 2.42)*
6A	*5746*	*2593*	*2.2*	*(1.84, 2.67)*
6B	*9813*	*1984*	*4.9*	*(4.13, 5.93)*
7F	*3249*	*1120*	*2.9*	*(2.41, 3.49)*
9V	*3339*	*1164*	*2.9*	*(2.34, 3.52)*
14	*2983*	*612*	*4.9*	*(4.01, 5.93)*
18C	*3989*	*1726*	*2.3*	*(1.91, 2.79)*
19A	*1580*	*682*	*2.3*	*(2.02, 2.66)*
19F	*1533*	*517*	*3.0*	*(2.44, 3.60)*
23F	*1570*	*375*	*4.2*	*(3.31, 5.31)*

[a] *Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR was greater than 0.5.*

[b] *Statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR was greater than 1.*

[c c] *Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures.*

In adults aged 18-49 years, OPA GMTs to all 13 serotypes in Prevenar 13 were non-inferior to the Prevenar 13 responses in adults aged 60-64 years.

One year after vaccination with Prevenar 13 OPA titers had declined compared to one month after vaccination, however OPA titers for all serotypes remained higher than levels at baseline.

	OPA GMT levels at baseline	*OPA GMT levels one year after Prevenar 13*
Adults 18-49 years not previously vaccinated with 23-valent pneumococcal polysaccharide vaccine	*5 to 186*	*23 to 2948*

Package Leaflet

1. What Prevenar 13 is and what it is used for

• adults aged 18~~50~~ years and older to help prevent disease such as: bacteraemic pneumonia (lung infection with bacteria in the blood stream), bacteraemia (bacteria in the blood stream) and meningitis (inflammation around the brain),

caused by 13 types of the bacteria Streptococcus pneumoniae.

4. Possible side effects

The following side effects include those reported for Prevenar 13 ~~in adults aged 50 years and older~~:

The most common side effects (these may occur with more than 1 in 10 doses of the vaccine) are:

• Decreased appetite; headaches; diarrhoea; vomiting (for those 18 to 49 years of age)

• Chills; tiredness; rash; pain, redness, swelling hardness or tenderness at the vaccination site, interfering with arm movement(severe pain or tenderness at vaccination site for those 18-39 years of age and severe limitation of arm movements for those 18 to 39 years of age)

• Worsening or new pain in your joints, worsening or new pain in your muscles

• Fever (for those 18 to 29 years of age)

Common side effects (these may occur with up to 1 in 10 doses of the vaccine) are:

• Vomiting (for those 50 years and older); fever

Uncommon side effects (these may occur with up to 1 in 100 doses of the vaccine) are:

• Nausea

• Allergic (Hypersensitivity) reaction, including swelling of the face and/or lips, difficulty in breathing

• Enlarged lymph nodes or glands (lymphadenopathy) near the vaccination site, such as under the arm

Reporting of side effects

If you or your child get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

3. Benefit Risk Balance

Benefits

Beneficial effects

The immune responses following vaccination with Prevenar 13 in healthy adults are very likely to be protective, as both OPA titres and ELISA GMCs were high. This is also expected considering that the immune responses in younger children and elderly have already been demonstrated to be protective

(younger children), or at least non-inferior to the responses to a 23-valent polysaccharide vaccine (elderly).

Uncertainty in the knowledge about the beneficial effects

Overall the expected benefit of vaccination of healthy adults 18-49 years is considered limited as the incidence of disease is low in this age group.

A similar discussion was held regarding the extension of indication to include children 6-17 years of age in type II variation 55. The benefit of vaccination of healthy children 6-17 years of age is also very limited, but by extending the indication to that age group enables the use of Prevenar 13 in risk groups also in this age group, although there is currently limited data on the use Prevenar 13 in risk groups. Since then, a type II variation (II76) was submitted, and inclusion of data from three different studies in risk groups was proposed by the MAH, i.e. premature children, children with sickle cell disease and HIV positive adults. The procedure is still ongoing, but it is clear that at least some data in risk groups are available. Therefore, the current variation allows the use of Prevenar 13 in risk groups 18-49 years where the benefit of vaccination is greater compared to healthy adults. The indication section should include the consideration of the risk of invasive disease in different age groups.

Risks

Unfavourable effects

Rates of local and systemic reactions are higher in the age group 18-49 years compared to those older adults for which Prevenar 13 is currently indicated. Rates of at least one local reaction are 97.3% and at least one systemic reaction of 96% in this age group.

Uncertainty in the knowledge about the unfavourable effects

These local and systemic reactions are well characterised and generally well tolerated manifestations of immunogenicity; however, there are no safety data provided for risk groups for which Prevenar 13 might be indicated in this age group. Additional safety data in the risk groups may be obtained in the aforementioned 2 studies included in the pharmacovigilance plan as well as from routine pharmacovigilance for pregnant women.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The benefit of pneumococcal vaccination in healthy adults is considered limited, as the incidence of disease is low in this age group. The benefit is greater in risk groups, although the data provided in this application is limited to generally healthy adults. However, at least some data in risk groups are now available as seen in the ongoing type II variation 76. It is reasonable to extrapolate immunogenicity data and safety data between age groups e.g. younger (6-17 years) and older (>50 years) where Prevenar 13 is already approved.

The local and systemic reactions are well characterised and generally well tolerated manifestations of immunogenicity. Rates of at least one local reaction of 97.3% and at least one systemic reaction of 96%

could be considered unacceptable if there is no foreseen benefit of vaccination in this population. In contrast, for adults belonging to risk groups for pneumococcal infection, the benefit of vaccination Prevenar 13 would outweigh these risks.

Benefit-risk balance

The benefit of vaccinating healthy adults 18-49 years of age with Prevenar 13 is considered limited, but the benefit of vaccinating adults belonging to risk groups with Prevenar 13 is considered greater. It is considered reasonable to extrapolate immunogenicity and safety data from younger and older age groups, where Prevenar 13 is already approved. The high incidence of adverse events was high, but the events were generally transient and mild to moderate. Thus, the benefit of vaccination subjects 18-49 years of age, taking risk factors of disease into account outweighs the risks.

Discussion on the Benefit-Risk Balance

The current variation is in principle similar to the recently assessed type II variation 55, which was an extension to include children 6-18 years of age. In that variation the benefit of vaccinating healthy children >5 years was considered limited, but the benefit of vaccinating risk group children was assumed to be much greater. The MAH justified the use of Prevenar in risk group children 6-18 years of age based on literature and company sponsored studies using mostly Prevenar. As discussed above, it is reasonable to extrapolate the use in younger and older age groups to the age group 18-49 years, and additional data have become available in another ongoing type II variation, and therefore the benefit is considered demonstrated, although specific data on risk groups were not submitted in the current variation.

4. Recommendations

☒ The application for extension of the indication to include adults aged from 18 to 49 years is approvable as major objections and other concerns have all been resolved.

Final Outcome

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

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

Extension of indication to include adults aged from 18 to 49 years for Prevenar 13.

As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8 and 5.1 of the Summary of Product Characteristics have been updated with data from study 6115A1-004. The Package Leaflet is updated in accordance.

Furthermore, the Product Information is being brought in line with the latest QRD template version 9.0.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

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

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The proposed post-authorisation Pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

- **Obligation to conduct post-authorisation measures**

Not applicable.

5. EPAR changes

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

Scope

Extension of indication to include adults aged from 18 to 49 years for Prevenar 13.

As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8 and 5.1 of the Summary of Product

Characteristics have been updated with data from study 6115A1-004. The Package Leaflet is updated in accordance.

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

Summary

Please refer to Assessment Report EMEA/H/C/1104/II/71.