EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 February 2015
EMA/126200/2015
Committee for Medicinal Products for Human Use (CHMP)

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

Prevenar 13

(Pneumococcal saccharide conjugated vaccine, adsorbed)

Procedure No. EMEA/H/C/001104

P46 041

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

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I. INTRODUCTION

On 2010-12-16 the MAH submitted completed paediatric studies for Prevenar 13, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do influence the benefit risk for Prevenar13 and that there is no consequential regulatory action.

II. SCIENTIFIC DISCUSSION

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

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

II.2 Clinical aspects

1. Introduction

The MAH submitted final reports for:

6096A1-3012: To assess the pneumococcal immune responses induced by 13vPnC in children that have previously received 1 or 2 doses of Prevenar at approximately 3 or 3 and 5 months of age, when measured 1 month after the last scheduled dose of 13vPnC in each of 2 age groups in Sweden.

6096A1-3013 To characterize the immune response by ELISA and OPA at approximately 1 month after vaccination to a single dose of 13vPnC challenge in children vaccinated with a primary series (3 or 2 doses) of pneumococcal conjugate vaccine (9vPnC-meningococcal serogroup C) followed by a booster dose of either pneumococcal conjugate vaccine (PcV) or 23-valent pneumococcal polysaccharide vaccine (PPV23) in Iceland.

2. Clinical studies

6096A1-3012: To assess the pneumococcal immune responses induced by 13vPnC in children that have previously received 1 or 2 doses of Prevenar at approximately 3 or 3 and 5 months of age, when measured 1 month after the last scheduled dose of 13vPnC in each of 2 age groups in Sweden.

- **Description**

- **Methods**

  - Objective(s)

The primary objective of this study was to assess the pneumococcal immune responses induced by 13-valent pneumococcal conjugate vaccine (13vPnC) when measured 1 month after the last scheduled dose of 13vPnC in each of 2 age groups. The secondary objective of this study was to assess the pneumococcal immune response induced by 13vPnC when measured 1 month after the infant dose of 13vPnC in group 1. The safety objective of this study was to evaluate the acceptability of the safety profile of 13vPnC as measured by the incidence rates of local reactions, systemic events, and adverse events (AEs).

  - Study design

This was an open-label, multicenter study in which all subjects were enrolled into 1 of 2 groups based on age. The immunogenicity of 13vPnC was evaluated in children who had previously received 1 or 2 doses of Prevenar. A 2+1 vaccination schedule was followed with vaccinations at 3, 5, and 12 months of age. The study included 2 groups:
Blood samples for group 1 were to be obtained at approximately 1 month (28 to 42 days) after the 13vPnC infant dose, prior to the toddler dose, and 1 month (28 to 42 days) after the toddler dose. For

group 2, blood samples were to be collected immediately before vaccination and approximately 1 month (28 to 42 days) after vaccination. Blood samples from all subjects were to be tested for serotype-specific immunoglobulin G (IgG) antibodies elicited by the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) present in 13vPnC.

- Study population /Sample size

This was a descriptive study and was not powered for formal statistical comparisons. Based on previous experience, 115 subjects per group to provide 100 evaluable subjects per group was to be sufficient to provide adequate precision in study results for descriptive assessment.

Main Criteria for Inclusion: Subjects were eligible to be enrolled in this study if they were healthy infants; were available for the entire study period; and if their parent(s)/legal guardian(s) could be reached by telephone and were able and willing to comply with all study procedures.
Main Criteria for Exclusion: Exclusion criteria included: previous vaccination with licensed or investigational pneumococcal vaccine other than Prevenar; contraindication to vaccination with pneumococcal conjugate vaccine; previous anaphylactic reaction or allergy to any vaccine or vaccine-related component; bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate intramuscular injection; history of culture-proven invasive disease caused by S pneumoniae; known or suspected immune deficiency or immune suppression; major known congenital malformation or serious chronic disorder; significant neurologic disorder or history of seizure, including febrile seizure, or significant stable or evolving disorders such as cerebral palsy, encephalopathy, hydrocephalus, or other significant disorder; received blood products or gamma globulin during the last 3 months; participation in another interventional or investigational trial, although participation in purely observational studies was acceptable; direct descendant (eg, child or grandchild) of the study site personnel; any major illness or condition that, in the investigator's judgment, would have substantially increased the risk associated with the subject's participation in, and completion of, the study, or could have precluded the evaluation of the subject's response.

- Treatments

Group 1: Subjects were aged ≥140 to ≤196 days and were to receive 2 doses of 13vPnC at 5 and 12 months of age. These subjects had received a single dose of Prevenar at approximately 3 months of age prior to enrollment in the study.
Group 2: Subjects were aged ≥336 to ≤392 days and were to receive 1 dose of 13vPnC at 12 months of age. These subjects had received Prevenar at approximately 3 and 5 months of age prior to enrollment in the study. Thus, subjects continued on a 2+1 vaccination schedule (3, 5, and 12-month).

- Outcomes/endpoints

Immunogenicity Assessment Methods: Blood samples for group 1 were obtained at approximately 1 month (28 to 42 days) after the 13vPnC infant dose, prior to the toddler dose, and 1 month (28 to 42 days) after the toddler dose. For group 2, blood samples were collected immediately before vaccination and approximately 1 month (28 to 42 days) after vaccination. For all blood samples, serum concentrations (µg/mL) of anticapsular IgG were determined by enzyme-linked immunosorbent assay (ELISA) for each of the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F).

Safety Assessment Methods: Safety assessment was based on e-diary recordings of local reactions (redness, swelling, and tenderness) and systemic events (decreased appetite, irritability, increased sleep, decreased sleep, temperature, and use of antipyretic medication to treat or prevent symptoms) for 7 days after each vaccination. AEs were also monitored during the study. For any reactions that persisted at day 7, the e-diary prompted the parent(s)/legal guardian(s) on a daily basis regarding the status of the reaction until the parent(s)/legal guardian(s) recorded an end date in the e-diary.

- Statistical Methods

Analysis Populations: For immunogenicity analyses, 2 analysis populations were defined: evaluable and all-available immunogenicity populations. The evaluable immunogenicity population was the primary immunogenicity population.
To be included in an evaluable immunogenicity population, the subject was eligible, within the age range for the administered dose (infant or toddler), received study vaccine at all expected doses, had

blood drawn within the protocol specified time frames, had at least 1 valid and determinate assay result for the proposed analysis, and had no other major protocol violations.

All subjects meeting these criteria were included. To be included in an all-available immunogenicity population, a subject was to have at least 1 valid and determinate assay result related to the proposed analysis.

All subjects who received at least 1 dose of the study vaccine were included in the safety population. Separate safety populations were defined for each vaccination: dose 1 and dose 2 (group 1) and all vaccinated subjects (group 2). Subjects who lacked any safety data for a particular vaccination were excluded from that analysis.

Immunogenicity: The primary endpoint for each of the serotypes was the IgG antibody concentration after the last scheduled dose of 13vPnC in each group. The geometric mean IgG concentrations and corresponding 2-sided 95% confidence intervals (CIs) were calculated for each group following the last scheduled dose. The proportion of subjects achieving a serotype-specific IgG antibody concentration ≥0.35 µg/mL measured 1 month after the infant dose of 13vPnC in group 1 was a secondary endpoint.

The pneumococcal IgG serotype antibody concentrations were logarithmically transformed for analysis. Within each age group and for each antibody concentration separately, geometric means of the antibody concentrations from each of the blood draws were calculated. Two (2)-sided, 95% CI were constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using the Student t distribution.

To assess the within-subject post-vaccination and pre-vaccination differences in concentration for the last scheduled dose, the fold rise in geometric mean concentration (GMC) from pre-vaccination to post-vaccination and 2-sided 95% CIs were estimated for each age group using the logarithmically transformed assay results.

Safety: The safety endpoints were AEs, local reactions, and systemic events including fever and use of antipyretic medications. Fever was defined as axillary temperature of 38.0°C (100.4°F) or higher.
For local reactions and systemic events, including fever and use of antipyretic medications, the duration of the local reaction/systemic events were summarized using descriptive statistics, by age group. The mean, minimum, maximum, and standard deviation were presented along with the number of unknown durations. Only subjects actually experiencing the reaction/event were included in the summary statistics. Subjects with no reported reaction/event were included in the number of subjects with a known value.
The minimum and maximum diameters for redness and swelling as well as temperature were summarized by age group using descriptive statistics. The mean, median, minimum, maximum, and standard deviation were presented. The number and percentage of subjects in each category of tenderness were summarized by age group. This tabulation was performed for each dose separately.
All AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA). The relationship between AEs and the study vaccine (13vPnC) was characterized as related or not related as described in the protocol. The severity of AEs was characterized as mild, moderate, severe, or life-threatening. Any deaths were included in the last category, namely, life-threatening.
AE summaries were produced separately for each age group and for each vaccination. All summaries showed, by age group, the number and percentage of subjects experiencing at least 1 event of each preferred term, arranged by system organ class, and the number of occurrences of the event. Separate summaries were produced for related AEs, for events characterized as severe, and for events characterized life-threatening.
SAEs (which included life-threatening events) were summarized for age group. A listing of SAEs was generated as an aid for the statistician during the clinical study report review.

- **Results**

- Recruitment/ Number analysed

A total of 234 subjects were enrolled. Subjects in group 1 (N=118) were assigned to receive two doses of 13vPnC (infant and toddler dose) and subjects in group 2 (N=116) were assigned to receive a single dose of 13vPnC (toddler dose). All 118 subjects in group 1 received the infant vaccination. Two (2, 1.7%) subjects were withdrawn after the infant dose; 1 because of parent/legal guardian request and

1 because of an AE. Thus, 116 (98.3%) subjects in group 1 received the toddler dose. All 116 subjects in group 2 received the toddler dose.

- Efficacy results

Table 9-5 presents a summary of pneumococcal IgG GMCs 1 month after the infant dose in the evaluable infant immunogenicity population.

Table 9-5: Pneumococcal IgG GMCs (µg/mL) 1 Month After Infant Dose – Evaluable Infant Immunogenicity Population

	Vaccine Group (as Enrolled)		
	13vPnC Group 1		
Serotype	n[a]	GMC[b]	(95% CI[c])
7vPnC			
4	115	2.90	(2.48, 3.40)
6B	115	0.40	(0.32, 0.50)
9V	115	1.73	(1.50, 1.99)
14	114	4.70	(3.72, 5.92)
18C	115	1.56	(1.29, 1.89)
19F	115	3.01	(2.34, 3.88)
23F	115	0.57	(0.46, 0.70)
Additional			
1	115	0.89	(0.73, 1.08)
3	115	1.88	(1.65, 2.14)
5	115	0.72	(0.62, 0.84)
6A	114	0.28	(0.23, 0.34)
7F	115	1.78	(1.48, 2.15)
19A	115	0.85	(0.73, 0.99)

a. n = Number of subjects with a determinate IgG antibody concentration to the given serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified postvaccination blood draw. GMC after vaccination 1 for group 1.
c. Confidence intervals (CIs) are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations.

Table 9-6 presents a summary of pneumococcal IgG GMCs before the toddler dose in the evaluable infant immunogenicity populations. The serotype-specific pneumococcal IgG GMCs observed before the toddler dose were lower when compared to the GMCs noted 1 month after the infant dose, except for serotypes 5, 6A, and 6B.

Table 9-6: Pneumococcal IgG GMCs (µg/mL) Before Toddler Dose – Evaluable Toddler Immunogenicity Population

	Vaccine Group (as Enrolled)					
	13vPnC Group 1			13vPnC Group 2		
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])
7vPnC						
4	111	0.66	(0.57, 0.77)	115	0.62	(0.53, 0.72)
6B	111	0.83	(0.67, 1.02)	109	0.65	(0.51, 0.82)
9V	111	0.74	(0.65, 0.85)	115	0.70	(0.60, 0.82)
14	111	1.99	(1.63, 2.42)	115	2.23	(1.85, 2.69)
18C	110	0.35	(0.30, 0.41)	115	0.44	(0.38, 0.51)
19F	111	0.85	(0.70, 1.03)	114	0.81	(0.66, 1.00)
23F	110	0.33	(0.27, 0.39)	115	0.41	(0.34, 0.49)
Additional						
1	111	0.46	(0.40, 0.53)	115	0.01	(0.01, 0.02)
3	110	0.40	(0.34, 0.47)	115	0.05	(0.04, 0.07)
5	111	1.18	(1.02, 1.36)	106	0.33	(0.26, 0.42)
6A	111	0.71	(0.60, 0.85)	110	0.24	(0.19, 0.31)
7F	111	1.08	(0.95, 1.23)	114	0.02	(0.02, 0.02)
19A	111	1.06	(0.88, 1.28)	115	1.55	(1.32, 1.81)

a. n = Number of subjects with a determinate IgG antibody concentration to the given serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified prevaccination blood draw. GMC before vaccination 2 for group 1; GMC before vaccination 1 for group 2.
c. Confidence intervals (CIs) are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations.

Table 9-7 presents a summary of pneumococcal IgG GMCs 1 month after the toddler dose in the evaluable toddler immunogenicity population. The serotype-specific pneumococcal IgG GMCs for all 13 serotypes observed 1 month the toddler dose were higher when compared to the GMCs noted before the toddler dose. For group 1 the GMCs after the toddler dose were higher compared to the GMCs after the infant dose, except for serotype 3, which was similar.

Table 9-7: Pneumococcal IgG GMCs (µg/mL) 1 Month After Toddler Dose – Evaluable Toddler Immunogenicity Population

	Vaccine Group (as Enrolled)					
	13vPnC Group 1			13vPnC Group 2		
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])
7vPnC						
4	114	5.27	(4.43, 6.26)	114	5.06	(4.22, 6.06)
6B	112	9.63	(8.01, 11.57)	113	8.75	(6.76, 11.32)
9V	114	3.50	(3.01, 4.07)	114	3.33	(2.88, 3.84)
14	114	9.22	(7.66, 11.09)	114	9.30	(7.90, 10.95)
18C	113	2.93	(2.50, 3.44)	114	3.87	(3.30, 4.53)
19F	114	7.70	(6.12, 9.69)	113	8.31	(6.39, 10.81)
23F	114	3.27	(2.68, 3.99)	113	4.40	(3.70, 5.22)
Additional						
1	114	14.65	(12.50, 17.17)	114	1.58	(1.30, 1.93)
3	114	1.85	(1.59, 2.15)	114	1.34	(1.13, 1.58)
5	114	7.02	(5.98, 8.25)	113	1.44	(1.21, 1.72)
6A	114	6.14	(5.08, 7.43)	113	2.48	(1.89, 3.26)
7F	114	5.86	(5.11, 6.72)	114	3.55	(3.09, 4.08)
19A	113	7.25	(6.14, 8.57)	114	13.16	(11.26, 15.38)

a. n = Number of subjects with a determinate IgG antibody concentration to the given serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified postvaccination blood draw. GMC after vaccination 2 for group 1; GMC after vaccination 1 for group 2.
c. Confidence intervals (CIs) are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations.

When comparing the GMCs before and after vaccination with the toddler dose, the GMFRs for the 7 common serotypes ranged from 4.45 (serotype 14) to 11.49 (serotype 6B) for group 1 and from 4.17 (serotype 14) to 14.32 (serotype 6B) for group 2. For the 6 additional serotypes, the GMFRs ranged from 4.51 (serotype 3) to 30.58 (serotype 1) for group 1 and from 4.3 (serotype 5) to 177.31 (serotype 7F) for group 2.
In group 1 for the infant dose, the proportion of subjects achieving an IgG concentration ≥0.35 µg/mL to the 7 serotypes in common with Prevenar ranged from 53.0% (serotype 6B) to 99.1% (serotypes 4 and 9V). The proportions of responders to the 6 additional serotypes ranged from 36.8% (serotype 6A) to 100.0% (serotype 3).

- Safety results

Local Reactions: After the infant dose in group 1, tenderness was reported for 36.1% of subjects. Significant tenderness (defined as tenderness interfering with limb movement) was reported for only 3.0% of subjects. Swelling and redness were reported for 33.7% and 40.2% of subjects, respectively. Most reports of swelling and redness were mild (0.5 to 2.0 cm in diameter) and none were severe (>7.0 cm). The mean duration of both tenderness and redness was 1.5 days, while the mean duration of swelling was 3.4 days.
After the toddler dose, tenderness was reported for 59.6% of subjects in group 1 and for 52.7% of subjects in group 2. Significant tenderness was reported for ≤7.8% of subjects in either group. Swelling was reported for 53.8% of subjects in group 1 and for 54.5% of subjects in group 2, while the incidence of redness was 62.5% in group 1 and 59.3% in group 2. Most reports of swelling and redness were mild, and none were severe. In group 1, the mean durations of tenderness, swelling, and redness, respectively, were 2.6, 4.7, and 2.4 days; and in group 2 the mean durations were 2.5, 4.8, and 2.4 days.

Systemic Events: After the infant dose in group 1, mild fever (≥38°C but ≤39°C) was reported for 26.2% of subjects, moderate fever (>39°C but ≤40°C) was reported for 2.0% of subjects, and no subjects reported severe fever (>40°C). Use of antipyretic medication to treat or prevent symptoms was reported for 35.2% of subjects. Irritability was the most frequently reported type of systemic event (80.7% of subjects), followed by increased sleep (50.9%), decreased sleep (39.3%), and

decreased appetite (36.4%). The mean duration of fever (≥38°C) was 1.4 days, while the mean duration of other types of systemic events ranged from 2.0 to 2.8 days.
After the toddler dose, the incidence of mild fever was 31.3% and 32.4% in group 1 and group 2, respectively; the incidence of moderate fever was 5.2% and 3.9%, and no subjects had severe fever. Antipyretic medication was used to treat or prevent symptoms in 45.5% and 44.9% of subjects in group 1 and group 2, respectively. The incidence of other systemic events in group 1 and group 2, respectively, was 82.0% and 76.1% for irritability, 49.5% and 38.9% for increased sleep, 46.6% and 44.0% for decreased appetite, and 36.2% and 33.0% for decreased sleep. The mean duration of fever was 1.6 days and 1.7 days, respectively; and the mean duration of other systemic events ranged from 2.3 to 3.7 days in group 1 and from 2.2 to 3.3 days in group 2.

Adverse Events: In general, the types of unsolicited AEs reported were consistent with the types of childhood illnesses and conditions commonly occurring in this age group. In group 1, AEs occurring within 1 month after the infant dose were reported for 14 subjects (11.9%). The types of AEs reported most frequently were infections and infestations (8 subjects, 6.8%) and gastrointestinal disorders (3 subjects, 2.5%). The most frequent individual AEs reported during this period were nasopharyngitis (5 subjects, 4.2%) and diarrhea (2 subjects, 1.7%). All other AEs occurred in 1 subject each. Only 1 AE was considered related to study vaccine (mild diarrhea beginning on day 2). Between the postinfant series visit and the toddler dose, AEs were reported for 8 subjects (6.8%).
After the toddler dose, AEs were reported for 21.6% of subjects in group 1 and for 23.3% of subjects in group 2. The most frequent types of AEs were infections and infestations (14.7% in group 1; 13.8% in group 2). In group 1, the most frequently reported individual AEs (≥3% of subjects) were nasopharyngitis (6.9%), vomiting (5.2%), and pyrexia (3.4%); and in group 2, nasopharyngitis (6.0%) and pyrexia (3.4%). After the toddler dose, 5 AEs considered related to study vaccine were reported for 3 subjects in group 1 (diarrhea and vomiting; nasopharyngitis and cough; and lower extremity mass) and 1 subject in group 2 (rash). The lower extremity mass was described as a "non-tender lump on the left leg."
One serious AE (SAE) was reported within 1 month after the infant dose (severe diarrhea lasting 6 days, considered not related to study vaccine). Between the postinfant series visit and the toddler dose, 6 SAEs were reported for 4 subjects; these included gastroenteritis (in 4 subjects), foreign body, and intussusception. After the toddler dose, 4 SAEs were reported for 1 subject: bronchitis, asthma, diarrhea, and vomiting. There were no deaths during the study. One subject was withdrawn from the study on day 194 due to severe eczema (not considered related to study vaccine).

Assessor's comment on study 6096A1-3012: The immunogenicity results of this study show that the responses to the 7vPnC vaccine serotypes were very similar between the two groups. Group 1, which received the 13vPnC vaccine for the 5- and 12-month doses had higher GMCs to some of the additional serotypes (1, 5, 6A and 7F) compared with group 2, which received the 13vPnC vaccine for the 12-month dose only. Group 2 had higher GMCs for serotype 19A than group 1. No OPA results were available for this study, but it is likely that the response to 19A in group 2 to some degree consists of non-functional antibodies. No new safety concerns arise from this study. Overall, the responses are acceptable, and do not conflict with what has been demonstrated in other studies previously.

6096A1-3013 To characterize the immune response by ELISA and OPA at approximately 1 month after vaccination to a single dose of 13vPnC challenge in children vaccinated with a primary series (3 or 2 doses) of pneumococcal conjugate vaccine (9vPnC-meningococcal serogroup C) followed by a booster dose of either pneumococcal conjugate vaccine (PcV) or 23-valent pneumococcal polysaccharide vaccine (PPV23) in Iceland.

- **Description**

- **Methods**

  - Objective(s)

The primary objective of this study was as follows:
- To characterize the immune response by enzyme-linked immunosorbent assay (ELISA) and opsonophagocytic activity (OPA) at approximately 1 month after vaccination with a single dose of 13-valent pneumococcal conjugate vaccine (13vPnC) in children vaccinated with a primary

infant series (2- or 3-dose schedule) of pneumococcal conjugate vaccine (PCV) followed by a toddler dose of either PCV or 23-valent pneumococcal polysaccharide vaccine (23vPS).

The secondary objectives of this study were as follows:

- To describe the immune response by avidity assay to a single dose of 13vPnC in children previously vaccinated with a primary infant series (2- or 3-dose schedule) of PCV followed by a toddler dose of either PCV or 23vPS.
- To describe the kinetics of the immune response over the entire observation period after a single dose of 13vPnC in children previously vaccinated with a primary infant series (2- or 3-dose schedule) of PCV followed by a toddler dose of either PCV or 23vPS.

The safety objective of this study was as follows:

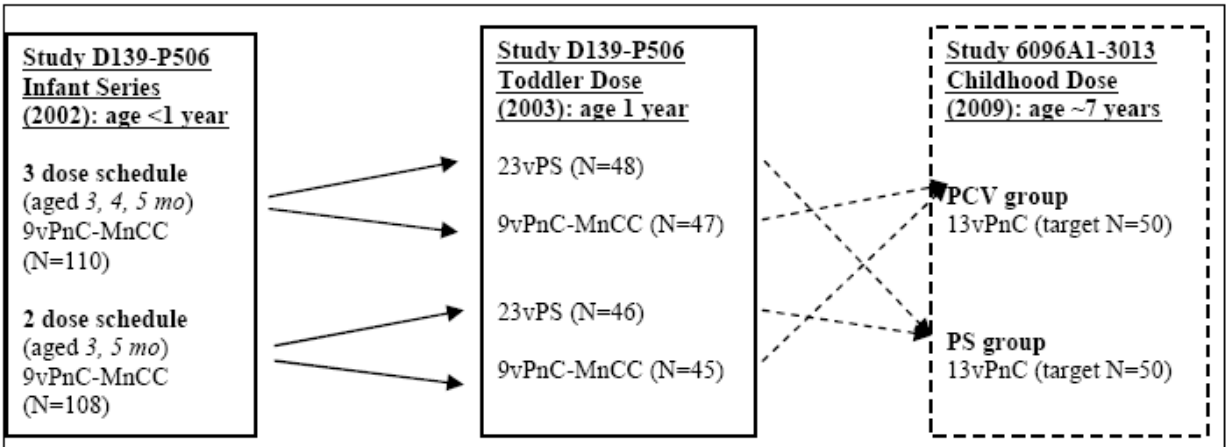
- To evaluate the safety profile of 13vPnC as measured by the occurrence of serious adverse events (SAEs), adverse events (AEs), and solicited local and systemic reactions in the 2 vaccine treatment groups.

The results from the infant series and toddler dose analyses are presented in a separate study report (CSR-54901).

- Study design

Study 6096A1-3013 was a phase 3, single-center, open-label study to evaluate the immunogenicity and safety of 13vPnC in healthy children in Iceland who had participated in study D139-P506. These subjects had previously received a primary infant series of 9-valent pneumococcal conjugate, meningococcal group C saccharide conjugate combination vaccine (9vPnC-MnCC; includes polysaccharides of serotypes 1, 4, 5 6B, 9V, 14, 18C, 19F, and 23F; referred to in this study as PCV) in a 2- or 3-dose schedule followed by a toddler dose of either PCV or 23vPS (ie, PCV/PCV or PCV/23vPS). A minimum of 100 subjects from study D139-P506 (50 subjects each from the PCV and 23vPS toddler dose groups) were to enroll in study 6096A1-3013 and were to receive a childhood dose of 13vPnC (ie, vaccine sequence PCV/PCV/13vPnC or PCV/23vPS/13vPnC).

Study Design



Abbreviations: 9vPnC-MnCC = 9-valent pneumococcal conjugate, meningococcal group C saccharide conjugate combination vaccine; 23vPS = 23-valent pneumococcal polysaccharide vaccine; mo = month; PCV = pneumococcal conjugate vaccine; PS = polysaccharide.
Source: /GLOBAL MEDICAL AFFAIRS/VACCINES/PCV13-PEDIATRIC/Issued/Clinical Protocols/6096A1-3013-EU/.PROTOCOL AND AMENDMENTS/PCV13-PEDIATRIC PRO - 6096A1-3013-EU GMA Protocol - Clean Copy (modified).

- Study population /Sample size

Main Criteria for Inclusion and exclusion:
Subjects were enrolled in the study if they satisfied all of the following inclusion criteria:

participated in study D139-P506 and received all study vaccinations (infant series and toddler dose) as specified in the protocol; and, were healthy children as determined by medical history, physical examination, and judgment of the investigator.
Subjects were excluded from participation in the study if they met any of the following exclusion criteria:
known or suspected hypersensitivity to any component of 7-valent pneumococcal conjugate vaccine (7vPnC) or 13vPnC; history of culture-proven invasive disease caused by S pneumoniae; known or suspected immune deficiency or suppression (including but not limited to: HIV infection, malignancy, immunosuppressive therapy, sickle cell hemoglobinopathy, diabetes); receipt of concomitant vaccination during study period; receipt of immunoglobulin within the previous 3 months; any medical condition that would, in the opinion of the investigator, substantially increase the subject's risk associated with participation and completion of the study or interfere with the evaluation of the study objectives or subject's response; or, receipt of 23vPS or 7vPnC since the completion of study D139-P506.
The sample size for this study was limited by the number of subjects who participated in the original study D139-P506 (CSR-54901; N=224) and the ability to recruit eligible subjects from that study. A minimum of 100 subjects from study D139-P506 were to be enrolled (50 subjects each from the PCV and 23vPS toddler dose groups). However, if it was not possible to enroll the minimum number of subjects within the 6 month enrollment period, then the analysis was to be performed with the number of subjects enrolled at the end of the 6 months.

- Treatments

Each subject was to receive 1 dose (0.5 mL) of 13vPnC following enrollment.

- Outcomes/endpoints

Pneumococcal Antibody Response
Blood samples were to be obtained from all subjects before 13vPnC administration at visit 1 and at visit 3 (28–42 days after 13vPnC administration). A second optional blood draw at day 5–7 after 13vPnC administration was planned in order to describe the kinetics of the immune response. Immunogenicity was to be assessed by ELISA, OPA, and avidity assays.

Safety
The safety parameters included reactogenicity, local reactions and systemic events that occurred for a total of 4 days (day of 13vPnC administration [day 0] and days 1 through 3 after 13vPnC administration), and AEs that occurred from consent to completion of the study at visit 3 (day 28 through day 42 after 13vPnC administration).

- Statistical Methods

The co-primary endpoints were the proportion of subjects achieving a serotype-specific IgG antibody concentration ≥0.35µg/mL by ELISA and the proportion of subjects achieving a titer ≥1:8 by OPA for each of the pneumococcal serotypes at visit 3 (28–42 days after vaccine administration). Two additional endpoints were added to further evaluate response. These were the proportion of subjects achieving a serotype-specific IgG antibody concentration ≥1.0µg/mL by ELISA and the proportion of subjects achieving OPA titers ≥ lower limit of quantitation (LLOQ).
Immunogenicity was also evaluated by avidity assay as a secondary endpoint. The assay performed to measure avidity had a measurable range of 0.117 to 7.5 units. In accordance with the recommendation of the lab performing the assays, values above the upper limit were assigned a value of 8.0 and those below the lower limit were assigned a value of 0.10. Results were expressed as avidity index (AI). The AI was provided for each of the following 5 pneumococcal serotypes: 1, 5, 6B, 19F, and 23F.
The kinetics of the immune response following 13vPnC administration were described based on the antibody levels over time as assessed by IgG ELISA, OPA, and avidity assays.
The proportion of subjects achieving a serotype-specific IgG antibody concentration ≥1.0 µg/mL measured 1 month after the last scheduled dose of 13vPnC was also calculated. In addition, the proportion of subjects achieving OPA titers ≥LLOQ measured 1 month after the last scheduled dose of 13vPnC was calculated. For each serotype, exact, unconditional, 2-sided 95% confidence intervals (CIs) on the proportions were calculated. To assess treatment differences, exact, unconditional, 2-sided, 95% CIs on the difference in proportions [23vPS/13vPnC - PCV/13vPnC] were calculated.
Within each vaccine group and for each antibody concentration or titer, geometric mean concentrations/titers (GMCs/GMTs) were calculated. The geometric mean fold rises (GMFRs) in

antibody concentration/titers (postvaccination/prevaccination) were summarized by geometric means and 95% CIs,. With regard to OPA titers, for analysis purposes, titers below the LLOQ were set equal to 4 (one-half the limit of detection). To assess differences between the 2 vaccine groups, 2-sided, 95% CIs for the ratio of the GMCs and the GMTs were constructed. In addition, the ratio of the GMFRs and corresponding 2-sided, 95% CIs were calculated. The CIs were computed using the Student t distribution for the mean difference of the measures on the logarithmic scale (23vPS/13vPnC relative to PCV/13vPnC).
The safety endpoints were AEs, local reactions, and systemic events, including fever. Fever was defined as an oral temperature ≥38.0°C (100.4°F). Use of antipyretic medication to treat and prevent symptoms was reported with systemic events but analyzed separately. The proportion of subjects with local reactions and systemic events reported on any day within the 4-day period after vaccination was summarized for each type of event.

- **Results**

- Recruitment/ Number analysed

A total of 89 eligible subjects from study D139-P506 consented to participate and received a subsequent 13vPnC dose as part of vaccine sequence 9vPnC-MnCC (primary series)/23vPS (toddler dose)/13vPnC or 9vPnC-MnCC (primary series)/PCV (9vPnC-MnCC; toddler dose)/13vPnC; for convenience, these groups are described as "23vPS/13vPnC" and "PCV/13vPnC" groups.

- Immunogenicity results

At 1 month after vaccination, the proportion of responders achieving a serotype-specific IgG concentration ≥0.35 µg/mL was ≥97% in both vaccine groups for all 13 serotypes (Table 9-3). IgG GMCs were higher in the PCV/13vPnC group than in the 23vPS/13vPnC group for all serotypes except serotype 3 (Table 9-5). The GMC ratios (23vPS/13vPnC relative to PCV/13vPnC) were 1.14 for serotype 3, and for all other serotypes ranged from 0.27 (serotype 1) to 0.89 (serotype 7F). The upper limit of the 95% CI for the GMC ratio was <1.0 for serotypes 1, 4, 5, 9V, 18C, and 23F, indicating a statistically significant difference between the vaccine groups for these 6 serotypes. For the 23vPS/13vPnC group, GMFRs from before vaccination to 1 month after vaccination ranged from 1.83 (serotype 3) to 7.87 (serotype 7F); in the PCV/13vPnC group GMFRs ranged from 1.88 (serotype 19F) to 6.9 (serotype 14), except for serotype 1 (GMFR = 25.51) and serotype 4 (GMFR = 26.07).

Table 9-3: Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After Vaccination (Visit 3) – Evaluable Immunogenicity Population

	Vaccine Group									
	23vPS/13vPnC				PCV/13vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	50	50	100.0	(92.9, 100.0)	37	36	97.3	(85.8, 99.9)	2.7	(-5.0, 14.2)
6B	50	50	100.0	(92.9, 100.0)	37	37	100.0	(90.5, 100.0)	0.0	(-7.3, 9.5)
9V	50	50	100.0	(92.9, 100.0)	37	37	100.0	(90.5, 100.0)	0.0	(-7.3, 9.5)
14	49	49	100.0	(92.7, 100.0)	37	37	100.0	(90.5, 100.0)	0.0	(-7.8, 9.5)
18C	50	50	100.0	(92.9, 100.0)	37	36	97.3	(85.8, 99.9)	2.7	(-5.0, 14.2)
19F	50	50	100.0	(92.9, 100.0)	37	37	100.0	(90.5, 100.0)	0.0	(-7.3, 9.5)
23F	50	50	100.0	(92.9, 100.0)	37	37	100.0	(90.5, 100.0)	0.0	(-7.3, 9.5)
Additional										
1	50	50	100.0	(92.9, 100.0)	37	36	97.3	(85.8, 99.9)	2.7	(-5.0, 14.2)
3	50	50	100.0	(92.9, 100.0)	37	37	100.0	(90.5, 100.0)	0.0	(-7.3, 9.5)
5	50	50	100.0	(92.9, 100.0)	37	37	100.0	(90.5, 100.0)	0.0	(-7.3, 9.5)
6A	50	50	100.0	(92.9, 100.0)	37	37	100.0	(90.5, 100.0)	0.0	(-7.3, 9.5)
7F	50	50	100.0	(92.9, 100.0)	37	37	100.0	(90.5, 100.0)	0.0	(-7.3, 9.5)
19A	50	50	100.0	(92.9, 100.0)	37	37	100.0	(90.5, 100.0)	0.0	(-7.3, 9.5)

Note: PCV = investigational 9vPnC-MnCC vaccine.

a. N = number of subjects with a determinate IgG antibody concentration to the given serotype.
b. n = Number of subjects with an antibody concentration ≥0.35 µg/mL for the given serotype.
c. Exact 2-sided confidence interval based on the observed proportion of subjects.
d. Difference in proportions, 23vPS/13vPnC - PCV/13vPnC reference, expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, 23vPS/13vPnC - PCV/13vPnC reference, expressed as a percentage.

Table 9-5: Comparison of Pneumococcal IgG GMCs (µg/mL) After Vaccination (Visit 3) – Evaluable Immunogenicity Population

	Vaccine Group							
	23vPS/13vPnC			PCV/13vPnC				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	50	4.18	(3.38, 5.16)	37	11.34	(7.74, 16.62)	0.37	(0.25, 0.55)
6B	50	29.51	(21.32, 40.83)	37	41.70	(29.01, 59.96)	0.71	(0.44, 1.15)
9V	50	4.31	(3.68, 5.04)	37	7.39	(6.05, 9.03)	0.58	(0.45, 0.75)
14	49	17.47	(12.76, 23.93)	37	22.78	(15.75, 32.96)	0.77	(0.48, 1.24)
18C	50	2.76	(2.15, 3.56)	37	4.83	(3.48, 6.71)	0.57	(0.38, 0.85)
19F	50	9.78	(7.45, 12.83)	37	11.60	(8.46, 15.92)	0.84	(0.56, 1.27)
23F	50	7.89	(6.18, 10.07)	37	12.25	(8.92, 16.81)	0.64	(0.44, 0.95)
Additional								
1	50	5.28	(4.22, 6.61)	37	19.43	(13.77, 27.41)	0.27	(0.18, 0.40)
3	50	3.28	(2.44, 4.41)	37	2.87	(2.19, 3.76)	1.14	(0.76, 1.72)
5	50	5.75	(4.64, 7.12)	37	15.98	(11.99, 21.30)	0.36	(0.25, 0.51)
6A	50	11.16	(8.80, 14.16)	37	14.07	(10.64, 18.61)	0.79	(0.55, 1.14)
7F	50	7.13	(5.67, 8.96)	37	8.05	(5.94, 10.91)	0.89	(0.61, 1.28)
19A	50	14.62	(11.49, 18.59)	37	17.07	(12.92, 22.55)	0.86	(0.60, 1.23)

Note: PCV = investigational 9vPnC-MnCC vaccine.

a. n = Number of subjects with a determinate antibody concentration for the specified serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
d. Ratio of GMCs; 23vPS/13vPnC to PCV/13vPnC reference.
e. 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 (23vPS/13vPnC - PCV/13vPnC reference).

The proportions of subjects achieving an OPA titer ≥1:8 at 1 month after vaccination were ≥97.2% for all serotypes in both vaccine groups (Table 9-7). OPA GMTs for the 23vPS/13vPnC group ranged from 153 (serotype 3) to 11,156 (serotype 6B), and for the PCV/13vPnC group ranged from 188 (serotype 3) to 11,477 (serotype 6B). The ratio of the GMTs (23vPS/13vPnC to PCV/13vPnC) was ≤1.0 for 11 of the 13 serotypes (Table 9-9).

Table 9-7: Comparison of Subjects Achieving an OPA Antibody Titer ≥1:8 After Vaccination (Visit 3) – Evaluable Immunogenicity Population

	Vaccine Group									
	23vPS/13vPnC				PCV/13vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	50	49	98.0	(89.4, 99.9)	36	35	97.2	(85.5, 99.9)	0.8	(-8.6, 12.7)
6B	49	49	100.0	(92.7, 100.0)	36	36	100.0	(90.3, 100.0)	0.0	(-7.5, 9.7)
9V	49	49	100.0	(92.7, 100.0)	36	36	100.0	(90.3, 100.0)	0.0	(-7.5, 9.7)
14	49	49	100.0	(92.7, 100.0)	36	36	100.0	(90.3, 100.0)	0.0	(-7.5, 9.7)
18C	50	50	100.0	(92.9, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-7.4, 10.0)
19F	49	49	100.0	(92.7, 100.0)	35	35	100.0	(90.0, 100.0)	0.0	(-7.5, 10.0)
23F	50	49	98.0	(89.4, 99.9)	34	34	100.0	(89.7, 100.0)	-2.0	(-10.8, 8.1)
Additional										
1	50	50	100.0	(92.9, 100.0)	37	36	97.3	(85.8, 99.9)	2.7	(-5.0, 14.2)
3	49	48	98.0	(89.1, 99.9)	36	36	100.0	(90.3, 100.0)	-2.0	(-11.1, 7.9)
5	50	49	98.0	(89.4, 99.9)	37	36	97.3	(85.8, 99.9)	0.7	(-8.5, 12.2)
6A	50	50	100.0	(92.9, 100.0)	37	37	100.0	(90.5, 100.0)	0.0	(-7.3, 9.5)
7F	50	49	98.0	(89.4, 99.9)	36	36	100.0	(90.3, 100.0)	-2.0	(-11.3, 7.7)
19A	50	50	100.0	(92.9, 100.0)	37	37	100.0	(90.5, 100.0)	0.0	(-7.3, 9.5)

Note: PCV = investigational 9vPnC-MnCC vaccine.

a. N = number of subjects with a determinate OPA antibody titer to the given serotype.
b. n = Number of subjects with an antibody titer ≥1:8 for the given serotype.
c. Exact 2-sided confidence interval based on the observed proportion of subjects.
d. Difference in proportions, 23vPS/13vPnC - PCV/13vPnC reference, expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, 23vPS/13vPnC - PCV/13vPnC reference, expressed as a percentage.

Table 9-9: Comparison of Pneumococcal OPA GMTs After Vaccination (Visit 2) – Evaluable Immunogenicity Population

	Vaccine Group							
	23vPS/13vPnC			PCV/13vPnC				
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	41	4377	(2686.8, 7129.2)	27	9352	(4304.2, 20319.2)	0.5	(0.20, 1.10)
6B	41	8433	(5324.8, 13356.3)	27	10097	(6754.5, 15093.6)	0.8	(0.44, 1.59)
9V	41	2203	(1455.3, 3334.1)	27	2497	(1396.8, 4464.4)	0.9	(0.45, 1.74)
14	41	2850	(2110.7, 3848.2)	27	2980	(2021.8, 4391.1)	1.0	(0.59, 1.54)
18C	39	3820	(2567.4, 5683.8)	27	6091	(2731.4, 13581.7)	0.6	(0.28, 1.40)
19F	41	1148	(847.8, 1553.3)	27	887	(499.2, 1575.3)	1.3	(0.72, 2.32)
23F	38	1233	(818.3, 1858.6)	27	2134	(1601.1, 2844.0)	0.6	(0.34, 0.99)
Additional								
1	42	332	(250.9, 438.4)	27	1085	(607.8, 1937.8)	0.3	(0.17, 0.54)
3	42	175	(127.8, 240.9)	26	194	(154.5, 243.6)	0.9	(0.59, 1.40)
5	42	419	(255.2, 688.5)	27	1006	(589.2, 1716.9)	0.4	(0.20, 0.87)
6A	41	7640	(5237.8, 11142.5)	27	4163	(1928.4, 8988.3)	1.8	(0.86, 3.92)
7F	41	4982	(4202.7, 5905.3)	27	4120	(2218.1, 7654.2)	1.2	(0.71, 2.05)
19A	41	1149	(849.6, 1555.2)	27	1249	(810.3, 1925.9)	0.9	(0.56, 1.52)

Note: PCV = investigational 9vPnC-MnCC vaccine.

a. n = Number of subjects with a determinate antibody titer for the specified serotype.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
d. Ratio of GMTs; 23vPS/13vPnC to PCV/13vPnC reference.
e. 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 (23vPS/13vPnC - PCV/13vPnC reference).

Adjusted geometric mean avidity (GMA) values (assayed for serotypes 1, 5, 6B, 19F, and 23F only) were also higher in the PCV/13vPnC group than in the 23vPS/13vPnC group. In the 23vPS/13vPnC group, adjusted GMAs ranged from 1.50 (serotype 1) to 3.44 (serotype 23F), while in the PCV/13vPnC group, adjusted GMAs ranged from 2.39 (serotype 19F) to 5.35 (serotype 23F). The ratios of GMAs ranged from 0.34 (serotype 1) to 0.93 (serotype 19F).

- Safety results

Local Reactions: The percentage of subjects experiencing any local reaction was similar in the 23vPS/13vPnC group (90.0%) and the PCV/13vPnC group (87.2%). The incidences of local reactions were generally similar in the 23vPS/13vPnC and PCV/13vPnC groups, respectively, for tenderness (88.0%, 76.9%), redness (50.0%, 66.7%), and swelling (44.0%, 59.0%), and there were no statistically significant differences between the groups in the incidence of any type of local reaction. Significant tenderness was reported for 12.0% of subjects in the 23vPS/13vPnC group and for 20.5% of subjects in the PCV/13vPnC group; and in both groups, reports of redness and swelling were most often reported as being of moderate severity. The mean duration of each type of local reaction was ≤2.8 days in both vaccine groups.

Systemic Events: Fever was reported for only 1 subject in each vaccine group, and both reports were mild (≥38°C but ≤39°C). Use of antipyretic medications to treat or prevent fever was reported for 3 subjects (6.0%) in the 23vPS/13vPnC group and for 4 subjects (10.3%) in the PCV/13vPnC group. The incidences of each of the other types of systemic events were similar in the 23vPS/13vPnC and PCV/13vPnC groups, respectively, for irritability (18.4%, 11.4%), decreased appetite (12.2%, 10.3%), increased sleep (4.0%, 12.8%), rash (6.0%, 2.6%), and decreased sleep (0.0%, 5.1%). The mean duration of each type of systemic event was ≤2.2 days in both vaccine groups.

Unsolicited Adverse Events: Adverse events occurring within approximately 1 month after vaccination were reported for 8 subjects (16.0%) in the 23vPS/13vPnC group and for 7 subjects (17.9%) in the PCV/13vPnC group. The most frequently reported types of AEs were infections and infestations (4.0% of subjects in the 23vPS/13vPnC group and 12.8% of subjects in the PCV/13vPnC group), and

gastrointestinal disorders (6.0%, 2.6%). Most of the events were the types of diseases and conditions often seen in children of this age. Only 2 subjects (in the 23vPS/13vPnC group) had AEs considered related to study vaccine: 1 subject with lymphadenopathy and vomiting, and 1 subject with urticaria. There were no deaths, no serious AEs, and no discontinuations due to AEs during the study.

Assessor's comment: The immunogenicity results of this study show that the group receiving the 23vPS vaccine had lower responses to the majority of serotypes after the childhood dose (at 7 years of age). The 23vPS vaccine has been reported to induce immune hyporesponsiveness, and this could be the case even after 6 years. It is unclear why the results are presented for the 7vPnC serotypes and additional serotypes, when the primary vaccination was given using a 9-vPnC vaccine. However, all results are presented, and no additional information is requested. No new safety signal was detected in this study. Overall, the responses are acceptable, and do not conflict with what has been demonstrated in other studies previously.

3. Discussion on clinical aspects

Both studies present results for vaccination schedules involving other pneumococcal vaccine, i.e. 7vPnC and 23vPS vaccines respectively. They provide useful information, but the results are in agreement with the current SPC, and no type II variation is requested.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

No new information has been obtained from these studies that change the overall benefit/risk balance. No type II variation is requested.

- **Overall conclusion**
- **Recommendation**

Fulfilled: X

No further action required

Not fulfilled:

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable