EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 February 2015
EMA/135763/2015
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 038

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

I. INTRODUCTION

On September 15, 2010, 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 not influence the benefit risk for Prevnenar13 and that there is no consequential regulatory action.

II. SCIENTIFIC DISCUSSION

Information on the pharmaceutical formulation used in the study(ies)

The formulation used in the clinical studies is the currently approved formulation.

Clinical aspects

1. Introduction

The MAH submitted final reports for:

- 6096A1-010; A phase 2, randomized, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of a 13- valent pneumococcal conjugate vaccine in healthy infants given with routine pediatric vaccinations in Korea
- 6096A1-3009; A phase 3, open-label, single-arm trial evaluating the safety, tolerability, and immunogenicity of 13-valent pneumococcal conjugate vaccine in healthy infants given with routine pediatric vaccinations in Mexico.

2. Clinical studies

6096A1-010; A phase 2, randomized, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of a 13- valent pneumococcal conjugate vaccine in healthy infants given with routine pediatric vaccinations in Korea

- **Description**

- **Methods**

  - Objective(s)
    Assess pneumococcal immune responses induced by 13vPnC relative to those induced by 7vPnC when measured 1 month after the infant series (primary objective) and 1 month after the toddler dose (secondary objective).

    The safety objective was to evaluate acceptability of the safety profile of 13vPnC as measured by the rates of local reactions, systemic events, and AEs.

  - Study design
    Study 6096A1-010 was a phase 2, randomized, active-controlled, double-blind, parallel-group multicenter trial conducted to describe the safety, tolerability, and immunogenicity of 13vPnC compared with 7vPnC in healthy infants when administered with routine pediatric vaccines in Korea.

    Blood samples were to be obtained from all subjects 1 month (28 to 42 days) after the third dose in the infant series and 1 month (28 to 42 days) after the toddler dose. For each blood sample, serotype-specific immunoglobulin G (IgG) concentrations were to be determined for

each of the 13 pneumococcal serotypes in 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) using an enzyme-linked immunosorbent assay (ELISA).

- Study population /Sample size
  With a type I error of 0.05 (2-sided), 75 evaluable subjects per treatment group allowed estimation of the proportion of subjects achieving an antibody concentration ≥0.35 µg/mL for each serotype to be within ±7.3% precision. Assuming a dropout rate of at most 15%, enrollment of 180 subjects would ensure 150 evaluable subjects.

- Treatments
  Each subject was to receive 1 dose (0.5 mL) of either 13vPnC or 7vPnC at each of the 4 vaccination visits (2-, 4-, 6-, and 12-month visits). Diptheria, tetanus, and acellular pertussis vaccine (DTaP) was to be administered concomitantly with 13vPnC or 7vPnC at 2, 4, and 6 months of age. In addition, inactivated poliovirus vaccine (IPV) and Haemophilus influenzae type b (Hib) vaccine were to be administered 7 to 21 days after each dose of 13vPnC or 7vPnC during the infant series, and hepatitis B virus vaccine (HBV) was to be administered 7 to 21 days after dose 3. No concomitant vaccines were to be administered with the toddler dose (12-month visit).

- Outcomes/endpoints

Blood samples for determination of serum antibody concentrations were to be drawn 1 month (28 to 42 days) after dose 3 of the infant series and 1 month (28 to 42 days) after the toddler dose. An enzyme-linked immunosorbent assay (ELISA) was performed on these samples to measure the serum concentrations of anticapsular IgG for each of the 13 pneumococcal serotypes(1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F).

Safety assessments were based on information obtained from AE monitoring throughout the study and from the daily monitoring and recording of local reactions and systemic events (including the use of antipyretic medication) by the parent(s)/legal guardian(s) in an e-diary for 4 days after each vaccination (day 1 through day 4). For any local reaction or systemic event that persisted on day 4, the e-diary prompted the parent(s)/legal guardian(s) on a daily basis regarding the status of the local reaction or systemic event until the parent(s)/legal guardian(s) recorded an end date in the e-diary. If the parent(s)/legal guardian(s) did not record an end date, the investigator was asked to record the end date on the CRF Symptom Resolved Dates page. For all local reaction or systemic event that persisted on day 4, the investigator was to record the end date on the CRF Symptom Resolved Dates page.

- Statistical Methods

All statistical analyses for this study were descriptive, and any comparisons between the 13vPnC and 7vPnC groups were descriptive. All immunogenicity analyses were performed using the subjects' random vaccine assignment, regardless of the vaccine actually administered. Missing values were excluded from the immunogenicity analyses; no imputation or estimation of missing values was performed. Pneumococcal assay values reported in the database as being below the limit of quantification (BLQ) (ie, reported as a text value "BLQ", or a reported numeric value below the lower limit of quantification) were adjusted to one-half the lower limit of quantification for analysis. Indeterminate values were not assigned a numerical value.

Within each vaccine group and for each pneumococcal serotype separately, the proportion of subjects achieving serum IgG concentrations ≥0.35 µg/mL (the proportion of responders) was computed, and the exact, unconditional, 2-sided, 95% confidence interval (CI) on the proportion was calculated. To assess differences between the 2 vaccine groups for each of the 13 serotypes, the difference in proportions (13PnC – 7vPnC) was calculated. For each of the 6 additional serotypes, the difference in proportions (13PnC – 7vPnC reference) was also calculated using the lowest proportion of responders in the 7vPnC group among those for the 7 common serotypes as the 7vPnC reference value. Exact, unconditional, 2-sided, 95% CIs on the difference in proportions were computed using the procedure of Chan and Zhang,27 using the standardized test statistic and gamma=0.000001.

For each pneumococcal serotype, geometric mean concentrations (GMCs) of pneumococcal IgG antibodies were calculated, and 2-sided, 95% CIs 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 differences between vaccine groups, the ratios of the GMCs (13vPnC/7vPnC) were calculated and 2-sided, 95% CIs for the geometric mean ratio (GMR) were computed using the

Student t distribution for the mean difference of the measures on the log scale. For each of the 6 additional serotypes, the ratio of the GMCs (13vPnC/7vPnC reference) was also analyzed using the lowest GMC in the 7vPnC group among those for the 7 common serotypes as the 7vPnC reference value.

Empirical reverse cumulative distribution curves (RCDCs) are presented graphically by vaccine group for each of the 13 pneumococcal serotypes.

➢ Results

- Recruitment/ Number analysed

A total of 180 subjects were enrolled and randomly assigned in a 1:1 ratio to receive 13vPnC (N=91) or 7vPnC (N=89).
In the 13vPnC group, 3 subjects who were randomly assigned to treatment were not vaccinated because the parents/legal guardians decided not to participate in the study. Thus, 88 subjects (96.7%) in the 13vPnC group were vaccinated at dose 1; 86 (94.5%) received dose 2; and 85 (93.4%) received dose 3. In the 7vPnC group, all 89 subjects were vaccinated at dose 1, and 88 subjects (98.9%) received dose 2 and dose 3. Overall, 96.1% of subjects completed the infant series (ie, completed the visit for the postinfant series blood draw): 85 (93.4%) in the 13vPnC group and 88 subjects (98.9%) in the 7vPnC group.

- Immunogenicity results

Proportion of Subjects Achieving a Pneumococcal IgG Antibody Concentration≥0.35 µg/mL
Infant dose
For each of the 7 common serotypes, the proportion of subjects achieving IgG concentrations ≥0.35 µg/mL 1 month after dose 3 of the infant series was at least 97.6% in both vaccine groups (Table 9-2). For the 6 additional serotypes unique to 13vPnC, the proportion of responders in the 13vPnC group was 100% for all serotypes except 6A, for which the responder rate was 97.6%. In the 7vPnC group, the proportion of responders was low for serotypes 1, 3, and 7F (≤4.8%), with higher proportions for serotype 19A (100.0%), serotype 6A (72.3%), and serotype 5 (57.5%).

Comparing the responses in the 13vPnC group with those in the 7vPnC group, there was no marked difference between the 2 groups in the proportion of responders (13PnC – 7vPnC) for any of the 7 common serotypes. The differences ranged from -1.2% (for serotypes 6B and 19F) to 0.0% for the remaining 5 serotypes. For the 6 additional serotypes, there was a marked difference between the 2 groups in the proportion of responders for all serotypes except serotype 19A. The differences ranged from 0.0% (for serotype 19A) to 97.6% for serotypes 1 and 3 (Table 9-2).
For each of the 6 additional serotypes, the proportion of responders in the 13vPnC group was also compared with the lowest proportion of responders observed in the 7vPnC group for the 7 common pneumococcal serotypes (ie, 7vPnC reference = 98.8% [serotypes 19F and 23F]). For all of the 6 additional serotypes, the proportion of responders in the 13vPnC group was similar to the 7vPnC reference value, with no marked difference between the 2 groups (13vPnC – 7vPnC reference) for any serotype. The differences were -1.2% for serotype 6A and 1.2% for the remaining 5 serotypes.

Table 9-2: Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After Dose 3 of the Infant Series - Evaluable Infant Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC				7vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	83	83	100.0	(95.7, 100.0)	85	85	100.0	(95.8, 100.0)	0.0	(-4.4, 4.4)
6B	83	82	98.8	(93.5, 100.0)	85	85	100.0	(95.8, 100.0)	-1.2	(-6.5, 3.2)
9V	83	83	100.0	(95.7, 100.0)	85	85	100.0	(95.8, 100.0)	0.0	(-4.4, 4.4)
14	83	83	100.0	(95.7, 100.0)	84	84	100.0	(95.7, 100.0)	0.0	(-4.4, 4.5)
18C	83	83	100.0	(95.7, 100.0)	85	85	100.0	(95.8, 100.0)	0.0	(-4.4, 4.4)
19F	83	81	97.6	(91.6, 99.7)	85	84	98.8	(93.6, 100.0)	-1.2	(-7.3, 4.2)
23F	83	82	98.8	(93.5, 100.0)	85	84	98.8	(93.6, 100.0)	0.0	(-5.5, 5.3)
Additional										
1	83	83	100.0	(95.7, 100.0)	85	2	2.4	(0.3, 8.2)	97.6	(91.8, 99.7)
3	83	83	100.0	(95.7, 100.0)	85	2	2.4	(0.3, 8.2)	97.6	(91.8, 99.7)
5	83	83	100.0	(95.7, 100.0)	80	46	57.5	(45.9, 68.5)	42.5	(31.5, 54.1)
6A	83	81	97.6	(91.6, 99.7)	83	60	72.3	(61.4, 81.6)	25.3	(15.2, 36.3)
7F	83	83	100.0	(95.7, 100.0)	84	4	4.8	(1.3, 11.7)	95.2	(88.3, 98.7)
19A	83	83	100.0	(95.7, 100.0)	82	82	100.0	(95.6, 100.0)	0.0	(-4.5, 4.4)

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, 13vPnC - 7vPnC, expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, 13vPnC – 7vPnC, expressed as a percentage.

Toddler dose

For the 7 common serotypes, the 2 vaccine groups had similar proportions of subjects achieving IgG antibody concentrations ≥0.35 µg/mL after the toddler dose. The proportions of responders to the 7 common serotypes in the evaluable toddler immunogenicity population ranged from 98.7% to 100% in the 13vPnC group and were 100% for all serotypes in the 7vPnC group. The difference in the proportion of responders (13vPnC – 7vPnC) was -1.3% (serotype 14), and 0.0% (serotypes 4, 6B, 9V, 18C, 19F, and 23F). (Table 9-2).

For the 6 additional serotypes unique to 13vPnC, the proportion of responders in the 13vPnC group was 100% for all serotypes except serotype 6A (98.8%). In the 7vPnC group, responder rates were low for serotype 1 (1.3%), serotype 3 (12.0%), serotype 7F (23.6%), but higher for serotype 5 (92.4%), serotype 19A (98.8%), and serotype 6A (100.0%). The difference in the proportion of responders ranged from 76.4% to 98.7% (serotypes 7F, 3, and 1) and from -1.2% to 7.6% (serotypes 6A, 19A, and 5).

Table 9-2: Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After the Toddler Dose – Evaluable Toddler Immunogenicity Population

	Vaccine Group (as Randomzied)									
	13vPnC				7vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	80	80	100.0	(95.5, 100.0)	84	84	100.0	(95.7, 100.0)	0.0	(-4.7, 4.3)
6B	80	80	100.0	(95.5, 100.0)	84	84	100.0	(95.7, 100.0)	0.0	(-4.7, 4.3)
9V	80	80	100.0	(95.5, 100.0)	84	84	100.0	(95.7, 100.0)	0.0	(-4.7, 4.3)
14	79	78	98.7	(93.1, 100.0)	84	84	100.0	(95.7, 100.0)	-1.3	(-6.9, 3.1)
18C	80	80	100.0	(95.5, 100.0)	84	84	100.0	(95.7, 100.0)	0.0	(-4.7, 4.3)
19F	80	80	100.0	(95.5, 100.0)	84	84	100.0	(95.7, 100.0)	0.0	(-4.7, 4.3)
23F	80	80	100.0	(95.5, 100.0)	84	84	100.0	(95.7, 100.0)	0.0	(-4.7, 4.3)
Additional										
1	80	80	100.0	(95.5, 100.0)	78	1	1.3	(0.0, 6.9)	98.7	(93.0, 100.0)
3	80	80	100.0	(95.5, 100.0)	83	10	12.0	(5.9, 21.0)	88.0	(79.0, 94.1)
5	80	80	100.0	(95.5, 100.0)	79	73	92.4	(84.2, 97.2)	7.6	(2.2, 15.8)
6A	80	79	98.8	(93.2, 100.0)	84	84	100.0	(95.7, 100.0)	-1.2	(-6.8, 3.2)
7F	79	79	100.0	(95.4, 100.0)	55	13	23.6	(13.2, 37.0)	76.4	(63.0, 86.8)
19A	80	80	100.0	(95.5, 100.0)	84	83	98.8	(93.5, 100.0)	1.2	(-3.4, 6.5)

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, 13vPnC–7vPnC reference, expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, 13vPnC–7vPnC reference, expressed as a percentage.

Pneumococcal IgG Geometric Mean Concentrations
Infant dose
For the 7 common serotypes, IgG GMCs measured 1 month after dose 3 of the infant series were generally similar for the 13vPnC and 7vPnC groups. For both vaccine groups, IgG GMCs were lowest for serotype 9V (3.33 µg/mL and 3.78 µg/mL for the 13vPnC and 7vPnC groups, respectively) and highest for serotype 14 (14.83 µg/mL and 16.29 µg/mL, respectively) (Table 9-4). For all 6 additional serotypes, IgG GMCs were higher in the 13vPnC group than in the 7vPnC group. In the 13vPnC group, IgG GMCs ranged from 1.60 µg/mL for serotype 3 to 7.44 µg/mL for serotype 1; and in the 7vPnC group, GMCs ranged from 0.02 µg/mL for serotype 1 to 2.65 µg/mL for serotype 19A. IgG GMCs were low in the 7vPnC group, as expected, for serotypes 1, 3, and 7F (≤0.04 µg/mL), while higher IgG GMCs were observed for serotype 19A (2.65 µg/mL), serotype 6A (0.64 µg/mL), and serotype 5 (0.39 µg/mL). For the comparisons of IgG GMCs between the vaccine groups, the ratio of IgG GMCs (13vPnC/7vPnC) for the 7 common serotypes ranged from 0.77 for serotype 4 to 1.17 for serotype 6B; and for the 6 additional serotypes the ratios ranged from 2.24 for serotype 19A to 329.44 for serotype 1 (Table 9-4).

For the 6 additional serotypes, IgG GMCs in the 13vPnC group were also compared with the lowest IgG GMC observed in the 7vPnC group for the 7 common pneumococcal serotypes (ie, 7vPnC reference = 3.78 µg/mL [serotype 9V]). IgG GMCs in the 13vPnC group were higher than the 7vPnC reference value for all additional serotypes except serotype 3, with IgG GMC ratios (13vPnC/7vPnC reference) ranging from 0.42 for serotype 3 to 1.97 for serotype 1.

Table 9-4: Pneumococcal IgG GMCs (µg/mL) After Dose 3 of the Infant Series - Evaluable Infant Immunogenicity Population

	Vaccine Group (as Randomzied)							
	13vPnC			7vPnC				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	83	5.40	(4.62, 6.30)	85	6.97	(5.94, 8.18)	0.77	(0.62, 0.97)
6B	83	5.71	(4.64, 7.03)	85	4.88	(3.96, 6.01)	1.17	(0.87, 1.57)
9V	83	3.33	(2.90, 3.83)	85	3.78	(3.31, 4.33)	0.88	(0.73, 1.07)
14	83	14.83	(12.38, 17.77)	84	16.29	(13.36, 19.85)	0.91	(0.70, 1.19)
18C	83	4.57	(3.98, 5.24)	85	4.73	(4.09, 5.47)	0.97	(0.79, 1.18)
19F	83	3.88	(3.18, 4.72)	85	4.20	(3.55, 4.96)	0.92	(0.71, 1.19)
23F	83	4.29	(3.56, 5.16)	85	4.11	(3.40, 4.98)	1.04	(0.80, 1.36)
Additional								
1	83	7.44	(6.25, 8.85)	85	0.02	(0.02, 0.03)	329.44	(242.98, 446.67)
3	83	1.60	(1.35, 1.89)	85	0.04	(0.03, 0.05)	40.79	(30.27, 54.97)
5	83	5.06	(4.37, 5.85)	80	0.39	(0.30, 0.49)	13.12	(9.92, 17.34)
6A	83	5.73	(4.64, 7.07)	83	0.64	(0.49, 0.82)	9.01	(6.46, 12.56)
7F	83	6.97	(6.07, 8.00)	84	0.04	(0.03, 0.05)	165.90	(122.95, 223.85)
19A	83	5.94	(5.13, 6.89)	82	2.65	(2.29, 3.06)	2.24	(1.83, 2.75)

a. n = Number of subjects with 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; 13vPnC to 7vPnC 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 (13vPnC – 7vPnC reference).

Toddler dose

For the 7 common serotypes, GMCs were generally comparable between the 2 groups and ranged from 4.59 µg/mL (serotype 9V) to 16.81 µg/mL (serotype 6B) in the 13vPnC group and from 4.83 µg/mL (serotype 9V) to 15.64 µg/mL (serotype 14) in the 7vPnC group. For the 7 common serotypes, the GMC ratios ranged from 0.74 (serotype 14) to 1.45 (serotype 19F) (Table 9-4).

For the 6 additional serotypes, the GMCs were higher in the 13vPnC group. GMCs ranged from 1.65 µg/mL (serotype 3) to 13.58 µg/mL (serotype 6A) in the 13vPnC group and from 0.04 µg/mL (serotype 1) to 3.33 µg/mL (serotype 6A) in the 7vPnC group (Table 9-4). For the 6 additional serotypes, the GMC ratios ranged from 4.08 (serotype 6A) to 234.33 (serotype 1).

Table 9-4: Comparison of Pneumococcal IgG GMCs (µg/mL) After the Toddler Dose – Evaluable Toddler Immunogenicity Population

	Vaccine Group (as Randomzied)							
	13vPnC			7vPnC				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
7vPnC								
4	80	6.46	(5.29, 7.90)	84	8.25	(6.88, 9.89)	0.78	(0.60, 1.02)
6B	80	16.81	(14.36, 19.68)	84	15.14	(11.91, 19.25)	1.11	(0.83, 1.48)
9V	80	4.59	(3.91, 5.38)	84	4.83	(4.12, 5.67)	0.95	(0.76, 1.19)
14	79	11.51	(9.59, 13.80)	84	15.64	(13.07, 18.72)	0.74	(0.57, 0.95)
18C	80	6.86	(5.67, 8.29)	84	7.44	(6.27, 8.83)	0.92	(0.72, 1.19)
19F	80	7.75	(6.30, 9.53)	84	5.35	(4.52, 6.33)	1.45	(1.11, 1.88)
23F	80	10.95	(8.77, 13.66)	84	10.44	(8.60, 12.68)	1.05	(0.78, 1.40)
Additional								
1	80	9.29	(7.65, 11.28)	78	0.04	(0.03, 0.05)	234.33	(176.33, 311.41)
3	80	1.65	(1.40, 1.95)	83	0.10	(0.08, 0.13)	16.63	(12.19, 22.69)
5	80	8.92	(7.62, 10.45)	79	1.31	(1.09, 1.56)	6.84	(5.39, 8.67)
6A	80	13.58	(11.28, 16.36)	84	3.33	(2.67, 4.14)	4.08	(3.07, 5.43)
7F	79	11.17	(9.33, 13.37)	55	0.10	(0.07, 0.14)	110.92	(77.09, 159.59)
19A	80	10.12	(8.55, 11.98)	84	2.38	(2.04, 2.78)	4.25	(3.39, 5.33)

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; 13vPnC to 7vPnC 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 (13vPnC–7vPnC reference).

MAH´s Immunogenicity conclusions
These data support a conclusion that 13vPnC will be as effective as Prevenar against the 7 common serotypes, and will provide protection against the 6 additional serotypes.

Assessor's comments: The results of this study are in agreement with previously presented studies. If anything the immune responses were higher than observed in other studies. The results in the two groups were generally of the same magnitude. It is a limitation that no OPA results were presented.

- Safety results

In study 6096A1-010, the safety population for the infant series included 177 subjects who were administered vaccine (88 in the 13vPnC group and 89 in the 7vPnC group). The toddler dose safety population included 172 toddlers (84 in the 13vPnC group and 88 in the 7vPnC group).

Local Reactions – Infant Series
After each vaccine administration, the incidence and severity of each type of local reaction were similar for the 13vPnC and 7vPnC groups, and there were no statistically significant differences between groups in the incidence of any type of local reaction after any dose. For each type of reaction, there was no trend toward increasing or decreasing incidence from dose 1 through dose 3 for either vaccine group.

Across the 3 doses, tenderness was reported for between 23% and 39% of subjects vaccinated with 13vPnC, compared with between 27% and 38% of 7vPnC recipients, and the incidence of significant tenderness (defined as tenderness interfering with limb movement) was ≤8.8% for each group after any dose. At each dose, the incidence of swelling was between 19% and 36% in the 13vPnC group and between 23% and 29% in the 7vPnC group; and the incidence of redness was between 30% and 38% in the 13vPnC group and between 26% and 39% in the 7vPnC group. Most reports of swelling and redness were mild (0.5 cm to 2.0 cm in diameter), and none were severe (>7.0 cm). For both vaccine groups, the highest incidence of swelling and redness occurred consistently on day 2, while the highest incidence of tenderness was observed on day 1 or day 2.

Local Reactions – Toddler Dose
At least 1 local reaction was reported for 47.4% of subjects in the 13vPnC group and for 35.1% of subjects in the 7vPnC group during the 4 days after vaccination. Most cases of local reactions were mild or moderate in severity and the frequencies of local reactions were similar in the 13vPnC and 7vPnC groups, with no statistically significant differences between them.

Some degree of tenderness was reported in 19 (33.9%) subjects who received 13vPnC and 14 (25.9%) subjects who received 7vPnC. Significant tenderness was reported in 3 (5.9%) subjects in the 13vPnC group and 1 (2.0%) subject in the 7vPnC group. Some degree of swelling was reported in 11 (22.4%) 13vPnC subjects and 10 (18.9%) 7vPnC subjects; 1 case was severe (13vPnC group). Moderate swelling occurred in 9 (18.4%) subjects in the 13vPnC group and in 4 (7.8%) subjects in the 7vPnC group. Some degree of redness was reported in 15 (28.8%) 13vPnC subjects and 12 (22.2%) 7vPnC subjects. Eight (8; 16.0%) subjects in the 13vPnC group had moderate redness, and 3 (6.0%) subjects in the 7vPnC group had moderate redness; all other cases were mild.

Systemic Events - Infant Series
In 13vPnC recipients, 1 or more systemic events were reported by 79.5% of subjects after dose 1, 67.2% of subjects after dose 2, and 52.3% of subjects after dose 3. In 7vPnC recipients, 1 or more systemic events were reported by 90.7% of subjects after dose 1, 72.2% of subjects after dose 2, and 53.1% of subjects after dose 3.

All occurrences of fever were mild (≥38°C but ≤39°C), except for 1 occurrence of moderate fever (>39°C but ≤40°C) after dose 3 in a subject who had received 7vPnC. The incidence of mild fever was similar between vaccine groups, and was between 9% and 16% in each group after any dose.
The incidence of irritability was consistently lower in the 13vPnC group (21.0% to 49.4%) than in the 7vPnC group (41.7% to 70.9%) and the difference between groups was statistically significant at dose 1 and dose 3. The incidence of decreased sleep was consistently higher in the 7vPnC group (29.3% to 50.0%) than in the 13vPnC group (16.4% to 37.8%), while the incidence of increased sleep was consistently higher in the 13vPnC group (28.8% to 49.3%) than in the 7vPnC group (21.1% to 39.0%). However, there were no statistically significant differences between the groups for either of these events. The incidence of decreased appetite was generally similar between groups and was between 23% and 33% in each group after any dose, except after dose 2, when the incidence in the 7vPnC group was 44.4%.

Systemic Events – Toddler Dose
Systemic events were reported in 54.7% and 63.1% of subjects in the 13vPnC and 7vPnC groups, respectively. The percentages of subjects reporting any type of systemic event were similar in the 13vPnC and 7vPnC groups after the toddler dose.
Most cases of fever were mild (≥38.0°C but ≤39.0°C). Mild fever was reported in 13.7% and 19.6% of subjects in the 13vPnC and 7vPnC groups, respectively, after the toddler dose and moderate fever (>39.0°C but ≤40.0°C) in 2.0% and 0% of subjects in the 13vPnC and 7vPnC groups, respectively. No cases of fever >40°C were reported. Fever was more frequently reported on day 2 in the 13vPnC group, and on day 1 in the 7vPnC group.

The percentage of subjects reporting other systemic events was generally similar in the 2 vaccine groups. In the 13vPnC and 7vPnC groups, respectively, irritability was reported in 30.5% and 37.5% of subjects; decreased appetite in 22.8% and 27.8% of subjects; increased sleep in 21.2% and 15.4% of subjects; and decreased sleep in 20.4% and 34.5% of subjects.

Spontaneously Reported Adverse Events
The types and frequencies of subjects reporting AEs were similar in the 13vPnC and 7vPnC groups and few differences were noted between the groups. For the 13vPnC and 7vPnC groups, respectively, at least 1 AE was reported in 88.6% and 84.3% of subjects during the infant series; 27.3% and 28.1% of subjects after the infant series; and 33.3% and 43.2% of subjects after the toddler dose.

The AEs were consistent with the types of childhood illnesses and conditions that commonly occur in this age group. During and after the infant series and after the toddler dose, AEs occurring most often were categorized as infections and infestations (eg, upper respiratory tract infection, bronchiolitis, nasopharyngitis, gastroenteritis, and acute otitis media), and skin and subcutaneous tissue disorders (eg, atopic dermatitis, eczema, and rash). Respiratory, thoracic and mediastinal disorders were also common (eg, rhinorrhoea, cough). There were no statistically significant differences between groups in

the incidence of any type of AE during the infant series as a whole or after any individual dose, or after the infant series. After the toddler dose, the incidence of AEs was significantly higher in the 13vPnC group than the 7vPnC group for 1 category (respiratory, thoracic and mediastinal disorders, p=0.031), and 1 event (rhinorrhoea, p=0.026).

During the infant series, 4 subjects had AEs considered related to test article; they included injection site induration and rash in 1 subject each in the 13vPnC group, and pyrexia in 2 subjects in the 7vPnC group. There were no related AEs after the infant series blood draw to before the toddler dose or from the toddler dose through the toddler dose blood draw.

No subjects died during or after the infant series or after the toddler dose. For 13vPnC and 7vPnC, respectively, SAEs were reported in 8 (9.1%) and 9 subjects (10.1%) during the infant series, 9 (10.2%) and 12 (13.5%) subjects after the infant series, and 3 (3.6%) and 3 (3.4%) subjects during the toddler dose. Most of the SAEs were infections. None of the SAEs during the study were considered related to the test article. During the infant series, 1 subject in the 13vPnC group developed Kawasaki disease on day 49 after vaccination with 13vPnC and was withdrawn from the study. The investigator considered the Kawasaki disease not related to 13vPnC (subject recovered fully by day 77 after vaccination). No other subject discontinued from the study because of an AE during the study.

Overall, the safety profile of 13vPnC was acceptable and comparable to that of 7vPnC.

Assessor's comment: The safety profile seen in this study is largely in agreement with what has been seen in previously reported studies. There were no new safety signals.

6096A1-3009; A phase 3, open-label, single-arm trial evaluating the safety, tolerability, and immunogenicity of 13-valent pneumococcal conjugate vaccine in healthy infants given with routine pediatric vaccinations in Mexico

- **Description**

- **Methods**

- Objective(s)

Assess pneumococcal immune responses induced by 13vPnC when measured 1 month after the 3-dose infant series (primary objective), 1 month after the second dose of the infant series (secondary objective), and 1 month after the toddler dose (secondary objective).

The safety objective was to evaluate acceptability of the safety profile of 13vPnC as measured by the rates of local reactions, systemic events, and AEs.

- Study design

This was a phase 3, open-label, single-arm, multicenter trial to evaluate the safety, tolerability, and immunogenicity of 13vPnC administered concomitantly with routine vaccines to healthy infants in Mexico.

The immunogenicity analyses were based on results of assays performed on blood samples obtained 1 month after dose 2, 1 month after dose 3, and 1 month after the toddler dose.

- Study population /Sample size

The study was sized to allow estimation of the proportion of responders after the third dose of 13vPnC to within ±6.0% precision and after the second dose of 13vPnC to within ±7.7% precision. Assuming a dropout rate of at most 25%, 214 subjects overall were to be enrolled to ensure 160 subjects were evaluable.

- Treatments

Subjects were to receive 13vPnC at 2, 4, and 6 months of age (infant series) and at 12 months of age (toddler dose). DTaP-IPV-Hib was to be administered concomitantly with 13vPnC at 2, 4, and 6 months of age. HBV was to be administered concomitantly with 13vPnC at 2 and 6 months of age. Rotavirus vaccine was to be administered concomitantly with 13vPnC at 2 and 4 months of age. The MMR vaccine was to be administered concomitantly with 13vPnC at 12 months of age.

- Outcomes/endpoints

Blood samples (approximately 3 to 5 mL) were collected for immunogenicity assessments at visit 3 (28 to 42 days after dose 2, at 5 months of age), at visit 5 (28 to 42 days after the 3-dose infant series, at 7 months of age) and at visit 7 (28 to 42 days after the toddler dose, at 13 months of age). For all 3 blood samples, serum concentrations (µg/mL) of anticapsular IgG were determined using 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 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 4 days after each vaccination and on the monitoring of AEs during the study.

- Statistical Methods

The primary endpoint for each of the pneumococcal serotypes was the proportion of subjects achieving a serotype-specific IgG concentration ≥0.35 µg/mL measured 1 month after the infant series. This choice of endpoints was based upon the World Health Organization (WHO) guideline for the pneumococcal serotypes. The secondary endpoints for each of the 13 pneumococcal serotypes were the proportion of subjects achieving a serotype-specific IgG antibody concentration ≥0.35 □g/mL measured 1 month after the second infant dose and the toddler dose, and the serotype-specific geometric mean concentrations (GMCs) after the second and third doses of the infant series and after the toddler dose.
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 or higher.

➢ Results

- Recruitment/ Number analysed

A total of 225 subjects were enrolled and assigned to receive 13vPnC in combination with DTaP-IPV-Hib, HBV, rotavirus, and MMR vaccines. Of the 225 subjects enrolled in the study, 1 subject (3009-002-000037) was not vaccinated. This subject was diagnosed with hypospadias, which the investigator determined to be an exclusion criterion and, therefore, withdrew the subject from the study. One (1) additional subject (3009-001-000007) is also listed as not receiving study vaccine. However, this subject was re-enrolled and given another number (3009-001-000008) and was vaccinated.
Overall, 85.3% of the subjects completed the infant series (ie, completed the visit for the postinfant series blood draw). Of the 192 subjects who completed the infant series, 1 subject was withdrawn because of parent/legal guardian request before receiving the toddler dose. Thus, 191 subjects were vaccinated with the toddler dose. Overall, 81.3% of the subjects completed the toddler dose (ie, completed the visit for the toddler dose blood draw).

- Baseline data

The demographic characteristics for all 225 subjects are presented in Table 8-12.

Table 8-12: Demographic Characteristics - All Subjects

	Vaccine Group (as Enrolled) 13vPnC N=225	
	n	%
Sex		
Male	116	51.6
Female	109	48.4
Race		
Other	225	100.0
Ethnicity		
Hispanic or Latino	225	100.0
Age at enrollment (months)		
Mean (SD)	2.1 (0.5)	
Median	2.1	
Min, max	0.8, 3.3	
Weight at enrollment (kg)		
Mean (SD)	5.1 (0.8)	
Median	5.0	
Min, max	3.5, 7.5	

Subject 3009-001-000007 was not vaccinated and was reenrolled as 3009-001-000008.

- Efficacy results

Proportion of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL
Infant Series

For subjects with a valid concentration at both dose 2 and dose 3, Table 9-5 presents a summary of subjects achieving a pneumococcal IgG antibody concentration ≥0.35 µg/mL and the difference in percentages after dose 2 and dose 3 for the evaluable 2-dose and 3-dose infant immunogenicity populations.

Table 9-5: Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL and Difference in Percentages After Dose 2 and After Dose 3 of the Infant Series - Evaluable 2-Dose and 3-Dose Infant Immunogenicity Populations

	Vaccine Group (as Enrolled)									
	13vPnC After Dose 2				13vPnC After Dose 3					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	162	162	100.0	(97.7, 100.0)	162	162	100.0	(97.7, 100.0)	0.0	(-1.2, 1.2)
6B	161	131	81.4	(74.5, 87.1)	161	157	97.5	(93.8, 99.3)	16.1	(9.7, 22.2)
9V	161	153	95.0	(90.4, 97.8)	161	158	98.1	(94.7, 99.6)	3.1	(-0.7, 6.8)
14	162	160	98.8	(95.6, 99.9)	162	160	98.8	(95.6, 99.9)	0.0	(-2.7, 2.7)
18C	162	151	93.2	(88.2, 96.6)	162	160	98.8	(95.6, 99.9)	5.6	(1.4, 9.5)
19F	161	158	98.1	(94.7, 99.6)	161	158	98.1	(94.7, 99.6)	0.0	(-1.2, 1.2)
23F	160	124	77.5	(70.2, 83.7)	160	149	93.1	(88.0, 96.5)	15.6	(8.6, 22.3)
Additional										
1	162	159	98.1	(94.7, 99.6)	162	161	99.4	(96.6, 100.0)	1.2	(-1.4, 3.9)
3	160	155	96.9	(92.9, 99.0)	160	151	94.4	(89.6, 97.4)	-2.5	(-6.1, 1.1)
5	162	158	97.5	(93.8, 99.3)	162	159	98.1	(94.7, 99.6)	0.6	(-2.3, 3.5)
6A	162	153	94.4	(89.7, 97.4)	162	160	98.8	(95.6, 99.9)	4.3	(0.5, 8.0)
7F	162	160	98.8	(95.6, 99.9)	162	160	98.8	(95.6, 99.9)	0.0	(-2.1, 2.1)
19A	162	161	99.4	(96.6, 100.0)	162	161	99.4	(96.6, 100.0)	0.0	(-2.1, 2.1)

a. N = number of subjects with a determinate IgG antibody concentration to the given serotype both after dose 2 and after dose 3.
b. n = Number of subjects with an antibody concentration ≥0.35 µg/mL for the given serotype.
c. Exact 2-sided confidence interval based upon the observed proportion of subjects.
d. Difference in proportions, 13vPnC after dose 3 – 13vPnC after dose 2, expressed as a percentage.
e. Adjusted Wald 2-sided confidence interval for the difference in dependent proportions, 13vPnC after dose 3 – 13vPnC after dose 2, expressed as a percentage; using all subjects with available data from both after dose 2 and after dose 3 blood draws.

Toddler Dose

The proportions of responders to the 7 common serotypes in the evaluable toddler immunogenicity population ranged from 99.4% (serotypes 6B and 23F) to 100% (serotypes 4, 9V, 14, 18C, and 19F) (Table 9-6). For the 6 additional serotypes unique to 13vPnC, the proportion of responders ranged from 96.7% (serotype 3) to 100% (serotypes 1, 5, 6A, 7F, and 19A).

Table 9-6: Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL - Evaluable Toddler Immunogenicity Population

	Vaccine Group (as Enrolled) 13vPnC			
Serotype	**N[a]**	**n[b]**	**%**	**(95% CI[c])**
7vPnC				
4	155	155	100.0	(97.6, 100.0)
6B	155	154	99.4	(96.5, 100.0)
9V	155	155	100.0	(97.6, 100.0)
14	155	155	100.0	(97.6, 100.0)
18C	155	155	100.0	(97.6, 100.0)
19F	155	155	100.0	(97.6, 100.0)
23F	155	154	99.4	(96.5, 100.0)
Additional				
1	155	155	100.0	(97.6, 100.0)
3	152	147	96.7	(92.5, 98.9)
5	155	155	100.0	(97.6, 100.0)
6A	155	155	100.0	(97.6, 100.0)
7F	155	155	100.0	(97.6, 100.0)
19A	155	155	100.0	(97.6, 100.0)

a. N = number of subjects with a determinate IgG antibody concentration to the given serotype.
b. n = Number of subjects with an antibody concentration ≥0.35 µg/mL for the given serotype.
c. Exact 2-sided confidence interval based upon the observed proportion of subjects.

Pneumococcal IgG Geometric Mean Fold Rises
Infant Series
For subjects with a valid concentration at both dose 2 and dose 3, Table 9-7 presents a summary of pneumococcal IgG GMCs and GMFRs in the 2-dose and 3-dose evaluable infant immunogenicity populations.

Table 9-7: Pneumococcal IgG GMCs (µg/mL) and GMFRs After Dose 2 and After Dose 3 - Evaluable 2-Dose and 3-Dose Infant Immunogenicity Populations

	Vaccine Group (as Enrolled)								
	13vPnC After Dose 2			13vPnC After Dose 3					
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	n[a]	GMFR[d]	(95% CI[c])
7vPnC									
4	162	3.59	(3.16, 4.08)	162	3.47	(3.11, 3.89)	162	0.97	(0.87, 1.08)
6B	161	0.82	(0.69, 0.97)	161	5.00	(4.22, 5.93)	161	6.13	(5.07, 7.41)
9V	161	1.84	(1.58, 2.14)	161	2.36	(2.12, 2.63)	161	1.28	(1.12, 1.47)
14	162	5.59	(4.67, 6.70)	162	9.13	(7.85, 10.62)	162	1.63	(1.36, 1.96)
18C	162	1.80	(1.53, 2.11)	162	2.53	(2.24, 2.86)	162	1.41	(1.22, 1.62)
19F	161	4.19	(3.57, 4.91)	161	3.70	(3.22, 4.25)	161	0.88	(0.78, 1.00)
23F	160	0.81	(0.67, 0.96)	160	1.83	(1.53, 2.18)	160	2.27	(1.90, 2.72)
Additional									
1	162	3.44	(2.98, 3.97)	162	4.19	(3.69, 4.76)	162	1.22	(1.06, 1.39)
3	160	1.17	(1.05, 1.30)	160	1.18	(1.04, 1.35)	160	1.01	(0.92, 1.12)
5	162	1.88	(1.65, 2.14)	162	3.13	(2.76, 3.55)	162	1.66	(1.48, 1.86)
6A	162	1.82	(1.55, 2.15)	162	4.09	(3.54, 4.71)	162	2.25	(1.94, 2.59)
7F	162	2.97	(2.65, 3.32)	162	3.78	(3.39, 4.21)	162	1.27	(1.14, 1.43)
19A	162	3.53	(3.03, 4.10)	162	4.19	(3.69, 4.76)	162	1.19	(1.03, 1.37)

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 both the blood draws after dose 2 and after dose 3.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations, or the mean fold rise.
d. Geometric mean fold rises (GMFRs) were calculated using all subjects with available data from both the after dose 2 and after dose 3 blood draws.

Toddler Dose
Table 9-8 presents a summary of pneumococcal IgG GMCs and GMFRs in the evaluable toddler immunogenicity population.

Table 9-8: Pneumococcal IgG GMCs (µg/mL) and GMFRs for After Dose 3 and After the Toddler Dose - Evaluable Toddler Immunogenicity Population

	Vaccine Group (as Enrolled)								
	13vPnC After Dose 3			13vPnC After Toddler Dose					
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	n[a]	GMFR[d]	(95% CI[c])
7vPnC									
4	137	3.39	(3.00, 3.84)	137	5.10	(4.41, 5.89)	137	1.50	(1.32, 1.72)
6B	137	5.10	(4.23, 6.13)	137	15.41	(12.92, 18.38)	137	3.02	(2.49, 3.67)
9V	136	2.34	(2.09, 2.63)	136	3.76	(3.29, 4.29)	136	1.61	(1.40, 1.84)
14	137	9.33	(7.98, 10.91)	137	10.62	(9.16, 12.32)	137	1.14	(0.98, 1.32)
18C	137	2.49	(2.17, 2.85)	137	3.93	(3.45, 4.48)	137	1.58	(1.37, 1.82)
19F	137	3.68	(3.15, 4.30)	137	11.33	(9.68, 13.26)	137	3.08	(2.65, 3.58)
23F	135	1.86	(1.57, 2.20)	135	5.70	(4.81, 6.77)	135	3.07	(2.55, 3.70)
Additional									
1	137	4.43	(3.86, 5.08)	137	5.86	(5.08, 6.75)	137	1.32	(1.14, 1.54)
3	134	1.20	(1.05, 1.38)	134	1.62	(1.42, 1.84)	134	1.35	(1.16, 1.57)
5	137	3.15	(2.75, 3.62)	137	4.75	(4.18, 5.40)	137	1.51	(1.32, 1.72)
6A	137	4.03	(3.42, 4.75)	137	11.64	(9.93, 13.64)	137	2.89	(2.44, 3.42)
7F	137	3.75	(3.35, 4.21)	137	5.81	(5.18, 6.51)	137	1.55	(1.37, 1.74)
19A	137	4.05	(3.53, 4.65)	137	8.95	(7.84, 10.23)	137	2.21	(1.88, 2.59)

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 both the blood draws after dose 3 and after the toddler dose.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations, or the mean fold rise.
d. Geometric mean fold rises (GMFRs) were calculated using all subjects with available data from both the after dose 3 and posttoddler blood draws.

MAH´s Immunogenicity Conclusions
In conclusion, 13vPnC elicits substantial responses to all 13 serotypes after 2 or 3 doses of the infant series. Responses were comparable or higher after a 3-dose infant series. Responses to all 13 serotypes 1 month after the toddler dose were higher than after the infant series.

Assessor's comment: The results of this study were generally in agreement with previously reviewed studies. As mentioned for the other study above, 6096A1-010, it is a limitation that no OPA results were obtained in the study.

- Safety results

In study 6096A1-3009, the infant series safety population included 223 infants vaccinated with 13vPnC at dose 1 and 191 subjects vaccinated at the toddler dose.

Local Reactions
One (1) or more local reactions were reported by 72.0% of subjects after dose 1, 70.9% of subjects after dose 2, 66.7% of subjects after dose 3, and 47.4% of subjects after the toddler dose. Most of the local reactions (tenderness, swelling, and redness) were mild or moderate in severity and occurred on days 1 and 2 after each dose. The incidence of significant tenderness ranged from 12.4% to 15.4% during the infant series and was 3.8% after the toddler dose. There were no reports of severe swelling or redness.

Systemic Events
One (1) or more systemic events were reported by 83.9% of subjects after dose 1, 72.7% of subjects after dose 2, 73.3% of subjects after dose 3, and 59.3% of subjects after the toddler dose. Most

reports of fever were mild in severity. Mild fever ranged from 7.0% to 18.5% of subjects after any dose of the infant series and was 23% after the toddler dose. Moderate fever was reported by 4 subjects in the infant series (1 after dose 2 and 3 after dose 3); no subjects reported moderate fever after the toddler dose. In addition to fever, the most commonly reported systemic event was irritability (69.8% after dose 1, 62.2% after dose 2, 63.2% after dose 3, and 46.7% after the toddler dose).

Spontaneously Reported Adverse Events
At least 1 AE was reported for 35.9% of subjects during the infant series and 26.7% of subjects after the toddler dose. AEs were most frequently observed in the category of infections and infestations (29.6% during the infant series and 11.5% after the toddler dose). The most common individual AEs reported were nasopharyngitis, diarrhea, and viral upper respiratory tract infection during the infant series and pyrexia, nasopharyngitis, diarrhea, and vomiting after the toddler dose. Most AEs reported were generally illnesses/conditions common or expected in children of these age groups.

After the infant series blood draw (when only SAEs and AEs indicative of newly diagnosed chronic medical conditions were reported), 6 (2.7%) subjects reported a total of 7 AEs. AEs were most frequently observed in the category of skin and subcutaneous tissue disorders. Two (2) subjects reported seborrheic dermatitis; all other AEs occurred in 1 subject each.

There were no related AEs reported after any dose during the infant series or after the infant series. Overall, 4 (2.1%) subjects reported a total of 12 related AEs during the toddler dose. All of the related AEs were solicited events that were not recorded in the e-diary by the parent/guardian. Because the events were present, but not recorded, the site entered the symptoms on the AE page of the case report forms.

Severe AEs were reported by 2 (0.9%) subjects during the infant series, 3 subjects (1.3%) after the infant series, and 2 subjects (1.0%) after the toddler dose. One (1) subject reported a life-threatening AE (angioedema) during the infant series. No life-threatening AEs were reported after the infant series or after the toddler dose. None of these were considered to be related to 13vPnC.

No subjects died during the study. A total of 8 subjects reported SAEs during the study; 3 subjects during the infant series, 3 after the infant series, and 2 during the toddler dose phase. None of these were considered to be related to 13vPnC. During the infant series, 1 subject was withdrawn from the study because of an AE (Kawasaki disease), which was not considered to be related to 13vPnC. No subject was withdrawn from the study because of AEs after the infant series or during the toddler dose.

In conclusion, 13vPnC given as a 3-dose infant series followed by a toddler dose at 12 months of age was safe and well tolerated in Mexican infants.

Assessor's comment: the frequency of significant tenderness was slightly higher in this study than the average of the studies submitted previously. As there was no obvious increase in other solicited events, local or systemic, this does not cause further concern.

3. Discussion on clinical aspects
The submitted studies support the previously submitted results on immunogenicity and safety. The studies were performed as part of the global development program and will be used for licensure applications in Korea and Mexico respectively. No further regulatory action is requested.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

No new information has been obtained from these studies that change the overall benefit/risk balance.

- **Recommendation**

No further regulatory action is required.

☒ **Fulfilled**

No further action required

☐ **Not fulfilled:**

IV. ADDITIONAL CLARIFICATIONS REQUESTED

None.