MODULE 2.5 - CLINICAL OVERVIEW

(Addendum - Article 46 of Pediatric Regulation 1901/2006)

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LIST OF ABBREVIATIONS

Abbreviation	Definition
7vPnC	7-valent pneumococcal conjugate vaccine
13vPnC	13-valent pneumococcal conjugate vaccine
ADR	adverse drug reaction
AE	adverse event
AOM	acute otitis media
CI	confidence interval
CSR	clinical study report
EC	European Commission
EMEA	European Medicines Agency
FHA	filamentous hemagglutinin
FIM	fimbrial agglutinogens
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMT	geometric mean titer
Hib	*Haemophilus influenzae* type b
IgG	immunoglobulin G
IM	intramuscular/intramuscularly
IPD	invasive pneumococcal disease
IPV	inactivated poliovirus vaccine
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MMR	measles, mumps, and rubella vaccine
OPA	opsonophagocytic assay
PRN	pertactin
PT	pertussis toxoid
SAE	serious adverse event
SBA	serum bactericidal assay
SC	subcutaneous/subcutaneously
TRS	technical report series
WHO	World Health Organization

1.0 INTRODUCTION

1.1 Background to the Procedure

On 02 December 2008 the Marketing Authorization Holder (MAH) submitted an application for Marketing Authorization Application (MAA) to the European Medicines Agency (EMEA) for Prevenar 13, through the centralized procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. A positive Opinion was adopted on 24 September 2009 by the Committee for Medicinal Products for Human Use and the European Commission (EC) Decision was received on 09 December 2009.

At this time the MAH is submitting the additional data from 2 pediatric studies, which were not submitted in the MAA, but have been completed in the last 6 months in order to comply with the requirements stipulated in Article 46 of the Pediatric Legislation (1901/2006).

The clinical study reports (CSRs) of these studies are presented in Module 5.3.5 and a short critical review of the data is presented in this 2.5 Clinical Overview, which will be submitted as an addendum to the existing 2.5 Clinical Overview originating from the MAA.

1.2 Overview of Studies Presented in This Article 46 Submission

Table 1-1 lists the studies that will be submitted at this time. Immunogenicity and safety data from the infant series and toddler dose are presented in sections 2.0 and 3.0 for studies 6096A1-3003 and 6096A1-3008. Safety data for the 6-month follow-up period are also included for study 6096A1-3008.

Studies 6096A1-3003 and 6096A1-3008 are part of the global clinical development program for the use of Prevenar 13 in infants and were conducted to support licensure in Japan and in Canada, respectively.

Table 1-1: Overview of 13vPnC Clinical Studies

Study	Country	Study Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	Number Vaccinated per Group (as Randomized)
6096A1-3003	Japan	Assess the immune responses induced by 13vPnC 1 month after the infant series. Evaluate the acceptability of the safety profile of 13vPnC as measured by incidence rates of local reactions, systemic events, and AEs. Assess the immune responses induced by 13vPnC 1 month after the toddler dose. Evaluate the comparability/superiority of immunogenicity data after infant series and booster dose between this study in Japanese infants (6096A1-3003-JA) and pivotal licensure study in the United States (6096A1-004).	13vPnC (2, 4, 6, 12) Subcutaneous administration	NA	13vPnC: 193

Table 1-1: Overview of 13vPnC Clinical Studies (Cont'd)

Study	Country	Study Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	Number Vaccinated per Group (as Randomized)
6096A1-3008	Canada	Demonstrate that the immune response induced by NeisVac-C given with 13vPnC is non-inferior to that induced by NeisVac-C given with 7vPnC measured 1 month after the 2-dose NeisVac-C infant series (antigen assessed: MnC using SBA). Demonstrate that the immune responses induced by Pentacel given with 13vPnC are non-inferior to those induced by Pentacel given with 7vPnC measured 1 month after the 3-dose infant series (antigens assessed: PT, FHA, PRN, FIM, Hib). Evaluate the acceptability of the safety profile of 13vPnC as measured by incidence rates of local reactions, systemic events, and AEs. Assess the immune response to 13vPnC 1 month after a 3-dose infant series as measured by serum IgG levels. Assess the immune response to 13vPnC 1 month after the toddler dose as measured by serum IgG levels.	13vPnC or 7vPnC (2, 4, 6, 12) Intramuscular administration	Pentacel (2, 4, 6) NeisVac-C (2, 6, 12) MMR II (12) Varivax III (12)	13vPnC: 300 7vPnC: 303

Table 1-1: Overview of 13vPnC Clinical Studies (Cont'd)

Study	Country	Study Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	Number Vaccinated per Group (as Randomized)
		Assess the immune response induced by NeisVac-C given with 13vPnC relative to the immune response induced by NeisVac-C given with 7vPnC measured 1 month after the toddler dose (antigen assessed: MnC using SBA). Assess the immune response induced by Pentacel given with 13vPnC relative to the immune response induced by Pentacel given with 7vPnC at an alternative cutoff level measured 1 month after the infant series (antigen assessed: Hib).			

Abbreviations: FHA = filamentous hemagglutinin; FIM = fimbrial agglutinogens; Hib = *Haemophilus influenzae* type b; IPV = inactivated poliovirus vaccine; MMR = measles, mumps, rubella vaccine; MnC = meningococcal C; NA = not applicable; PRN = pertactin; PT = pertussis toxoid; SBA = serum bactericidal assay.

Components of vaccines by trade name: MMR II = measles, mumps, and rubella vaccine; NeisVac-C = meningococcal C vaccine; Pentacel = DTaP, IPV, and Hib; Varivax III= varicella vaccine.

2.0 OVERVIEW OF EFFICACY

The immunogenicity data from studies 6096A1-3003 and 6096A1-3008 are reviewed in this overview of efficacy below.

2.1 Immune Responses - Study 6096A1-3003

Study 6096A1-3003 was an open-label, single-group study designed to assess the safety and immunogenicity of 13vPnC in Japanese infants required for licensing in Japan. Immunogenicity data collected in this study were compared with data from the pivotal US study 6096A1-004. A total of 193 subjects were enrolled to receive 13vPnC administered subcutaneously (SC) at 2, 4, 6, and 12 months of age according to local Japanese practice. The primary objective of this study was to assess the immune response to the 13 pneumococcal conjugates induced by 13vPnC 1 month after the infant series. A secondary objective was to assess the immune response to the 13 pneumococcal conjugates induced by 13vPnC 1 month after the toddler dose. Another secondary objective was to evaluate the comparability/superiority of immunogenicity data after the infant series and toddler dose between study 3003 and the pivotal licensure study in the United States (study 004), in which 13vPnC was administered by intramuscular (IM) injection.

2.1.1 Pneumococcal Immunogenicity - Study 3003 Alone

Vaccination with 13vPnC elicited strong IgG responses to all 13 pneumococcal serotypes when measured both 1 month after the infant series and 1 month after the toddler dose. The proportion of subjects achieving an IgG concentration ≥0.35 μg/mL (ie, the proportion of responders) was ≥97.2% for all serotypes after the infant series and ≥98.9% after the toddler dose.

Geometric mean concentrations (GMCs) for the 13 serotypes 1 month after the infant series ranged from 2.57 μg/mL for serotype 23F to 6.97 μg/mL for serotype 19A, with the exception of serotype 14, for which the concentration was 14.69 μg/mL, more than twice that for any other serotype. For all serotypes, IgG GMCs were higher after the toddler dose than before the toddler dose, demonstrating the booster effect of the toddler dose. Geometric mean fold rises (GMFRs) from the pretoddler dose to the posttoddler dose determinations ranged from 2.83 to 7.48.

2.1.2 Pneumococcal Immunogenicity - Comparisons Between Study 3003 and Study 004

After the infant series, antibody responses were generally higher in study 3003 than in study 004. The proportion of responders after the infant series was higher in study 3003 than in study 004 for all serotypes except serotype 19F (for which the proportions were 97.2% for study 3003 and 98.0% for study 004). IgG GMCs were higher in study 3003 than in study 004 for all serotypes, and were more than twice as high in study 3003 as in study 004 for all but 2 serotypes (23F and 6A). The greatest difference between studies was observed for serotype 3 and serotype 4, for which IgG concentrations in study 3003 were more than 5 times as high as in study 004.

After the toddler dose, the proportion of subjects achieving an IgG concentration ≥0.35 μg/mL was ≥98.7% in both studies for all serotypes, except for serotype 3 in study 004 (90.5%). IgG GMCs were higher in study 3003 than in study 004 for all serotypes. In both studies, IgG concentrations declined from the postinfant series determination to the pretoddler dose determination. However, in study 3003, antibody responses were maintained to such an extent that the proportion of responders immediately before the toddler dose was >89% for all serotypes except serotype 3 (79.2%) and serotype 23F (83.0%). For all serotypes, the GMFR in serum antibody concentrations from the pretoddler dose determination to the posttoddler dose determination was higher in study 004 than in study 3003. This is due to the higher pretoddler dose IgG concentrations observed in study 3003 relative to those in study 004.

2.2 Immune Responses - Study 6096A1-3008

Study 6096A1-3008 was a parallel-group, randomized, active-controlled, double-blind, multicenter trial conducted to evaluate the safety, tolerability, and immunogenicity of 13vPnC compared with 7vPnC in healthy infants when coadministered with routine pediatric vaccinations in Canada. A total of 603 subjects were randomly assigned in a 1:1 ratio to receive 13vPnC or 7vPnC administered IM at 2, 4, 6, and 12 months together with concomitant Pentacel vaccine at 2, 4, and 6 months and NeisVac-C vaccine at 2 and 6 months for the infant series. Concomitant NeisVac-C, MMR-II, and Varivax III vaccines were given at the toddler dose. The primary objectives of this study were to demonstrate that the immune responses induced by the 2 concomitant vaccines, NeisVac-C and Pentacel, when administered with 13vPnC were non-inferior to those observed when these vaccines were administered with 7vPnC measured 1 month after the infant series. Immune responses to the 13 pneumococcal conjugate vaccine

serotypes as measured by the proportion of responders achieving a pneumococcal IgG concentration ≥0.35 μg/mL were also evaluated for subjects in the 13vPnC group after the infant series and after the toddler dose. A secondary objective was to assess the immune response induced by NeisVac-C given with 13vPnC relative to the immune response induced by NeisVac-C given with 7vPnC measured 1 month after the toddler dose. Another secondary objective was to assess the immune response induced by Pentacel given with 13vPnC relative to the immune response induced by Pentacel given with 7vPnC at an alternative cutoff level for Hib measured 1 month after the infant series.

2.2.1 Concomitant Vaccine Immunogenicity

The immune response induced by NeisVac-C given with 13vPnC was shown to be non-inferior to the immune response induced by NeisVac-C given with 7vPnC following the infant series and toddler dose. After the infant series, the proportion of responders was 96.8% for the 13vPnC group and 99.3% for the 7vPnC group. This non-inferiority conclusion was supported by the geometric mean titers (GMTs) for meningococcal C serum bactericidal assay (SBA) antibodies, which were approximately 361 for the 13vPnC group and 303 for the 7vPnC group. The ratio of GMTs (13vPnC to 7vPnC) was 1.19, and the lower limit of the 95% confidence interval (CI) of the ratio was 0.96, meeting the non-inferiority criterion. After the toddler dose, the proportion of responders was 100.0% for both the 13vPnC and 7vPnC groups. This non-inferiority conclusion was supported by the GMTs for meningococcal C SBA antibodies, which were approximately 1380 for the 13vPnC group and 1084 for the 7vPnC group. The ratio of GMTs (13vPnC to 7vPnC) was 1.27, and the lower limit of the 95% CI of the ratio was 1.08, meeting the non-inferiority criterion.

The immune responses induced by Pentacel given with 13vPnC were shown to be non-inferior to the immune responses induced by Pentacel given with 7vPnC after the infant series. The immune responses were very similar in the 2 vaccine groups for the specific antigens assessed (pertussis and Hib). All comparisons of the proportions of subjects achieving prespecified antibody levels for concomitant vaccine antigens met the non-inferiority criterion for the 4 pertussis antigens (pertussis toxoid [PT], filamentous hemagglutinin [FHA], pertactin [PRN], and fimbrial agglutinogens [FIM]) and Hib. When Hib was assessed at the higher antibody level (≥1.0 μg/mL), the responses were also shown to be non-inferior. Similarly, when the pertussis

antigen responses were assessed at the higher antibody concentration for FHA and the concentrations achieved by 95% of the 7vPnC group, non-inferiority criteria were also met. GMTs and GMCs in the 2 groups were comparable for all antigens and were formally non-inferior using the 2-fold criterion for each of these antigens.

2.2.2 Pneumococcal Immunogenicity

The proportion of responders (IgG concentrations ≥0.35 µg/mL) after the infant series in the 13vPnC group was greater than 90.0% for all serotypes common to both 13vPnC and 7vPnC. The proportion of responders was greater than 95.0% for each of the 6 additional serotypes unique to 13vPnC, except serotype 3 (79.6%) and serotype 5 (87.0%). IgG GMCs were 1.00 µg/mL or greater for all pneumococcal serotypes, except for serotype 3 (0.63 µg/mL) and serotype 5 (0.90 µg/mL).

The proportion of responders after the toddler dose was greater than 98% for all serotypes common to both 13vPnC and 7vPnC. The proportion of responders was 98.5% or greater for each of the 6 additional serotypes unique to 13vPnC, except serotype 3 (84.8%). IgG GMCs were 2.00 µg/mL or greater for all pneumococcal serotypes, except for serotype 3 (0.74 µg/mL).

3.0 OVERVIEW OF SAFETY

Safety data from 796 infants (493 in 13vPnC group and 303 in 7vPnC group) and 569 toddlers (287 in 13vPnC group and 282 in 7vPnC group) in studies 6096A1-3003 and 6096A1-3008 are reviewed in this 2.5 Clinical Overview addendum. Also included are 6-month follow-up safety data for 580 subjects (291 in the 13vPnC group and 289 in the 7vPnC group) from study 6096A1-3008.

3.1 Study 6096A1-3003

The prompted adverse events (AEs) following each SC dose and the spontaneously reported AEs and serious adverse events (SAEs) during the infant series, after the infant series, and after the toddler dose are reviewed in the sections below.

3.1.1 Prompted Adverse Events

3.1.1.1 Local Reactions

The incidence of local reactions differed markedly between subjects vaccinated SC in study 3003 and subjects vaccinated IM in study 004. After each dose in the infant series, the incidence of tenderness was lower in study 3003 (between 13% and 20% of subjects) than in study 004 (between 72% and 79%). In contrast, the incidence of induration after each dose was higher in study 3003 (between 47% and 54%) than in study 004 (between 27% and 38%), as was the incidence of erythema (between 67% and 75% in study 3003, and between 35% and 49% in study 004). In study 004, there was a trend toward higher incidences of local reactions with each subsequent dose (including the toddler dose), whereas in study 3003, no pattern of increasing or decreasing incidence across doses was apparent.

3.1.1.2 Systemic Events

In study 3003, fever was defined as an axillary temperature ≥37.5°C, while in study 004 fever was defined as a core (rectal) temperature ≥38.0°C. In study 3003, temperatures ≥37.5°C were reported for between 32% and 51% of subjects after any dose (including the toddler dose). The incidence of mild fever (defined as a temperature ≥38°C but ≤39°C) was substantially higher in study 004 (between 24% and 54% after any dose) than in study 3003 (between 6% and 21%). In contrast, the incidence of moderate fever (>39°C but ≤40°C) was similar in both studies, between 1.2% and 8.5% after any dose. There was only 1 report of severe fever (>40°C) in each study.

The frequency of antipyretic medication use after any dose (including the toddler dose) was much higher in study 004 than in study 3003, both when used to treat symptoms (≤8.1% of subjects after any dose in study 3003 compared with between 78% and 84% of subjects in study 004) and when used to prevent symptoms (≤3.3% of subjects after each dose in study 3003, compared with between 75% and 89% of subjects in study 004).

The incidence of other systemic events was consistently lower in study 3003 than in study 004. The frequencies of systemic events after any dose were, for study 3003 and study 004, respectively, as follows: decreased appetite, ≤19% versus ≥54%; irritability, ≤37% versus ≥88%; increased sleep, ≤41% versus ≥70%; and decreased sleep, ≤24% versus ≥45%.

3.1.2 Spontaneously Reported Adverse Events

During the infant series, spontaneously reported AEs were reported for approximately 92% of subjects in study 3003 and 83% of subjects in study 004. In general, the types of AEs reported in both studies were consistent with the types of childhood illnesses and conditions commonly occurring in this age group. In study 3003, the types of AEs reported most frequently during the infant series were infections (most often respiratory tract infection, nasopharyngitis, exanthema subitum, and bronchitis); skin disorders (mostly diaper dermatitis and eczema); general disorders and administration site conditions (mostly injection site erythema and injection site induration); gastrointestinal disorders (mostly diarrhea); and respiratory, thoracic, and mediastinal disorders (mostly rhinorrhea, asthma, and upper respiratory tract inflammation). Similar events were reported after the toddler dose. The types and frequencies of spontaneously reported AEs reported in study 004 were similar to those observed in study 3003.

In study 3003, a total of 30 SAEs were reported for 22 subjects (11.4%): 9 subjects (4.7%) during the infant series, 14 subjects (7.3%) after the infant series, and 1 subject (0.5%) after the toddler dose. Most were infections and infestations that required hospitalization. None of the SAEs were considered related to study vaccine by the investigator. There were no deaths during the study.

Three (3) subjects were withdrawn from study 3003 because of AEs: 2 because of febrile convulsions (considered not related to study vaccine) and 1 because of injection site swelling (considered related to study vaccine).

3.2 Study 6096A1-3008

The prompted AEs following each IM dose and the spontaneously reported AEs and SAEs during the infant series, after the infant series, and after the toddler dose are reviewed in the sections below.

3.2.1 Prompted Adverse Events

3.2.1.1 Local Reactions

The majority of local reactions were mild in severity after any dose. The incidence and severity of local reactions at the pneumococcal vaccine injection site were similar for the 13vPnC and 7vPnC groups. With the exception of significant tenderness (p=0.034) after dose 3 (3.8% and 0.8% in the 13vPnC and 7vPnC groups, respectively), there were no statistically significant differences between the 2 vaccine groups in the incidence of local reactions within 4 days of vaccination after any dose. Significant tenderness was reported by fewer than 4.5% of subjects in either vaccine group following any dose in the infant series and by 2.5% or fewer subjects in either vaccine group following the toddler dose. No subjects reported severe induration or severe erythema at the injection site after any dose.

3.2.1.2 Systemic Events

The incidence of each type of systemic event was generally similar for the 13vPnC and 7vPnC groups after each dose. There were no statistically significant differences between vaccine groups in the incidence of any type of prompted systemic event following any dose, except for irritability, which had a higher incidence in the 13vPnC group (68.8%) than in the 7vPnC group (58.5%; p=0.023) after the toddler dose.

Most occurrences of fever were mild and did not exceed 13.3% in the 13vPnC group and 12.2% in the 7vPnC group following any dose. The incidence of moderate fever did not exceed 2.0% and 1.4% among 13vPnC and 7vPnC recipients, respectively, after any dose. Severe fever (>40°C) was reported in 1 subject (0.5%) in the 7vPnC group.

3.2.2 Spontaneously Reported Adverse Events

During the infant series, spontaneously reported AEs were reported for 76.3% of 13vPnC recipients and 75.9% of 7vPnC recipients. Most of the AEs were the types of conditions and symptoms expected in infants in this age group. The types of AEs reported most frequently during the infant series were infections (most often nasopharyngitis, upper respiratory tract infection, and bronchiolitis); gastrointestinal disorders (mostly diarrhea, vomiting, teething, and constipation); general disorders and administration site conditions (mostly pyrexia, irritability,

and injection site erythema); respiratory, thoracic, and mediastinal disorders (mostly nasal congestion, cough, and rhinorrhea); and skin disorders (mostly eczema, rash, and diaper dermatitis). Similar events were reported after the toddler dose.

AEs that were assessed by the investigator as related to study vaccine were general disorders and administration site conditions (injection site erythema and irritability), gastrointestinal disorders (diarrhea and vomiting), and infections and infestations (nasopharyngitis and upper respiratory tract infection).

A total of 35 SAEs were reported for 25 subjects who received 13vPnC and 20 SAEs for 17 subjects who received 7vPnC. During the infant series, SAEs occurred in 5 subjects (8 events) vaccinated with 13vPnC and in 5 subjects (7 events) vaccinated with 7vPnC. After the infant series, 11 subjects reported 17 SAEs and 7 subjects reported 7 SAEs in the 13vPnC and 7vPnC groups, respectively. Two (2) SAEs in 2 subjects were reported in each of the 13vPnC and 7vPnC groups during the toddler dose. During the 6-month follow-up period, SAEs were reported for 7 subjects (8 SAEs) in the 13vPnC group and 3 subjects (4 SAEs) in the 7vPnC group. Most were infections and infestations that required hospitalization and were not considered related to study vaccine. One (1) subject reported a related SAE of severe pyrexia after receiving the 13vPnC toddler dose. There were no deaths during the study.

Five (5) subjects in the 7vPnC group withdrew from the study after dose 3 because of AEs (urticaria, febrile neutropenia, convulsion, febrile convulsion, and movement disorder).

4.0 BENEFITS AND RISKS CONCLUSIONS

Subcutaneous administration of 13vPnC in study 3003 elicited strong IgG responses to all 13 pneumococcal conjugate serotypes after the infant series and toddler dose. When compared with study 004, the antibody responses were generally higher in study 3003. The higher immune responses in study 3003 may be due to ethnic differences in response to pneumococcal conjugate vaccination. Studies with Prevenar given subcutaneously in Japan and intramuscularly in other Asian populations have also shown a high immune response.

Pneumococcal immunogenicity results from study 3008 with IM administration of 13vPnC also indicate a strong IgG response to all 13 serotypes following the infant series and toddler dose in the 13vPnC group.

Concomitant vaccine immunogenicity data from study 3008 show that the responses elicited by NeisVac-C given with 13vPnC are non-inferior to those elicited by NeisVac-C given with 7vPnC using a 2- and 6-month infant series followed by a toddler dose at 12 months of age. The immune responses to pertussis and Hib antigens induced by Pentacel given with 13vPnC were also shown to be non-inferior to the immune responses induced by Pentacel given with 7vPnC after the 2-, 4-, and 6-month infant series.

Overall, safety and tolerability in study 3003 was acceptable. The incidence of local reactions differed markedly between subjects vaccinated SC in study 3003 and subjects vaccinated IM in study 004. The difference in local reactions is likely due to the different route of administration. The incidence of systemic events was either similar to or lower in study 3003 compared with study 004.

Safety data from study 3008 demonstrate similar rates of local reactions and systemic events among 13vPnC and 7vPnC recipients. The rates and nature of SAEs and other AEs associated with 13vPnC were similar to those associated with 7vPnC. The safety profile of 13vPnC was shown to be comparable with that of 7vPnC and the frequency of adverse drug reactions (ADRs) has not changed compared with the frequency reported in the MAA.

The data presented in this Article 46 submission package do not alter the benefit-risk assessment of 13vPnC; therefore, no further regulatory action is required at this time with respect to the marketing authorization for Prevenar 13.