



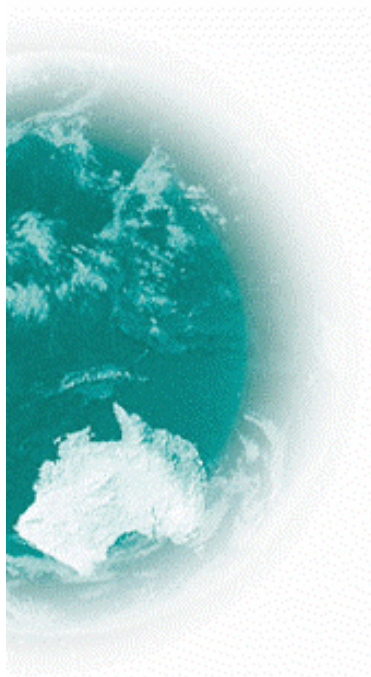
Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

**Australian Public Assessment Report
for
Pneumococcal Polysaccharide Conjugate Vaccine**

Proprietary Product Name: Prevenar 13

Submission No: PM-2009-00110-3-2

Sponsor: Wyeth Australia Pty Ltd



May 2010

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I. Introduction to Product Submission

Submission Details

<i>Type of Submission</i>	New Biological Entity
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	16 March 2010
<i>Active ingredient(s):</i>	13 capsular polysaccharide antigens of <i>Streptococcus pneumoniae</i> serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F - each individually conjugated to Diphtheria CRM ₁₉₇ protein
<i>Product Name(s):</i>	Prevenar 13 pneumococcal polysaccharide conjugate vaccine, 13 valent adsorbed, 0.5mL syringe
<i>Sponsor's Name and Address:</i>	Wyeth Australia Pty Ltd Locked 5002 Baulkham Hills BC NSW 2153
<i>Dose form(s):</i>	Suspension for Injection
<i>Strength(s):</i>	Potency is expressed in terms of the amounts of each polysaccharide in the 0.5mL dose. The vaccine contains 2.2 µg /dose of each of the serotypes, except for serotype 6B which is present at 4.4 µg/dose.
<i>Container(s):</i>	1mL glass syringe with latex-free rubber tip cap, sealed with a latex-free rubber stopper. The syringe presentation includes the following non-product contact components: plunger rod, backstop, and plastic rigid tip cap (PRTC) overseal.
<i>Pack size(s):</i>	Packs of 1 and 10
<i>Approved Therapeutic use:</i>	<p>Active immunisation for the prevention of disease caused by <i>Streptococcus pneumoniae</i> serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (including invasive disease, pneumonia and acute otitis media) in infants and children from 6 weeks up to 5 years of age.</p> <p>The use of Prevenar 13 should be determined by official recommendations, taking into consideration the impact of invasive pneumococcal disease in different age groups as well as variability of serotype epidemiology in different geographical areas.</p>
<i>Route(s) of administration:</i>	Intramuscular injection
<i>Dosage:</i>	0.5mL

Product Background

This is a submission presented by Wyeth Australia Pty Ltd (the sponsor) to register a 13-valent pneumococcal conjugate vaccine (13vPCV) (Prevenar 13) for paediatric use. The abbreviation predominantly used in the application is 13vPnC, although the abbreviation used here, 13vPCV, is consistent with the abbreviation used by the National Health and Medical Research Council

(NHMRC, 2008).¹ Also, in some countries, Prevenar is spelt Prevnar (for example USA) and the former has been used, wherever possible, for consistency.

Although a number of vaccines have been developed, pneumococcal diseases remain a major global cause of morbidity and mortality, especially amongst children, older adults and those at risk individuals, who are chronically ill or who have other serious medical conditions (WHO, 2003).² The aetiological agent, *Streptococcus pneumoniae* (the pneumococcus) is surrounded by a polysaccharide capsule. Differences in the composition of this capsule permit serological differentiation. At least 90 capsular antigenic types have been recognised; each eliciting type-specific immunity (WHO, 2003).² Some of these types are commonly carried in the upper respiratory tract, and some are more frequently associated with invasive disease. The emergence of antibiotic-resistant strains of this organism has become an increasing challenge with 2004 Australian data indicating that up to 18% of invasive strains are resistant to 2 or more classes of antibiotics (NHMRC, 2008).¹

Invasive pneumococcal disease (IPD) is defined as isolation of *S. pneumoniae* from a normally sterile site, most commonly blood. The major clinical syndromes of IPD include pneumonia, meningitis and bacteraemia without focus. In adults, pneumococcal pneumonia is the most common clinical presentation of IPD, while, in children, bacteraemia accounts for more than two-thirds of cases (NHMRC, 2008).¹ The risk of IPD is highest in patients who cannot mount an adequate immune response to pneumococcal capsular antigens, including those with:

- Functional or anatomical asplenia,
- Immunoglobulin deficiency,
- Acute nephrotic syndrome,
- Multiple myeloma,
- Human immunodeficiency virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS),
- Chronic renal failure,
- Organ transplantation, and
- Lymphoid malignancies (NHMRC, 2008).¹

Other groups of patients, although generally immunocompetent, develop IPD of higher incidence and/or severity. These include people with chronic cardiovascular or pulmonary disease, diabetes mellitus, alcohol-related problems, cirrhosis, or cerebrospinal fluid (CSF) leak after cranial trauma or surgery, and those who smoke (NHMRC, 2008).¹ In those without predisposing medical conditions, both frequent otitis media and recently commencing childcare are associated with increased risk of IPD in children, and tobacco smoking with increased risk in adults (NHMRC, 2008).¹ Among the common non-invasive manifestations of pneumococcal diseases are acute otitis media (AOM), sinusitis and bronchitis (WHO, 2003).²

There are currently two different types of pneumococcal vaccine available in Australia (Table 1). A 7-valent pneumococcal conjugate vaccine (7vPCV) became available in 2001 for immunisation of infants and children aged from six weeks to nine years. 7vPCV was added to the National Immunisation Program (NIP) for high-risk children in 2001 and for all children up to 2 years of age from January 2005. The 23-valent pneumococcal polysaccharide vaccine (23vPPV) has been available since 1983. The 23vPPV has an overall protective efficacy of about 60%–70% (WHO, 2003).² A funded program with 23vPPV for Indigenous Australians aged ≥ 50 years began in 1999.

¹ National Health and Medical Research Council. (2008) *Australian Immunisation Handbook*. 9th edn. Canberra: NHMRC.

² World Health Organization (2003) Pneumococcal vaccines. Last updated April 2003. URL. <http://www.who.int/vaccines/en/pneumococcus.shtml> (accessed 29 August 2009).

Non-Indigenous Australians aged 65 years became eligible to receive the vaccine under the NIP from January 2005. In addition, people aged <65 years with underlying chronic conditions predisposing them to IPD can access 23vPPV through the Pharmaceutical Benefits Scheme (PBS).

Currently, the National Health and Medical Research Council (NHMRC, 2008) recommends that 7vPCV be considered for the following groups:

- Healthy children;
- Aboriginal and Torres Strait Islander children living in the Northern Territory, Queensland, South Australia and Western Australia;
- Children with underlying medical conditions associated with greater risk or severity of IPD;
- Children with asplenia (functional or anatomical) ≤ 9 years of age (that is, before their 10th birthday);
- Children ≤ 9 years of age who have been diagnosed with an underlying medical condition (as noted in Table 3.15.2 in NHMRC, 2008) after they received the infant schedule of 7vPCV at 2, 4 and 6 months of age

Table 1: Pneumococcal Vaccines Currently Available In Australia (NHMRC, 2008)¹

Trade Name	Pharmaceutical Company	Type of Vaccine	Components of Vaccine
Prevenar	Wyeth	7-valent pneumococcal conjugate vaccine; 7vPCV	Each 0.5 mL monodose pre-filled syringe contains 2 μ g of pneumococcal serotypes 4, 9V, 14, 18C, 19F, 23F and 4 μ g of serotype 6B, conjugated to a mutant non-toxic diphtheria toxin (CRM ₁₉₇) carrier protein, adsorbed onto 0.5 mg aluminium phosphate. Available in packs of 10 monodose pre-filled syringes.
Pneumovax 23	CSL Biotherapies / Merck & Co Inc	23-valent pneumococcal polysaccharide vaccine; 23vPPV	Each 0.5 mL monodose vial contains 25 μ g of each of pneumococcal serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F; 0.25% phenol.

Currently, the National Health and Medical Research Council (NHMRC, 2008) recommends that 23vPPV be considered for the following groups:¹

- All people aged ≥ 65 years;
- Aboriginal and Torres Strait Islander people ≥ 50 years of age and those 15–49 years of age who have underlying conditions placing them at risk of IPD.
- People aged ≥ 10 years who have underlying chronic illnesses predisposing them to IPD including:
 - Asplenia either functional (including sickle-cell disease) or anatomical; where possible, the vaccine should be given at least 14 days before splenectomy,

- Conditions associated with increased risk of IPD due to impaired immunity, e.g. HIV infection before the development of AIDS, acute nephrotic syndrome, multiple myeloma, lymphoma, Hodgkin's disease and organ transplantation,
- Chronic illness associated with increased risk of IPD including chronic cardiac, renal or pulmonary disease, diabetes, alcohol-related problems,
- CSF leak.
- Tobacco smokers

Children under two years of age, and persons suffering from various states of immunodeficiency, for example HIV infection, do not consistently develop immunity following vaccination with 23vPPV, thus reducing the protective value of the vaccine in some major target groups for pneumococcal disease (WHO, 2003).² The new generation of conjugate vaccines, such as 7vPCV, are protein-polysaccharide combinations, known as conjugate vaccines, and contain various selected polysaccharides bound to a protein carrier. They are designed to induce a T-cell dependent immune response. These vaccines are "likely to be protective even in children under two years of age, and may reduce pneumococcal transmission through a herd effect" (WHO, 2003).² The present indication for Prevenar (7vPCV) is for the "active immunisation of infants and children from 6 weeks to 9 years of age against invasive disease, pneumonia and otitis media caused by *S. Pneumoniae*" (Donohoo, 2009).³

There is increasing evidence of an incidence shift towards serotypes not included in Prevenar. A particular challenge is serotype 19A, the incidence of which has nearly tripled in the US since 2000 (Pai et al., 2005).⁴ There has also been a rise in IPD cases due to non-vaccine serotypes in a number of countries, including the USA (Singleton et al, 2007). In Australia, there have been at least some increases in state jurisdictions in recent years in certain non-7vPCV serotypes, including 19A and 6A (Roche et al., 2008).⁵ It is not a consistent picture across Australia though, for example there have been no increases in 19A and increases in 1, 7F, 18A noted in some indigenous groups in northern Queensland (Hanna et al., 2008).⁶ As a consequence, there is thought to be a need for a multivalent conjugate vaccine with a more extended range of serotypes of *S. pneumoniae* than Prevenar. In the case of the vaccine evaluated in this submission, it builds on the existing 7vPCV (containing serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) serotypes with an additional six serotypes (1, 3, 5, 6A, 7F and 19A).

Wyeth Australia Pty Ltd has applied to register a 13-valent pneumococcal conjugated (PnC) vaccine, Prevenar 13, for active immunisation of infants and children from 6 weeks to 5 years of age against invasive pneumococcal disease (IPD), pneumonia, sepsis, meningitis, bacteraemia and acute otitis media, caused by *S. pneumoniae* (Pneumococcus). Prevenar 13 (13vPCV) has a proposed indication for:

active immunization for the prevention of disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (including sepsis, meningitis, bacteraemia, pneumonia, and AOM) in infants and children from 2 months to 5 years of age."

The caveat is that the use of Prevenar 13:

³ Donohoo E (Man. Ed) *MIMS Annual 2009*. MIMS Publishing.

⁴ Pai R, et al. Postvaccine genetic structure of *Pneumococcus pneumoniae* Serotype 19A from children in the United States. *Journal of Infectious Disease*. 2005; 192: 1988-1995.

⁵ Roche PW, et al. Invasive pneumococcal disease in Australia, 2006. Annual Report. *Communicable Diseases Intelligence*. 2008; 32: 18-30.

⁶ Hanna JN, Humphreys JL, Murphy DM. Invasive pneumococcal disease in indigenous people in north Queensland: an update, 2005-2007. *Medical Journal of Australia* 2008; 189: 43-46.

“should be determined on the basis of official recommendations, taking into consideration the impact of invasive disease in different age groups as well as variability of serotype epidemiology in different geographical areas”.

The NMHRC (2008) contains the official recommendations for pneumococcal vaccination, as previously discussed, and vaccination may be applicable in several at risk groups.¹

Regulatory Status

A similar application to the current Australian submission was approved in the European Union (EU) on 9 December 2009 for the indication:

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

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

The application was approved in Canada on 21 December 2009 for the indication:

Active immunization against Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F causing invasive pneumococcal disease (including sepsis, meningitis, bacteraemic pneumonia, pleural emphysema and bacteraemia) , in infants and children from 6 weeks through 5 years of age.

The application was approved in the USA on 24 February 2010 for the indication:

Prevnar 13 is indicated for active immunization for the prevention of invasive disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

Prevnar 13 is also indicated for the prevention of otitis media caused by Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. No otitis media efficacy data are available for serotypes 1, 3, 5, 6A, 7F, and 19A..

The application was approved in New Zealand on 25 March 2010 for the indication:

Active immunisation against disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (including sepsis, meningitis, pneumonia, bacteraemia and acute otitis media) in infants and children from 6 weeks up to 5 years of age.

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

Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substances (active ingredients)

There are 13 different Drug Substances – corresponding to each of the polysaccharide– Diphtheria CRM₁₉₇ (CRM₁₉₇) conjugates. All the Drug Substances have the carrier protein in common and differ from each other by virtue of the polysaccharide antigen.

Structure

Each serotype is identified by the repeating saccharide unit. The approximate molecular weight of the CRM₁₉₇ protein is 58.4 kDa. Seven of the serotypes (4, 6B, 9V, 14, 18C, 19F, 23F – all also

conjugated to CRM₁₉₇ protein) are contained in the currently registered vaccine Prevenar (AustR 73585 & 118375).

Manufacture

The manufacturing and supply arrangements for the intermediates, drug substances and final product, Prevenar 13 (also referred to as 13vPnC) were reviewed.

The manufacturing process for the drug substances consists of:-

1. Polysaccharide production (13 serotypes)
2. Polysaccharide activation (13 serotypes)
3. CRM₁₉₇ production
4. Conjugation (13 PS-CRM₁₉₇ conjugates)

Steps 1, 2 and 3 relate to intermediates while step 4 produces the drug substance.

1. Polysaccharide production

Fermentation and Harvesting: The production scheme for all polysaccharides, at both production sites, is a four-stage fermentation process followed by inactivation plus a harvest step. Production cultures are terminated by addition of sodium deoxycholate. Lysed cells are separated from the broth by centrifugation. The centrate, containing polysaccharide material, is then filtered and the product is transferred through a closed system to the purification area for further processing.

Purification: All polysaccharides undergo a multi-step purification process ending in filtration. Purified polysaccharide serotypes may be stored either as liquid ($5^{\circ} \pm 3^{\circ}\text{C}$) or frozen ($-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$).

2. Polysaccharide Activation:

Each lot of polysaccharide contains sufficient material for multiple activation and conjugation reactions. The pneumococcal polysaccharide oxidation reaction is performed using a quantity of sodium periodate solution sufficient to achieve the target degree of oxidation. For serotype 3, periodic acid is used as the oxidising agent. Flow charts for the activation process for each serotype were reviewed. The processes vary between serotypes. All are lyophilised for storage

3. CRM₁₉₇ production:

The CRM₁₉₇ manufacturing process is unchanged from that currently approved for Prevenar. The production scheme is a four stage fermentation process plus a harvest step. The four stages of the fermentation process are: primary flask, aspirator bottle, seed fermentor and production fermentor. After harvesting, the CRM₁₉₇ then undergoes purification by filtration, ion exchange column chromatography, concentration by ultrafiltration, and final filtration. It is stored at $-75 \pm 5^{\circ}\text{C}$ for up to 36 months.

4. Conjugation:

The process comprises reductive amination of the activated oligosaccharides or polysaccharides to the CRM₁₉₇ carrier protein. The activated, lyophilized saccharide and lyophilized CRM₁₉₇, or co-lyophilized saccharide and CRM₁₉₇, are reconstituted in either dimethylsulfoxide (DMSO) or an aqueous medium. Sodium cyanoborohydride is added to the saccharide/protein mixture and the reaction is incubated under agitation using time and temperature conditions specific to each serotype. The reaction mix is diluted and purified by ultrafiltration/diafiltration processes and column chromatography. The monovalent bulk conjugates are produced in a succinate buffer matrix, then filtered and dispensed into flexible containers. Before dispensing, the pneumococcal polysaccharide-CRM₁₉₇ conjugates can be stored at $5 \pm 3^{\circ}\text{C}$ for ≤ 30 days. The dispensed monovalent bulk conjugate is stored at $2-8^{\circ}\text{C}$ in containers that have been demonstrated to be compatible with the conjugates. The proposed storage condition for all the conjugates is 24 months at $2 - 8^{\circ}\text{C}$.

Cell banking processes for all 13 *S. pneumoniae* strains and the production *C. diphtheriae* strain are satisfactory.

All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Physical and Chemical Properties

The apparent sizes of the conjugates are based on size exclusion chromatography. Chemical analyses indicate the presence of both saccharide and protein in the conjugates as expected. Amino acid analyses of the conjugates demonstrate that multiple lysine residues in CRM₁₉₇ are modified during the conjugation process, presumably by attachment to the pneumococcal polysaccharides.

The conjugates induce protective immune responses in immunized individuals against the serotypes of pneumococcal bacteria included in the vaccine. The conjugation technology (polysaccharide chemically conjugated to a protein carrier) converts the T-independent polysaccharide antigen to a T-dependent antigen that is capable of eliciting an IgG immune response in young infants. It also results in induction of immunological memory with anamnestic responses observed on re-immunization in both infants and the elderly. CRM₁₉₇ was chosen as the carrier protein for the 13vPnC vaccine based on previous Wyeth experience with CRM₁₉₇ in the *Haemophilus influenzae* type b (Hib) polysaccharide vaccine (HibTITER), the *Neisseria meningitidis* type C polysaccharide vaccine (Meningitec) and the 7-valent Pneumococcal Polysaccharide vaccine (Prevenar).

Impurities arising from the purified polysaccharides, CRM₁₉₇ production, activation and conjugation processes are identified and their elimination to appropriate levels demonstrated.

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substances relevant to the dose form and its intended clinical use were reviewed. The specifications for the pneumococcal saccharide-CRM₁₉₇ conjugates are in compliance with the European Pharmacopoeia (Ph. Eur) monograph for pneumococcal polysaccharide conjugate vaccine (adsorbed) (2150) with one exception that was addressed by the sponsor.

Stability

Stability data have been generated under real time conditions to establish a shelf life and the proposed storage condition for all the conjugates is 24 months at 2 – 8°C. Testing results to date are consistent with the proposed storage period. There is an appropriate ongoing stability program.

Drug Product

Formulation

Prevenar 13 (13vPnC) vaccine is a sterile liquid suspension for intramuscular administration of capsular polysaccharide antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, with each saccharide individually conjugated to plasmid-derived diphtheria CRM₁₉₇ protein. The vaccine is formulated in 5 mM succinate buffer containing 0.85% sodium chloride (NaCl) and 0.02% polysorbate 80, at pH 5.8, and contains aluminium phosphate at 0.25 mg/mL aluminium as an adjuvant. Each 1 mL syringe contains a single 0.5 mL dose of vaccine for parenteral administration, with no preservative.

The container closure system is a pre-filled glass syringe - 1 mL disposable syringes constructed of Type I borosilicate glass. They are pre-assembled with a Luer-Lok adapter, a tip cap and a plastic rigid tip cap (PRTC) overseal. They are received washed, sterilized, and siliconised. The tip cap is composed of West 7025/65 latex-free isoprene bromobutyl rubber. The Luer-Lok adapter is composed of clear polycarbonate and the PRTC is composed of polypropylene. The Luer-Lok

adapter and the PRTC do not have product contact. The closure for the syringes is a plunger stopper composed of West 4432/50 latex-free chlorobutyl rubber. The stoppers are received washed, siliconised and sterilized. The backstop and plunger rod are composed of polypropylene. These components do not have product contact.

Manufacture

Manufacturing process and process controls were reviewed and demonstrated that differences in the process between the two manufacturing sites are minor. Buffers are sterile filtered into the mix and the sterile aluminium phosphate and 13 sterile monovalent bulk conjugates are added aseptically. The filling processes at the two sites are very similar. Filling is conducted aseptically using sterile plant, vaccine and syringe assemblies.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product were reviewed. The specifications for Prevenar 13 comply with the Ph. Eur. monograph for pneumococcal polysaccharide conjugate vaccine (adsorbed) (2150). Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. The product is photostable. Stability data support the proposed shelf-life of 24 months at 2-8 °C. There is an appropriate ongoing stability program.

Quality Summary and Conclusions

The administrative, chemical, pharmaceutical and microbiological data (as applicable) submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

A number of issues requiring resolution before the product could be recommended for approval were identified during the evaluation and were referred to the applicant for comment or resolution. The sponsor responded to all the issues raised.

For each batch of vaccine imported into Australia, TGA Office of Laboratories and Scientific Services (OLSS) should be provided with:-

- Complete protocol of manufacture and quality control testing of the batch.
- 30 doses of the vaccine in the final container.
- Evidence of a Certificate of Release for each batch from the relevant National Control Authority.
- Documentation including appropriate temperature monitors to show that the recommended storage conditions were maintained during the transportation of the vaccine to Australia.
- Reference materials and standard operating procedures (SOPs) necessary for the testing of the vaccine as requested by OLSS.

Distribution of each batch is conditional upon fulfilment of these conditions and approval of release by OLSS.

III. Nonclinical Findings

Pharmacology

Primary pharmacology

A major aim in the development of the original 7-valent Prevenar conjugate vaccine was to improve the efficacy in infants (< 2 years of age), by the induction of a T-cell-dependent immunological response, which is poor or lacking with unconjugated pneumococcal polysaccharides. Conjugation of CRM₁₉₇ protein to the bacterial capsular polysaccharides induces the required T-cell-dependent immunity, and the subsequent immune memory required for an effective vaccine (polysaccharides alone induce T-cell independent immune responses).

Studies on 13vPnC (Prevenar 13) showed strong specific antibody responses against all 13 conjugated pneumococcal capsular polysaccharides contained in the vaccine for rat, rabbit and cynomolgus monkey. A rat study also included a control group vaccinated with 7-valent Prevenar. For the pneumococcal serotypes shared between 7vPnC and 13vPnC, antibody responses (as measured by geometric mean ratio [GMR]) were stronger for 7vPnC compared to 13vPnC. This raises the issue of antigenic overload (and induction of T-cell/B-cell anergy) diminishing immunogenicity (particularly for children). Serum bactericidal assay (SBA) data were not provided, therefore an assessment of protective function at these titres was not possible. Some awareness is recommended on antigenic thresholds for future multivalent vaccine development.

While 13vPnC-induced serum antibody responses were impressive for all species tested, dose regimens need to be considered before extrapolation to humans. For all animal studies, the human clinical dose (30.8 µg total pneumococcal polysaccharide/0.5 mL dose) was used. Furthermore, this 13vPnC dose was administered intramuscularly (IM) to rabbits 5 times and to rats (both studies) and monkeys subcutaneously (SC) 7 times, prior to serum collection for antibody assessment. Blood collection for antibody analysis occurred generally at interim (Day 85 - 87) necropsy and recovery (Day 115) necropsy. This represents a massive vaccine dose for the species tested, so strong antibody responses are expected. Serum antibody levels after 1, 2 or 3 doses would be helpful to determine the true potency of 13vPnC immunogenicity. Relative exposure calculations (Table 2) emphasise the extent of excessive dosage for the test species, based on body surface area (BSA).

While generally declining in titre, specific serum antibody was detected in each species at recovery necropsy (Day 115), 30 days after the final 13vPnC dose, indicating a persistent 13vPnC-induced antibody response.

Secondary Pharmacology

No secondary pharmacology studies were submitted.

Toxicology

Repeat-dose toxicity and local tolerance

There were no systemic toxicological effects caused by 13vPnC in rat, rabbit or cynomolgus monkey, as reflected by a number of measures including mortality rate, body weight fluctuation and food consumption. However, across test species vaccinated via the SC route, there was consistent nodule/ mass/granuloma formation at the injection site, which in some cases persisted for weeks after the final dose, and was associated with persistent and chronic inflammation (determined histologically). This has been observed previously for other vaccines containing aluminium-based adjuvants. Nodules and other injection site irritation were not as problematic after IM vaccine injection (see rabbit studies).

Oedema and erythema were noted regularly for all animal studies, but was not marked or severe, but generally slight, mild or moderate and resolved within a few days (≤ 1 week). While aluminium adjuvants are associated with nodules and other signs of local irritation, comparisons with aluminium phosphate (Al)-containing vehicle controls suggested that antigen was also essential, and that multiple vaccinations could lead to local injection site hyper-sensitivity.

Safety Pharmacology

Three safety pharmacology studies were performed for 13vPnC; a central nervous system (CNS) safety study (male rats), a respiratory safety study (male rats) and cardiovascular study (cynomolgus monkeys). All studies were done after a single 13vPnC dose (SC), but at double the clinical dose (61.6 μ g total pneumococcal polysaccharide).

No respiratory, cardiac or CNS problems related to 13vPnC exposure were detected by these studies.

Post-injection intramuscular irritation study

Male rabbits received one IM dose of 13vPnC, with or without Al, at the standard clinical dose, or saline as a control. After a single 13vPnC dose, no nodules, oedema, erythema or any other signs of dermal irritation were noted. There were no histological signs of inflammation or tissue damage at the injection site. Rabbit body weight and other measures of systemic function were not affected by a single 13vPnC IM dose.

Subcutaneous toxicity study in juvenile rats

A separate study evaluated the safety of the 13-valent pneumococcal conjugate vaccine (13vPnC) in juvenile male and female rats. The 13vPnC vaccine comprised 30.8 μ g total pneumococcal polysaccharide (covering 13 Pn serotypes) and 29 μ g CRM₁₉₇, adsorbed to 0.125 mg Al per 0.5 mL injection volume (0.15 mL volume for 7 day old juvenile rats). Juvenile rats received a total of 5 SC vaccine doses, separated by 2-week intervals (rats were inoculated with 13vPnC on postnatal days (PND) 7, 21, 35, 49 and 63). The control groups were SC administered an equivalent volume of 0.85% sterile saline at the same time points as the vaccine groups. Sub-groups of animals were sacrificed on PND 23 (2 days post second vaccine dose) and on PND 65 (2 days post fifth dose) for blood and tissue collection and analysis. A range of in-life observations and measurements were performed, for example, body weight fluctuations and food consumption, with blood analyses including clinical chemistry and haematology investigations. Pharmacodynamics was also assessed through serum antibody studies.

Unusually high background titres were found at PND 23 for some serotypes (saline control inoculated rats), making it difficult to be certain of 13vPnC immunogenicity after 2 doses. Crucially, 19A was one of the high baseline serotypes. By PND 65 (5 x 13vPnC doses), both by geometric mean titre (GMT) and geometric mean ratio (GMR), specific antibodies against all 13 Prevenar 13 serotypes were significantly boosted by the subcutaneous vaccination regimen. 13vPnC was immunogenic for all serotypes in juvenile rats.

All vaccinated and control rats survived until scheduled termination. No deleterious impact was observed on juvenile rat body weight gain or food consumption due to vaccination, nor did clinical pathology analysis of blood/serum reveal any signs of disease and/or toxicity. No organ weight differences of concern were observed at either necropsy.

Similar to adult rats and monkeys, nodules/masses and other local effects were observed at the vaccine SC injection sites (not saline controls). Nodules and masses were rare until after the third 13vPnC dose, after which the majority of male and female juvenile rats had skin nodules at or near the injection site. Nodule incidence peaked around PND 52, but showed signs of resolution by PND 63. Injection site irritation (oedema/erythema) was also observed in male and female rats, but was

only of slight to mild severity. The greatest length of skin irritation persistence was observed at PND 63 (2.1 ± 0.37 days), although local irritation persistence was generally ≤ 1.5 days.

The high incidence and persistence of nodules/masses/granulomas at or near the vaccine injection site, after multiple injections, was the primary vaccine toxicity concern in juvenile rats.

Relative exposure

The highest exposure to total vaccine antigen, as determined by conversion to body surface area (BSA), was for the rat, followed by the rabbit and monkey (Table 2). The pharmacodynamic, injection site irritation and repeat-dose studies of the included test species all used the expected human (clinical) total pneumococcal polysaccharide concentration of 30.8 µg per 0.5 mL injection dose. The safety pharmacology studies used a double clinical dose (61.6 µg per dose), and are not included in the Table 2 calculations.

Table 2: Body surface area (BSA) calculations of 13vPnC dose exposures in humans and the three study species included in non-clinical evaluations. The anticipated human dose of 30.8 µg total pneumococcal polysaccharide (13 serotypes) was used for all pharmacodynamic and repeat-dose toxicity studies, in all species.

Species (Study)	<u>Weight (kg)</u>	<u>Vaccine Dose*</u> (µg)	<u>Vaccine Dose</u> (mg)	<u>Vaccine Dose</u> (mg/kg)	<u>Dose by Body Surface Area ♦</u> (BSA - mg/m ²)
Human (Proposed human dose)	50	30.8	0.031	0.00062	0.02
Rabbit	3.0	30.8	0.031	0.01	0.15
Rat	0.2	30.8	0.031	0.154	0.92
Monkey	3.0	30.8	0.031	0.01	0.12

* Total pneumococcal antigen per vaccine dose, comprising PnC 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

Pharmacokinetics, carcinogenicity, genotoxicity, reproductive toxicity

No studies were submitted with this submission for pharmacokinetics, carcinogenicity, genotoxicity or reproductive toxicity, in accordance with regulatory guidelines for vaccines. The Australian Medicines in Pregnancy category of B2 is appropriate for the paediatric vaccine.

Nonclinical Summary and Conclusions

Immunogenicity studies in rats (2 studies), rabbits and cynomolgus monkeys showed a significant development of specific immunity (antibody) to all 13 vaccine serotypes after 5 intramuscular (rabbit) or seven subcutaneous (rat and monkey) vaccine injections at the human clinical dose.

Repeat-dose toxicity studies were conducted in rat, rabbit and monkey. No systemic toxicological effects were observed in any test species after several Prevenar13 doses at the human clinical dose.

Injection site nodules/masses/granulomas were consistently observed in species that received the vaccine via the subcutaneous route (rats and monkeys). Two-three doses were needed to see nodule formation, and nodules persisted in some animals until the end of the recovery phase of the studies. Slight to mild oedema was observed, and was associated with acute and chronic inflammatory cell infiltrates into the injection site. Nodules and/or injection site irritation were not observed in rats after a single subcutaneous dose.

Juvenile rat studies showed that the vaccine was fully immunogenic in young animals. No systemic toxicity was observed, but injection site nodules and irritation was noted, similar to that found for adult rats.

Safety studies in rats found no central nervous system, respiratory or cardiac problems after a single double dose of Prevenar13 subcutaneously.

In light of the results contained within this report, there are no nonclinical concerns on the capacity for Prevenar13 to induce immunity in rat, rabbit and monkey, as measured by antibody, to all 13 vaccine serotypes.

There are also no general concerns on systemic vaccine toxicity in animals (juvenile and adult rats, rabbit and monkey). Nodule/ granuloma formation, however, was found consistently after subcutaneous 13vPnC inoculation in all animal species, including juvenile rats. Nodules generally persisted until the end of the recovery phase and were likely associated with AI adjuvant action. Local injection site irritation (oedema/erythema) was also consistently found after subcutaneous inoculation, along with associated acute and chronic inflammation. Macroscopic observations showed that this irritation was generally slight to mild, and while persistent, was resolving towards the end of the post-vaccine recovery phase.

IV. Clinical Findings

Introduction

The sponsor submitted data on two Phase I/II studies, two pivotal Phase III studies and seven supportive Phase III studies. The studies were of very good quality with moderate numbers of subjects and the presentation of the submission was excellent. Individual patient data was available, if required.

The sponsor, in interpreting the EMEA (2006) *Guideline on Clinical Evaluation of New Vaccines*, equates pharmacodynamic studies with studies that characterise the immune response to the vaccine.⁷ The novel components in Prevenar 13 (13vPCV) came from the additional six polysaccharides, building on the polysaccharide components of Prevenar. The IM route of vaccination is not novel and is used for Prevenar (7vPCV). The measurement of the humoral immune response after vaccination is considered by the sponsor to appropriately evaluate the action of the product. The control in all the following studies, which was Prevenar (7vPCV) or 23vPPV, was actually a comparator or “active-control”. It would be unethical to use a non-active control (Paradiso, 2009).⁸

⁷ European Medicines Agency, Committee for Medicinal Products for Human Use (EMA CHMP (2006a) *Guideline on Clinical Evaluation of New Vaccines*. EMA/CHMP/VWP/164653/2005 dated 18 October 2006. European Medicines Agency, Committee for Medicinal Products for Human Use (EMA CHMP (2006b) Annex: SPC Requirements. *Guideline on Clinical Evaluation of New Vaccines*. EMA/CHMP/VWP/382702/2006 dated 18 October 2006.

⁸ Paradiso P. Essential criteria for evaluation of pneumococcal vaccine candidates. *Vaccine* 2009; 275: C15-C18.

There were two Phase I/II studies examining tolerability and immunogenicity of 13vPCV compared with 23vPPV, which included:

- Phase I, randomised controlled trial of the safety, tolerability, and immunogenicity of 13vPCV in healthy adults conducted in the USA (Protocol 6069A1-002)
- Phase I/II, two stage randomised, double-blind trial of the safety, tolerability, and immunogenicity of 13vPCV in healthy infants conducted in the USA (Protocol 6069A1-003)

The first of these studies appears to be substantially published (Scott et al., 2007).⁹

There were two **pivotal studies** constituting pneumococcal non-inferiority trials, which included:

- Phase III, randomised, active-controlled, double-blind trial evaluating the safety, tolerability and immunologic non-inferiority of 13vPCV compared with 7vPCV in healthy infants given with routine paediatric vaccines conducted in the USA (Protocol 6096A1-004); and
- Phase III, randomised, active-controlled, double-blind trial of the safety, tolerability, and immunogenic non-inferiority of 13vPCV compared with 7vPCV in healthy infants given in a 2-, 3-, 4-, and 11- to 12-month schedule with routine paediatric vaccinations conducted in Germany (Protocol 6096A1-006).

The latter study was conducted in toddlers and infants, that is, two studies within one protocol.

There were several supporting studies, examining vaccine scheduling and concomitant vaccination, which included:

- Phase III, randomised, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of 13vPCV in healthy infants given with routine paediatric vaccinations in the UK (Protocol 6069A1-007);
- Phase III, randomised, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of 13vPCV in healthy infants given with routine paediatric vaccinations in France (Protocol 6069A1-008);
- Phase III, randomised, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of 13vPCV in healthy infants given with routine paediatric vaccinations in India (Protocol 6069A1-011);
- Phase III, randomised, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of 13vPCV in healthy infants given with routine paediatric vaccinations in Italy (Protocol 6069A1-500);
- Phase III, randomised, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of 13vPCV in healthy infants given with routine paediatric vaccinations in Spain (Protocol 6069A1-501);
- Phase III, randomised, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of 13vPCV in healthy infants given with a meningococcal C-tetanus toxoid conjugate vaccine and other routine paediatric vaccinations in Spain (Protocol 6069A1-3007); and
- Phase III, open-label trial evaluating the safety, tolerability, and immunogenicity of 13vPCV in older infants and children, who were naïve to previous vaccination with pneumococcal conjugate vaccine, conducted in Poland (Protocol 6069A1-3002).

There were also a number of bridging trials presented including:

⁹ Scott DA, Komjathy SF, Hu BT et al. Phase 1 trial of a 13-valent pneumococcal conjugate vaccine in healthy adults. *Vaccine*. 2007; 25: 6164-6166.

- A formulation bridging trial (Protocol 6069A1-009) conducted in Poland: A Phase 3, randomised, double-blind trial evaluating the safety, tolerability, and immunogenicity of a 13-vPCV manufactured with and without polysorbate 80 (P80) in healthy infants and toddlers (2 study reports) given in a 2-, 3-, 4-, and 12-month schedule with routine paediatric vaccinations; as well as,
- Two manufacturing scale bridging trials (Protocols 6069A1-3000 and 6069A1-3005 respectively): a Phase 3, randomised, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of manufacturing scale 13vPCV; and a Phase 3, randomized, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of 3 lots of 13vPCV in healthy infants given with routine paediatric vaccinations in the United States.

The evaluator concurred with the sponsor and the clinical expert that relevant studies appeared to conform to the principles of Good Clinical Research Practice (GCP). It also appeared that appropriate ethical standards were met in the studies presented.

Efficacy and Immunogenicity

In 2003, the WHO (2005) recommended a threshold antibody concentration of enzyme-linked immunosorbent assay (ELISA) immunoglobulin G (IgG) anti-capsular antibody of 0.35 µg/mL after three doses in infants as a reference value that correlates to protection against IPD, against which new pneumococcal conjugate vaccines (PCVs) should be evaluated.¹⁰ Assessment to determine this level was conducted in a number of ways, including through the use of aggregate pneumococcal serotype data and examination using the reverse cumulative distribution curves (RCDC) (Paradiso, 2009).⁸ This threshold, further discussed at a recent WHO consultation in Canada (WHO, 2008), can be used to demonstrate immunologic non-inferiority of a new vaccine in head-to-head comparison trials that use registered PCVs as a comparator, as a control group would be considered unethical.¹¹ The antibody threshold serves as a correlate for protection against IPD only (WHO, 2008). The sponsor indicates that “clinical studies suggest that vaccine-elicited anticapsular polysaccharide immune responses are also protective against non-bacteraemic pneumonia and AOM”. However, specific IgG antibody concentrations associated with protection against the latter have not been established. The non-inferiority margin recommended in the submission to preserve varying percentages of the 7vPCV vaccine treatment effect is presented in Table 3. From these findings, it may be inferred that the non-inferiority bound (10%) applied in the 13vPCV program’s non-inferiority studies for 13vPCV testing preserves between 85% to 90% of the control effect and, therefore, is reasonably conservative for such non-inferiority trials (Lange et al., 2005).¹²

Other criteria include opsonophagocytic activity (OPA) and immunologic memory (Paradiso, 2009).⁸ Anticapsular polysaccharide antibody is known to mediate protection against pneumococcal disease through opsonophagocytosis, which results in bacterial elimination by phagocytic cells. Opsonic activity of the vaccine-elicited immune responses was determined using serotype-specific functional OPA assays. Unlike ELISA, OPA assays are not standardised to an external standards. OPA assays are compared within a given serotype. The ELISA is only of value as a primary assay as long as it is a strong predictive value for a positive OPA, which is a surrogate of protective immunity (WHO, 2008).¹¹ A study by Henckaerts et al (2007) demonstrated that

¹⁰ World Health Organization (2005) Recommendations for the production and control of pneumococcal conjugate vaccines. *Technical Report Series*. No. 027. Geneva: WHO: 64-68.

¹¹ World Health Organization. Meeting Report: WHO/Health Canada Consultation on Serological Criteria for Evaluation and Licensing of New Pneumococcal Vaccines, Ottawa, Canada, 7-8 July 2008. Geneva: WHO.

¹² Lange S, Freitag G. Choice of delta: requirements and reality-results of a systemic review. *Biometrical Journal*. 2005; 47:12-27.

seropositivity measured by a standardised OPA assay was predictive for a serotype-specific IPD efficacy of PCVs at a threshold titre of ≥ 1.8 . All of these considerations have been taken into consideration by the sponsor (including clinical experts) in the submission.¹³

Table 3: Recommended Non-Inferiority Margin

Preserved Control Effect	Non-Inferiority Margin	
	Control effect = 87.5	Control effect = 95.9
50% (the “usual” level of preservation in non-inferiority studies)	43.8	48.0
60%	35.0	38.4
70%	26.3	28.8
80%	17.5	19.2
85%	13.1	14.4
90%	8.8	9.6

Phase I/II studies

6096A1-002

This was a Phase 1, randomised controlled trial of the safety, tolerability, and immunogenicity of 13vPCV in healthy adults conducted in Kansas, USA in 2004. It appears to have been substantially published as previously indicated (Scott et al., 2007).⁹ Of 30 participants aged 18 to 50 years, 15 healthy subjects were randomised to receive a 13vPCV and 15 to receive a commercially available 23vPPV (1:1 allocation) IM. All completed the study (Table 4).

Table 4: Details of Study 6096A1-002

Design, purpose of study, duration	Parameters studied	Safety	Comments
<p>The primary objective was to evaluate the safety and tolerability of 13vPCV as assessed by local reactogenicity, temperature, and clinical adverse events (AEs).</p> <p>The secondary objectives were to assess the postimmunization responses to the 13 pneumococcal serotypes in the 13vPCV vaccine and to obtain sera to be used as reagents for further development, validation, and standardization of pneumococcal assays. All subjects were scheduled to return on day 15 and day 29</p>	<p>IgG antibodies against the 13 serotypes present in 13vPCV using an ELISA. Oral temperature, local reactions, AEs, serious adverse events (SAEs)</p>	<p>More subjects in the 13vPCV group than in the 23vPPV group reported tenderness at the injection site. This tenderness interfered with arm movement in 10 of the 13vPCV recipients compared with 4 of the 23vPPV recipients; Five (5) subjects (two 13vPCV recipients and three 23vPPV recipients) reported 6 adverse events during the study.</p> <p>The investigator judged all of them as mild or moderate in severity. None of the events was considered at least possibly related to vaccination.</p>	<p>13vPCV well tolerated and immunogenic compared to the comparison (23vPPV)</p>

Results from this study demonstrated an increase in post-vaccination pneumococcal geometric mean concentrations (GMCs) from baseline for all 13 serotypes in the 13vPCV group. Similar increases were noted in the 23vPPV group. The increases in geometric means were statistically significant for all serotypes in both treatment groups, except for serotype 6A that is not present in 23vPPV. Post-vaccination serum IgG GMCs were higher in the 13vPCV group compared with the 23vPPV group for 12 of the 13 serotypes in 13vPCV. Although the study was not powered to show statistically significant differences between groups, post-vaccination GMCs for 6A, 6B, 18C, 19A,

¹³ Henckaerts I, et al. Validation of a routine-opsonophagocytosis assay to predict invasive pneumococcal disease efficacy of conjugate vaccine in children. *Vaccine*. 2007; 25: 2518-2527.

19F, and 23F were statistically significantly higher in the 13vPCV group compared with those in the 23vPPV group. Geometric mean fold rises (GMFRs) from pre-vaccination to post-vaccination were statistically significant for both vaccine groups (except serotype 6A in the 23vPPV group). In the 13vPCV treatment group, GMFRs from baseline were at least 3.74-fold for each of the 13 serotypes in 13vPCV.

6096A1-003

This was a Phase I/II, two stage randomised, double-blind trial of the safety, tolerability, and immunogenicity of 13vPCV in healthy infants conducted in 19 centres in the USA. During stage 1, a total of 48 subjects (24 per study group) were randomly assigned to receive either 3 doses of 13vPCV or 3 doses of 7vPCV. All 48 subjects completed their 3-dose infant series. A total of 10 subjects enrolled in stage 1 and given 13vPCV met the rescue criteria. Eight subjects met the Hib vaccine criteria and 2 met the Prevnar criteria and were withdrawn from the study after stage 1. As part of stage 2, an additional 201 subjects were enrolled, yielding a total of 249 subjects enrolled and randomly assigned in a 1:1 ratio to either the 13vPCV group (122 subjects) or the 7vPCV group (127 subjects). One hundred four subjects in the 13vPCV group and 116 subjects in the 7vPCV group completed the 3-dose infant series. Eighty-four subjects in the 13vPCV group and 100 subjects in the 7vPCV group completed the toddler dose. Overall, 80 subjects in the 13vPCV group and 98 subjects in the 7vPCV group completed the study (Table 5).

Table 5: Details of Study 6096A1-003

Design, purpose of study, duration	Parameters studied	Safety	Comments
Parallel-group, 2-stage, randomized, active-controlled, double-blind study to evaluate the safety, tolerability, and immunogenicity of 13vPCV when administered to healthy infants at 2, 4, 6, and 12 to 15 months of age;	IgG antibodies against the 13 pneumococcal serotypes; a random subset of subjects were also to be analysed for antibodies induced by the concomitant vaccines; Local reactions; systemic events; AEs, SAEs.	<p>The occurrence of local reactions did not differ in frequency or duration between the 13vPCV and 7vPCV groups.</p> <p>There were no reports of severe erythema or swelling/induration after any dose in either the analyses after the infant series or after the toddler dose. Reports of fever in subjects in the 13vPCV group were similar to those in the 7vPCV group. No severe fever was reported during the study. Subjects vaccinated with 13vPCV had a similar pattern of other systemic events when compared with subjects vaccinated with 7vPCV. No SAEs were considered related to study vaccination by the investigator. No statistically significant differences were noted between vaccine groups in incidence of all AEs for all doses in the infant series population. After the toddler dose, otitis media was reported in significantly fewer subjects vaccinated with 13vPCV (1.2%) than those vaccinated with 7vPCV (9.7%; $p=0.013$).</p>	Although this study was not sufficiently powered to demonstrate non-inferiority, the percentage of subjects with antibody concentrations ≥ 0.35 $\mu\text{g/mL}$ to the 7 common Prevnar serotypes met the non-inferiority criterion for phase 3 studies. The non-inferiority criterion was met for each serotype if the lower bound of the 95% CI for the difference in proportion of responders (13vPCV - 7vPCV) was greater than -10%.

Data from this study demonstrated that 13vPCV given intramuscularly with routine paediatric vaccines to healthy infants on a 2, 4, 6, and 12 to 15 month schedule is safe and immunogenic and does not impede the immune response of the infants to the Hib, diphtheria-tetanus-acellular pertussis vaccine (DTPa), hepatitis B vaccine (HBV), and inactivated poliovirus vaccine (IPV) paediatric vaccinations. Responses to all 13 pneumococcal serotypes in 13vPCV were observed as shown by the following: increases in antibody concentrations from pre-vaccination through post-infant series; sustained levels through the pre-toddler dose; and increased serum IgG concentrations after the toddler dose. The responses to the 7 common Prevnar serotypes in subjects in the 13vPCV and 7vPCV groups were similar. No significant differences in antibody response were observed after the infant series or after the toddler dose between the 13vPCV and 7vPCV groups. Although this study was not sufficiently powered to demonstrate non-inferiority, the percentage of subjects with antibody concentrations ≥ 0.35 $\mu\text{g/mL}$ to the 7 common Prevnar serotypes met the

non-inferiority criterion for phase 3 studies. The non-inferiority criterion was met for each serotype if the lower bound of the 95% CI for the difference in proportion of responders (13vPCV - 7vPCV) was greater than -10%.

Pivotal studies

There were two pivotal studies conducted, as nominated by the sponsor. The summary of non-inferiority immunogenicity assessment for the common serotypes in the two pivotal studies is given in Table 6.

Table 6: Summary of Non-Inferiority Immunogenicity Assessment in the Two Pivotal Studies – Protocol 6096a1-004 (German Infants) and Protocol 6069a1-006 (UU Infants) for the Common Serotypes

Serotype	Postinfant Series						Posttoddler Dose			
	% ≥ 0.35 $\mu\text{g/mL}$		GMC Ratio		% ≥ 0.15 $\mu\text{g/mL}$		GMC Ratio		GMFR Ratio	
	Study 004	Study 006	Study 004	Study 006	Study 004	Study 006	Study 004	Study 006	Study 004	Study 006
4	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
6B	Fail	Fail	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
9V	Fail	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
14	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
18C	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
19F	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
23F	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass

Abbreviations: GMC = geometric mean concentration; GMFR = geometric mean fold rise.

Fail = fail non-inferiority criterion; Pass = pass non-inferiority criterion.

6096A1-004 (Pivotal Study)

This was a Phase III, randomised, active-controlled, double-blind trial evaluating the safety, tolerability and immunologic non-inferiority of 13vPCV compared with 7vPCV in healthy infants given with routine paediatric vaccines conducted in 38 sites in the USA. It was one of the two pivotal studies for this application. A total of 666 subjects were randomly assigned to either the 13vPCV group (n=334) or the 7vPCV group (n=332). Of the 666 subjects, 663 (99.5%) received dose 1 of pneumococcal vaccine. Overall, 584 (87.7%) subjects completed the infant series, 294 (88.0%) in the 13vPCV group and 290 (87.3%) in the 7vPCV group. A total of 537 (80.6%) subjects received the toddler dose and 516 (77.5%) subjects completed the toddler dose (that is, had the post-toddler dose visit), 264 (79.0%) in the 13vPCV group and 252 (75.9%) in the 7vPCV group. Overall, 552 (82.9%) of the 666 randomly assigned subjects were contacted via a follow-up telephone call after the last vaccination (whatever dose that might have been). For 534 (80.2%) of these subjects, 272 (81.4%) subjects in the 13vPCV group and 262 (78.9%) subjects in the 7vPCV group), the parents(s)/guardian(s) were reached by telephone and provided the requested information (Table 7).

Overall, 10 of the 13 serotypes met the primary non-inferiority endpoint based on the proportion of subjects achieving a pre-specified antibody concentration measured 1 month after the infant series for each pneumococcal serotype (≥ 0.35 $\mu\text{g/mL}$). In addition, 12 of the 13 serotypes met the non-inferiority endpoint for the comparison of GMCs, both after the infant series and after the toddler dose.

All 13 serotypes met the non-inferiority criterion with respect to the additional antibody level of 0.15 $\mu\text{g/mL}$ (both after the infant series and after the toddler dose). Functional OPA activity was

observed for all 13 serotypes, indicating that the 13vPCV vaccine will likely be effective against pneumococcal disease caused by all 13 serotypes in 13vPCV.

Non-inferiority of 13vPCV relative to 7vPCV was demonstrated for the selected antigens in the concomitant vaccines Pediarix (diphtheria and pertussis) and ActHIB (polyribosylribitol phosphate [PRP]) after the infant series and ProQuad (measles, mumps, rubella, and varicella) and PedvaxHIB (PRP) after the toddler dose.

Table 7: Details of Study 6906A1-004

Design, purpose of study, duration	Parameters studied	Safety	Comments
<p>Demonstrate that the PCV serotype specific IgG responses (proportion of responders at ≥ 0.35 $\mu\text{g/mL}$) induced by 13vPCV are non-inferior to those induced by 7vPCV or 7vPCV reference measured 1 month after the infant series.</p> <p>Demonstrate that the serotype-specific geometric mean IgG concentrations induced by 13vPCV are non-inferior to those induced by 7vPCV or 7vPCV measured 1 month after the toddler dose.</p> <p>Assess the non-inferiority of antigen-specific response (Dip, PT, FHA, PRN, Hib) 1 month after dose 3 of PCV and concomitant vaccine in the 13vPCV group relative to the 7vPCV group.</p>	<p>Samples were to be tested for IgG antibodies against the 13 pneumococcal serotypes; Serum OPAs for the 13 pneumococcal serotypes were to be performed on a randomly selected subset of 200 subjects (100 per vaccine group) using blood samples obtained 1 month after the infant series and 1 month after the toddler dose, as well as various other IgG levels for other vaccine components. Monitoring of local reactions; use of antipyretic medication; AEs; SAEs.</p>	<p>The safety analysis of infant series and toddler data showed that most local and systemic events, including fever, were mild in severity. The AEs observed were characteristic of infants of this age. There were few statistically significant differences between vaccine groups in incidences of individual events and no statistically significant differences between vaccine groups for any related AE. One (1) subject vaccinated with 13vPCV had related SAEs of febrile convulsion and pyrexia after dose 2 of the infant series. These results indicate that the safety profile of 13vPCV is similar to that of 7vPCV, the standard of care for infants and young children.</p>	<p>Results are very encouraging that 13vPCV will be effective with a similar profile of reactions and AEs to 7vPCV.</p>

6099A1-006 (Pivotal Study)

This was a Phase III, randomised, active-controlled, double-blind trial of the safety, tolerability, and immunogenic non-inferiority of 13vPCV compared with 7vPCV in healthy infants given in a 2-, 3-, 4-, and 11- to 12-month schedule with routine paediatric vaccinations conducted in 56 sites in Germany. There were two studies within in this protocol-one looking at infants and the other examining toddlers (Table 8).

Table 8: Details of Study 6096A1-006

Design, purpose of study, duration	Parameters studied	Safety	Comments
<p>Demonstrate that the PCV serotype-specific IgG responses induced by 13vPCV are non-inferior to those induced by 7vPCV or 7vPCV measured 1 month after the infant series.</p> <p>Assess the non-inferiority of antigen-specific response (Dip, HBV, Hib) 1 month after dose 3 of PCV and concomitant vaccine in the 13vPCV group relative to the 7vPCV group.</p>	<p>Assays performed</p> <p>on these blood samples were to include: serotype-specific anticapsular IgG for the 13 pneumococcal serotypes, functional levels as measured by OPA for the 13 pneumococcal serotypes, serum concentrations of total IgG antibodies to Hib polyribosylribitol phosphate (PRP), serum levels of IgG antibodies to diphtheria toxoid, and serum levels of IgG antibodies to hepatitis B surface antigen (HbsAg).</p> <p>Local and systemic reactions, use of antipyretic medication, AEs and SAEs.</p>	<p>The safety analysis of infant series data showed that most local and systemic events, including fever, were mild in severity. No statistically significant differences between vaccine groups were noted for any individual AE or related AE. In addition no related SAEs or deaths were reported in the infant series. These results indicate that the safety profile of 13vPCV is similar to that of 7vPCV, the standard of care for infants and young children.</p>	<p>13vPCV appears to be immunogenic and safe</p>

Infants

A total of 604 subjects were enrolled in the study; 301 were randomly assigned to the 13vPCV group and 303 subjects to the 7vPCV group. The actual number of vaccinated subjects was 603, that is, 300 subjects in the 13vPCV group and 303 subjects in the 7vPCV group. Of 603 vaccinated subjects, 564 subjects were included in the evaluable infant immunogenicity population, the primary immunogenicity analysis population.

The analysis of pneumococcal response showed that non-inferiority of 13vPCV relative to 7vPCV was met for 12 of 13 serotypes at the primary $\geq 0.35 \mu\text{g/mL}$ level; the exception was 6B. However, all serotypes, including 6B, met the non-inferiority criterion for IgG GMCs and at the additional $\geq 0.15 \mu\text{g/mL}$ comparison level, as well as for functional OPA activity. Results from the infant series of this study showed similar variability of response to serotype 6B, as well as cross reactivity between serotype 6B and 6A in both ELISA and OPA results. This finding suggests that 13vPCV will have enhanced effectiveness against disease caused by serotype 6A. Because serotype 6B did not meet the primary non-inferiority criterion, the proportion of responders was computed at the additional comparison level of $\geq 0.15 \mu\text{g/mL}$. This was a pre-specified analysis if any serotype failed at the $\geq 0.35 \mu\text{g/mL}$ cut-off. The $\geq 0.15 \mu\text{g/mL}$ level, which was 1 of the 2 cut-offs used for the approval of Prevenar, was chosen primarily because it has been shown to correlate with efficacy when double preabsorption of the test sera for nonspecific antibody reactivities is performed, as in the current study.

Toddlers

The number of subjects planned for this study was 600, 300 per group, in order to achieve 270 evaluable subjects per group. The evaluable toddler immunogenicity population included 547 subjects: 279 subjects received 13vPCV and 268 subjects received 7vPCV. The vaccine groups were similar with respect to race, ethnicity, and age. Most subjects (96.7%) were white. The mean age was 11.7 (± 0.5) months in each vaccine group. Overall, 53.4% of the evaluable subjects were male; however, the 7vPCV group had more male subjects (57.8%) than the 13vPCV group (49.1%).

The analysis of pneumococcal response showed that non-inferiority of 13vPCV relative to 7vPCV after the toddler dose was met for 12 of 13 serotypes at the primary level of $0.35 \mu\text{g/mL}$; the exception was serotype 3. All serotypes met the non-inferiority criterion at the $0.15 \mu\text{g/mL}$ level. When IgG GMCs were compared between the 2 vaccine groups, 12 of the 13 pneumococcal serotypes had a lower limit of the 95% CI greater than 0.5 for the geometric mean ratio (GMR), thus meeting the prespecified non-inferiority criterion. Although the GMR for serotype 3 was 0.3, the GMC in the 13vPCV group was almost 15 times higher than that in the 7vPCV group.

The proportion of subjects achieving an OPA antibody titre $\geq 1:8$ was similar in the 2 vaccine groups for each of the 7 common serotypes. The lower limits of the 95% CIs for the differences between groups were at least -4.0%. For the 6 additional serotypes, the lower limits of the CIs were at least 0.7%. When OPA GMTs were compared between the 2 vaccine groups, GMTs for the 7 common serotypes were high in both groups, and GMTs for the 6 additional serotypes were significantly greater in the 13vPCV group than in the 7vPCV group. The analyses demonstrated the ability of 13vPCV to elicit a higher level of functional antibody to each of the 6 additional serotypes compared to 7vPCV, while maintaining similar responses to the 7 common serotypes.

For concomitant vaccine antigens, the lower limits of the 95% CIs for the GMRs were 0.71 or higher, exceeding 0.5, the 2-fold non-inferiority criterion for each of the 3 antigens.

Supporting studies

There were several supporting studies. A number of these were examining the immunogenicity and efficacy results of 13vPCV when combined with concomitant vaccines.

This was a multi-centre, Phase III, randomised, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of 13vPCV in healthy infants given with routine paediatric vaccinations conducted in the UK. Approximately 600 subjects were to be randomly assigned in a 1:1 ratio to each of 2 vaccine groups: 300 in the 13vPCV + Pediacel + NeisVac-C (meningitis C vaccine) + Menitorix (meningitis C/Hib vaccine) group and 300 in the 7vPCV + Pediacel + NeisVac-C + Menitorix group. For the infant series (2 and 4 month doses), 278 subjects were enrolled and randomly assigned in a 1:1 ratio to receive either 13vPCV (n=139) or 7vPCV (n=139). The distribution by sex showed more male subjects (56%) than female subjects (42.6%) in the 13vPCV group and more female subjects (51%) than male subjects (44.8%) in the 7vPCV group. The majority of subjects were characterized as being white (88.5%) in the 2 vaccine groups. The mean age (\pm SD) at dose 1 was 2.1 (\pm 0.3) months in each vaccine group, with ages ranging from 1.1 months to 3.1 months (Table 9).

The difference in percentage of responders to the Hib component of Pediacel in the 13vPCV group was -1.5 (95% CI: -7.1, 3.7) at the primary endpoint of serum IgG concentrations ≥ 0.15 μ g/mL. The GMCs in the 13vPCV group and 7vPCV group were 3.40 μ g/mL (95%CI: 2.65, 4.37) and 4.44 μ g/mL, respectively with a GMR of 0.77 (95%CI: 0.54, 1.08). At the higher secondary comparison threshold of ≥ 1.0 μ g/mL, the proportion of responders in the 13vPCV group was similar to the 7vPCV group (85.1% vs. 89.2%; difference = -4.1) and the lower 95% CI of the difference was 13.4.

The difference in responses to the pertussis components (PT, FHA, PRN, and FIM) of Pediacel in the 13vPCV group were greater than -5 (95% LCI) compared to the responses in the 7vPCV group for the primary endpoint of proportion of responders at 5 EU/mL (PT, FHA, PRN) and 2.2 EU/mL (FIM). At the additional analysis points of 7.82 EU/mL for FHA, and when comparing to the level achieved by 95% of 7vPCV recipients, differences in responses for all antigens were greater than -8, except for PRN. For PRN at the ≥ 15 EU/mL level, the difference was only -3.1, but the 95% LCI was -10.0. The RCDC curves for PRN in the 13vPCV and 7vPCV groups were nearly identical across the entire range of antibody concentrations for all antigens when comparing GMCs; geometric mean ratios were 0.98 to 1.00.

Table 9: Details of Study 6096A1-007

Design, purpose of study, duration	Parameters studied	Safety	Comments
<p>Evaluate the immune response after NeisVac-C (MnC using SBA) and 13vPCV relative to NeisVac-C and 7vPCV measured 1 month after the infant series.</p> <p>Evaluate the immune response after Pediacel (antigens assessed: PT, FHA, PRN, FIM, Hib) and 13vPCV relative to Pediacel and 7vPCV measured 1 month after the infant series.</p> <p>Assess the immune responses to 13vPCV measured 1 month after the infant series.</p>	<p>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) were determined for each blood sample and expressed as microg/mL.</p> <p>In addition, the following assays were performed on blood samples collected 1 month after the infant series and 1 month after the toddler dose. Serum conc. of total IgG antibodies to Hib PRP were determined by ELISA. Results were reported as anti-PRP in units of μg/mL. Serum levels of IgG antibodies to PT, FHA, PRN (69 kDa outer membrane protein), and FIM were measured using anti-Bordetella pertussis ELISAs. Results were reported as EU/mL. Serum was analysed by SBA to measure anti-group C meningococcal functional antibodies.</p> <p>Results were reported as the reciprocal of the highest dilution of specimen giving greater than 50% bacterial killing, as determined by comparison to assay background controls.</p> <p>Local and systemic reactions, use of antipyretic medication, AEs and SAEs.</p>	<p>The safety analysis of infant series data showed that most local and systemic events were mild and no clinically important differences between vaccine groups were noted for these prompted symptoms or unsolicited adverse events. These results indicate that the safety profile of 13vPCV is similar to that of 7vPCV, the standard of care for infants and young children.</p>	<p>Good evidence that 13vPCV can be given with other vaccines</p>

The observed point estimate for proportion of responders to the meningitis C antigen in NeisVacC at a geometric mean titre ≥ 1.8 was identical (99.2%) in the 13vPCV and 7vPCV groups. The ratio of geometric mean titres between groups was 0.89 (95% CI: 0.68, 1.16).

With respect to the pneumococcal serotypes, the percentage of subjects who had antibody concentrations above the WHO-defined protective threshold of ≥ 0.35 $\mu\text{g/mL}$ for the 7 common Prevenar serotypes ranged from 40.2% (serotype 6B) to 95.3% (serotype 4). The percentage of subjects in the 13vPCV group with antibody concentrations ≥ 0.35 $\mu\text{g/mL}$ for the 6 additional non-Prevenar serotypes was also high, ranging from 79.2% (serotype 6A) to 97.2% (serotype 1). GMCs for the 13vPCV group after dose 2 of the infant series ranged from 0.26 $\mu\text{g/mL}$ for serotype 6B to 2.38 $\mu\text{g/mL}$ for serotype 19F for the 7 common Prevenar serotypes and from 0.63 $\mu\text{g/mL}$ for serotype 3 to 2.14 $\mu\text{g/mL}$ for serotype 7F for the additional non-Prevenar serotypes.

6096A1-008

This was a multicentre, Phase III, randomised, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of 13vPCV in healthy infants given with routine paediatric vaccinations conducted in 49 centres in France. There were 613 subjects (304 in the 13vPCV group and 309 in the 7vPCV group) consented and were randomly assigned. Twenty-four subjects (14 in the 13vPCV group and 10 in the 7vPCV group) were withdrawn during the infant series. Overall, 589 subjects (290 in the 13vPCV group and 299 in the 7vPCV group) completed the infant series (Table 10).

The immunogenicity analysis was based on results of assays performed on blood samples obtained 1 month after dose 3 of the infant series. For 6 of the 8 concomitant vaccine antigens (tetanus, Hib, polio types 1 and 3, and pertussis [FHA and PT]), the immune responses induced by Pentavac given with 13vPCV were non-inferior to the immune responses induced by Pentavac given with 7vPCV. However, the non-inferiority criteria for the diphtheria and polio type 2 were not met. As noted below, the lower than expected responses to these concomitant vaccines in both the 13vPCV and 7vPCV arms of the study contributed to the inability to meet the non-inferiority criteria. The responses to the Hib component of Pentavac met non-inferiority criteria at the primary endpoint of PRP ≥ 0.15 $\mu\text{g/mL}$, which indicates an adequate response after Hib vaccination. At the alternative, higher threshold of ≥ 1.0 $\mu\text{g/mL}$ the proportions of responders in the 13vPCV and 7vPCV groups were lower (58.6% and 63.1%, respectively). The 95% lower CI of the difference was -13.2%, so non-inferiority criteria were not met. However, the GMCs in the two groups were comparable (GMR: 0.91) and met non-inferiority criteria. Pertussis responses met non-inferiority criteria at the primary endpoint of ≥ 5 EU/mL. Non-inferiority criteria were also met at the limit of quantitation for FHA, ≥ 7.82 EU/mL, and for both PT and FHA using the antibody concentrations achieved by 95% of the 7vPCV group as the comparison level. The GMCs were comparable for both PT and FHA and non-inferiority criteria were met. Tetanus responses met non-inferiority criteria at the primary endpoint of ≥ 0.1 IU/mL, and at the lower, alternative threshold of ≥ 0.01 IU/mL. The GMCs for tetanus were similar in the 13vPCV and 7vPCV groups (0.20 IU/mL and 0.21 IU/mL, respectively) and met non-inferiority criteria.

At the primary endpoint of ≥ 0.1 IU/mL, the proportion of responders to diphtheria in both the 13vPCV and 7vPCV groups were lower than expected (76.5% and 84.6%, respectively), and non-inferiority criteria were not met. However, at the secondary endpoint of ≥ 0.01 IU/mL the proportion of responders was 100% in both groups and non-inferiority criteria were met. The IgG GMCs for diphtheria in the 13vPCV group and in the 7vPCV group were 0.19 IU/mL and 0.24 IU/mL, respectively, and these also met non-inferiority criteria. The responses to poliovirus type 1 and type 3 met non-inferiority criteria both at the primary endpoint of proportion of responders $\geq 1:8$ and when GMCs in the 13vPCV and 7vPCV groups were compared. The responses to polio type 2 were lower than expected in both the 13vPCV and 7vPCV groups (77.7% and 82.0%, respectively) and non-inferiority criteria were not met. The lower than expected proportion of responders contributed

to the failure to meet non-inferiority. However, the GMCs to polio type 2 were comparable (17.75 vs 21.55) and non-inferiority criteria were met. For the pneumococcal IgG endpoints in the 13vPCV group, at least 84% of subjects achieved antibody concentrations ≥ 0.35 $\mu\text{g/mL}$ for each serotype except 6B and 23F (72.6% and 82.8%, respectively). The GMCs for all but serotype 6B were ≥ 0.92 ; the GMC for 6B was 0.74.

Table 10: Details of Study 6096A1-008

Design, purpose of study, duration	Parameters studied	Safety	Comments
<p>Demonstrate that the immune responses after Pentavac (antigens assessed: PT, FHA, Hib, Dip, Tet, polio types 1, 2, 3) and 13vPCV are non-inferior to the response after Pentavac and 7vPCV measured 1 month after the infant series.</p> <p>Assess the immune responses to 13vPCV measured 1 month after the infant series.</p>	<p>An enzyme-linked immunosorbent assay (ELISA) was performed to measure concentration of antibodies to the 13 pneumococcal serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. Serum concentrations of anticapsular immunoglobulin G (IgG) were determined in the blood sample collected 1 month after the infant series in the 13vPCV group and in the blood sample collected before and 1 month after the toddler dose in all vaccine groups.</p> <p>Antibody responses to the pertussis antigens (PT and FHA), Hib antigen polyribosylribitol phosphate (PRP), diphtheria, tetanus, and poliovirus types 1, 2, and 3 antigens were measured in the blood sample collected 1 month after the infant series and 1 month after the toddler dose, in all subjects.</p> <p>Local and systemic reactions, use of antipyretic medication, AEs and SAEs.</p>	<p>The analysis of safety presented no notable safety concerns for subjects receiving 13vPCV. Although more than 65% of subjects in each vaccine group reported local reactions, the majority of these were mild in severity and the profile of the 13vPCV vaccine was very similar to that of 7vPCV. Fewer than 7% of subjects reported significant tenderness in either vaccine group; no cases of severe induration or severe erythema were reported during the infant series. A statistically significantly higher percentage of 13vPCV recipients than 7vPCV recipients reported moderate erythema after dose 1, but there were no differences at other time points and for other reactions. Most cases of fever were mild in severity and 13vPCV recipients reported the use of antipyretic medication to prevent symptoms significantly less often than did 7vPCV recipients after dose 3 (28.4% vs 37.6%, respectively, $p=0.048$). Over the entire infant series, severe fever (>40 degrees C) was reported in 1 subject after a third dose of 13vPCV. A significantly lower percentage of 13vPCV recipients compared with 7vPCV recipients reported at least 1 AE ($p=0.043$). This appears to be primarily due to a larger percentage of 7vPCV subjects experiencing infections and infestations. The only event that was significantly more common in the 13vPCV group was bronchiolitis.</p> <p>The safety analysis of infant series data showed that most local and systemic events, including fever, were mild in severity and no statistically significant differences between vaccine groups were noted for any related AE or the percentage of subjects experiencing 1 or more AE after each dose. In addition, no related SAEs were reported in the infant series. These results indicate that the safety profile of 13vPCV is similar to that of 7vPCV.</p>	<p>Good response rate;</p> <p>13vPCV can be given safely with other vaccines</p>

6096A1-011

This was a multicentre, Phase III, randomised, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of 13vPCV in healthy infants given with routine paediatric vaccinations conducted in 12 sites in India during 2008. A total of 355 subjects were randomly assigned, and 353 subjects were vaccinated. Of the 355 subjects (13vPCV: 179; 7vPCV: 176) randomly assigned, 114 (63.7%) subjects in the 13vPCV group and 110 (62.5%) subjects in the 7vPCV group completed the infant series; 353 (99.4%) subjects received dose 1; 277 (77.5%) subjects received dose 2; and 227 (63.9%) subjects received dose 3. The low completion rate (63.1%) for the infant series is due to the large number of subjects who discontinued from the study due to the clinical hold (31.8%). The duration of the hold resulted in many subjects discontinuing

from the study at the request of the parents, the investigators, or the sponsor in order to maintain the routine paediatric vaccination schedule (Table 11).

Table 11: Details of Study 6096A1-11

Design, purpose of study, duration	Parameters studied	Safety	Comments
<p>Assess the PCV immune response after 13vPCV relative to 7vPCV measured 1 month after the infant series.</p> <p>Assess the immune response after Easyfive, ie, DTP-Hib-HBV vaccine (antigens assessed: PT, FHA, PRN) and</p> <p>13vPCV relative to DTP-Hib-HBV and 7vPCV measured 1 month after the infant series.</p>	<p>Samples were to be tested for IgG antibodies against the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) present in 13vPCV. In addition, serum levels of IgG antibodies to PT, FHA, and PRN (69-kDa outer membrane protein) were to be measured on blood samples collected 1 month after the infant series.</p> <p>Local and systemic reactions, use of antipyretic medication, AEs and SAEs.</p>	<p>Overall, the safety profile of 13vPCV was similar to that of 7vPCV. The safety analysis of infant series data showed that most local reactions and systemic events, including fever, were mild in severity; there were no differences between 7vPCV and 13vPCV. The incidences of significant local tenderness were higher than usually observed in clinical studies and ranged from 29.8% to 46.5% and from 26.5% to 43.6% in the 13vPCV and 7vPCV groups, respectively; the incidences were highest after dose 1. The consensus opinion noted by the investigator was that the high rate of reported significant tenderness was most likely due to parental perceptions and not due to reactogenicity of the vaccine. There were no statistically significant differences between vaccine groups for any individual AE, except for injection site nodule (at the site of concomitant vaccine injection and higher for 7vPCV than for 13vPCV), for severe AEs, or for related AEs. In addition, no related SAEs were reported in the infant series.</p>	<p>There were significant problems with response rate with a relatively low completion rate of 63.1%.</p>

The responses to 13vPCV were comparable to those for 7vPCV for the common serotypes. The responses for the additional serotypes were good. The 3 most common pneumococcal serotypes in the younger-than-5-year age group in India are 1, 6, and 19. The response rates were above 90% in the 13vPCV group for 2 of these 3 serotypes. Response rates were 99% for serotype 19A, 92.7% for serotype 19F, and 96.1% for serotype 1. Response rates were above 80% for the other most common serotype (that is, serotype 6): 88.5% for serotype 6A and 80.4% for serotype 6B. The results for the antigens in the concomitant whole-cell pertussis vaccine are nearly the same for 13vPCV and 7vPCV; this indicates that 13vPCV does not interfere with the response to whole-cell pertussis vaccine.

6096A1-500

This was a multicentre, Phase III, randomised, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of 13vPCV in healthy infants given with routine paediatric vaccinations conducted in nine centres in Italy during the period 2006-2008. A total of 606 subjects were randomly assigned (303 in each group) to receive either 13vPCV + Infanrix Hexa (containing diphtheria, tetanus, acellular pertussis, poliomyelitis, hepatitis B and Haemophilus influenzae type B vaccines) or 7vPCV + Infanrix Hexa; however, this includes 1 subject (13vPCV group) who was pre-randomized and counted twice. The safety population included 604 subjects who received at least 1 vaccination. Two hundred ninety-four (294) subjects in the 13vPCV group and 291 in the 7vPCV group completed the infant series. Five hundred sixty nine (569; 93.9%) subjects received the toddler dose, 287 subjects in the 13vPCV group and 282 in the 7vPCV group. The evaluable infant immunogenicity population included 275 in the 13vPCV group and 279 in the 7vPCV group. The evaluable toddler immunogenicity population included 254 in the 13vPCV group and 261 in the 7vPCV group (Table 12).

This study demonstrated non-inferiority of the responses to all antigens in Infanrix Hexa when given with the 13vPCV relative to 7vPCV in infants and toddlers. Responses to all of the

concomitant antigens (hepatitis B, Hib, PT, FHA, and PRN, diphtheria, tetanus, and polio) met the primary protocol-specified criteria. Analysis of pneumococcal responses after the toddler dose showed that the non-inferiority criterion was met for each of the common pneumococcal serotypes and for the 6 additional serotypes. The proportion of responders at 0.35 µg/mL for the 13vPCV group was 93.9% or more and there were functional responses to all 13 serotypes. The proportion of 13vPCV recipients with an OPA titre $\geq 1:8$ was 90.0% or higher for all serotypes after the infant series and was 97.9% or higher for all serotypes after the toddler dose. The OPA GMTs were higher than the GMTs after the infant series, ranging from 294.07 (serotype 1) to 16384.00 (serotype 9V) after the toddler dose.

Table 12: Details of Study 0696A1-500

Design, purpose of study, duration	Parameters studied	Safety	Comments
<p>Demonstrate that the immune response after Infanrix Hexa (antigen assessed: HBV) and 13vPCV is non-inferior to the response after Infanrix Hexa and 7vPCV measured 1 month after the toddler dose.</p> <p>Assess the immune response to 13vPCV measured 1 month after the infant series and just before the toddler dose.</p> <p>Assess the immune responses induced by 13vPCV relative to 7vPCV measured 1 month after the toddler dose.</p>	<p>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) were determined in the 13vPCV group for the 1 month Post-infant series and the pre-toddler dose blood samples and in all subjects for sample drawn 1 month after the toddler dose.</p> <p>Antibody responses to the hepatitis B, Hib antigen polyribosylribitol phosphate (PRP), and pertussis antigens (PT, FHA, and PRN) were measured in the blood drawn 1 month after the infant series and 1 month after the toddler dose in all subjects.</p> <p>Antibody responses to tetanus toxoid, diphtheria toxoid, and polio were measured in the blood drawn 1 month after the infant series and 1 month after the toddler dose in subjects with adequate sera.</p> <p>Serum OPAs for the 13 pneumococcal serotypes were performed on blood obtained 1 month after the infant series and 1 month after the toddler dose in a randomly selected subset of approximately 100 subjects in the 13vPCV group.</p> <p>Local and systemic reactions, use of antipyretic medication, AEs and SAEs.</p>	<p>Overall, the safety profile of 13vPCV was similar to that of 7vPCV. Few statistically significant differences were noted for local reactions, systemic events, or AEs after any infant or toddler dose, or after the infant series as a whole. The safety analysis of infant series data showed that most local and systemic events, including fever, were mild in severity. Significant tenderness was reported in $\leq 5\%$ of subjects in each vaccine group after each dose in the infant series and in $\leq 8.5\%$ of subjects in each vaccine group after the toddler dose. The only significant differences between vaccine groups for systemic events were for irritability with dose 1 and mild fever after the toddler dose (both higher with 13vPCV).</p> <p>No statistically significant differences between vaccine groups were noted for related AEs at any time during the study or for any AE during the infant series; a significant difference between the groups after the toddler dose was noted only for pharyngitis. In addition, no related SAEs were reported in the infant series or after the toddler dose; 1 related SAE was reported after the infant series.</p>	<p>13vPCV appears to give good immunogenicity and safety comparable to 7vPCV</p>

6096A1-501

This was a multicentre, Phase III, randomised, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of 13vPCV in healthy infants given with routine paediatric vaccinations conducted in 38 centres in Spain from 2006-2008. Overall, 593 (95.8%) subjects completed the infant series, 299 (94.9%) in the 13vPCV group and 294 (96.7%) in the 7vPCV group. A total of 616 subjects (99.5%) received dose 1, 605 (97.7%) received dose 2, and 597 (96.4%) received dose 3. Twenty-six (26) subjects (4.2%) were withdrawn from the study during the infant series and an additional 11 subjects (1.8%) withdrew after the infant. A total of 582 (94.0%) subjects received the toddler dose and 578 (93.4%) completed the toddler dose (that is, had the post-toddler dose visit), 292 (92.7%) in the 13vPCV group and 286 (94.1%) in the 7vPCV group (Table 13).

Table 13: Details of Study 6096A1-501

Design, purpose of study, duration	Parameters studied	Safety	Comments
<p>Demonstrate that the immune response after Meningitec (antigen assessed: MnC by SBA) and 13vPCV is non-inferior to response after Meningitec and 7vPCV measured 1 month after a 2-dose Meningitec infant series. Assess the non-inferiority of antigen-specific response to PT, FHA, PRN, Dip, Tet, and polio types 1, 2, 3 after Infanrix Hexa and 13vPCV relative to Infanrix Hexa and 7vPCV. Assess the immune responses to 13vPCV measured 1 month after dose 2 and 1 month after dose 3 of the infant series and 1 month after the toddler dose.</p>	<p>Blood samples from all subjects drawn 1 month after the second dose (ie, after the 2-dose infant Meningitec series) and 1 month after the toddler dose were analysed to determine antibodies induced by Meningitec using an SBA. The immune responses to the tetanus, pertussis (PT, FHA, and PRN), and poliovirus (types 1, 2, and 3) antigens contained in the Infanrix Hexa and Infanrix-IPV+Hib vaccines were to be assessed in blood samples from all subjects drawn 1 month after the 3-dose Infanrix infant series and 1 month after the toddler dose.</p> <p>Serum levels of antibodies to diphtheria toxoid were measured for each blood sample, ie, after the second dose, after the infant series, and after the toddler dose. In addition, samples from subjects in the 13vPCV group for all 3 time points were to be tested for IgG antibodies against the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) present in 13vPCV.</p> <p>Local and systemic reactions, use of antipyretic medication, AEs and SAEs.</p>	<p>Overall, the safety profile of 13vPCV was similar to that of 7vPCV. The safety analysis of the infant series and toddler dose data showed that most local reactions and fever were mild in severity. There was a statistically significant difference in moderate induration reported after dose 1 (12 subjects [4.9%] in the 13vPCV group compared with 4 subjects [1.6%] in the 7vPCV group; $p=0.045$). There was also a statistically significant difference in significant tenderness noted after dose 3 (11 subjects [6.1%] in the 13vPCV group versus 0 subjects in the 7vPCV group; $p<.001$). The percentage of subjects reporting other systemic events was generally similar in the 2 vaccine groups after all doses. The AEs observed were characteristic of infants of this age. There were few statistically significant differences between vaccine groups in incidences of individual events and no statistically significant differences between groups for any related AE. Only 2 SAEs were considered related to the test article; 1 subject vaccinated with 7vPCV (dose 3) reported high fever and another subject vaccinated with 7vPCV (dose 3) experienced a febrile convulsion. Statistically significant differences between the 2 vaccine groups in incidence of individual AEs after each dose of the infant series were infrequent. After dose 1, a statistically significant difference was observed in the category of general disorders and administrative site conditions (3.2% versus 0.7% in the 13vPCV and 7vPCV groups, respectively, $p=0.037$).</p>	<p>13vPCV can be given with other vaccines; appears safe</p>

13vPCV can be given safely in a 3-dose infant series regimen and a toddler dose, administered at 2, 4, 6, and 15 months of age with concomitant Meningitec and Infanrix Hexa/Infanrix-IPV+Hib. The immunogenicity of the meningococcal group C, diphtheria, tetanus, pertussis, and polio components of these vaccines was not adversely affected by concomitant administration of 13vPCV. The 13vPCV was immunogenic with substantial responses seen to all 13 serotypes after the infant series and toddler dose. Immune responses to the 13 pneumococcal conjugate vaccine serotypes were also evaluated, but only for subjects in the 13vPCV group. The proportion of responders achieving a pneumococcal IgG antibody concentration $\geq 0.35 \mu\text{g/mL}$ was evaluated after dose 2 and after dose 3 of the infant series, and after the toddler dose. The proportion of responders after dose 2 was greater than 84% for all pneumococcal serotypes, except serotypes 6B (57.3%) and 23F (68.1%). The proportion of responders increased from dose 2 to dose 3 for all serotypes except serotype 14, which remained approximately the same (98.5% after dose 2 to 97.4% after dose 3 [difference of -1.1%, 95% CI = -3.4, 1.2]). For most other serotypes, the proportion of responders increased from 1.5 to 13.0 percentage points, except for serotype 6B (41.2 percentage point increase, 95% CI = 34.9, 46.9) and serotype 23F (increase of 26.5 percentage points, 95% CI = 20.7, 31.9). After dose 3, the proportion of responders was 97% or higher for all serotypes, except serotypes 3 (90.3%) and 23F (94.6%). After the toddler dose, the proportion of responders was greater than 98.7% for all pneumococcal serotypes, except serotype 3 (92.2%). The GMCs for IgG antibodies to each of the 13 pneumococcal serotypes were determined after dose 2 and after dose 3 of the infant series, and after the toddler dose. Geometric mean fold rises (GMFRs) from dose 2 to dose 3 of the infant series were also evaluated. After dose 2, IgG GMCs were $1.00 \mu\text{g/mL}$ or greater for all

pneumococcal serotypes except serotype 6B (0.42 µg/mL), serotype 23F (0.54 µg/mL), and serotype 3 (0.79 µg/mL). The IgG GMCs increased from dose 2 to dose 3, and GMFRs were from 1.15 to 9.28 for all serotypes except 19F: For serotype 19F, GMC decreased from dose 2 to dose 3 (GMFR = 0.93, 95% CI = 0.83, 1.03). The GMC for serotype 6B increased substantially from 0.42 µg/mL after dose 2 to 3.88 µg/mL after dose 3 (GMFR = 9.28, 95% CI = 8.18, 10.53). After dose 3, IgG GMCs for the 13 serotypes ranged from 0.97 µg/mL for serotype 3 to 6.17 µg/mL for serotype 14.

After the toddler dose, IgG GMCs were 1.00 µg/mL or greater for all pneumococcal serotypes, ranging from 1.07 µg/mL to 11.88 µg/mL for the 13 serotypes. From dose 3 of the infant series to the post-toddler dose, IgG GMCs increased for all 13 serotypes, except serotype 3, which was about the same (GMC = 0.97 µg/mL after the infant series vs 1.07 µg/mL after the toddler dose). The GMC increased by 3-fold for serotype 19A, from 3.07 µg/mL after dose 3 to 11.64 µg/mL after the toddler dose.

6096A1-3007

This was a multicentre, Phase III, randomised, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of 13vPCV in healthy infants given with a meningococcal C-tetanus toxoid conjugate vaccine and other routine paediatric vaccinations in 23 sites across Spain conducted during 2007-2008. 218 subjects were randomly assigned to the 13vPCV group and vaccinated at dose 1; 213 completed the infant series. In the 7vPCV group, 220 completed the infant series (Table 14).

The immune response induced by NeisVac-C given with 13vPCV was shown to be non-inferior to the immune response induced by NeisVac-C given with 7vPCV. The immune responses induced by Infanrix Hexa given with 13vPCV were shown to be non-inferior to the immune responses induced by Infanrix Hexa given with 7vPCV. The percentage of subjects in the 13vPCV group who achieved a pneumococcal IgG antibody concentration ≥ 0.35 µg/mL after dose 3 of the infant series was 93% or greater for all pneumococcal serotypes except serotype 3, for which the proportion of responders was 86%.

The percentage of subjects in the 13vPCV group who achieved a pneumococcal IgG antibody concentration ≥ 0.35 µg/mL after dose 2 of the infant series was greater than 73% for all pneumococcal serotypes except serotypes 6B (27.9%) and 23F (55.8%). The proportion of responders increased from dose 2 to dose 3 for all serotypes except 19F, for which the proportion decreased from 100% after dose 2 to 99% after dose 3. For most serotypes, the increase in the proportion of responders was between 2.5 and 18.2 percentage points, with the exceptions being serotype 6B (67.0 percentage point increase) and serotype 23F (increase of 37.2 percentage points). After dose 3, the proportion of responders was 93% or higher for all serotypes except serotype 3, for which the proportion of responders was 86.2%.

After dose 2, IgG GMCs were 0.81 (µg/mL) or greater for all pneumococcal serotypes except serotype 6B (0.21 µg/mL), serotype 23F (0.40 µg/mL), and serotype 3 (0.55 µg/mL). For most of the 13 pneumococcal serotypes, IgG GMCs increased from dose 2 to dose 3, and geometric mean fold rises (GMFRs) were between 1.31 and 4.15 for all but 2 serotypes. For serotype 19F, the GMC decreased from dose 2 to dose 3 (GMFR = 0.83, 95% CI = 0.74, 0.92), and for serotype 6B the GMC increased substantially from 0.21 µg/mL after dose 2 to 2.59 µg/mL after dose 3 (GMFR = 12.40, 95% CI = 10.74, 14.32). After dose 3, IgG GMCs for the 13 serotypes ranged from 0.85 µg/mL for serotype 3 to 4.51 for serotype 14.

Table 14: Details of Study 6096A1-3007

Design, purpose of study, duration	Parameters studied	Safety	Comments
<p>Demonstrate the non-inferiority of immune response after NeisVac-C and 13vPCV relative to NeisVac-C (antigen: MnC using SBA) and 7vPCV measured 1 month after a 2-dose NeisVac-C infant series.</p> <p>Demonstrate the non-inferiority of immune response after Infanrix Hexa and 13vPCV relative to Infanrix Hexa (antigens assessed: Dip, Tet) and 7vPCV measured 1 month after a 3-dose infant series. Assess the immune responses to 13vPCV measured 1 month after dose 2 and 1 month after dose 3 of the infant series.</p>	<p>Samples from subjects in the 13vPCV group for all 3 time points were to be tested for IgG antibodies against the 13 pneumococcal serotypes present in 13vPCV. Blood samples from all subjects drawn 1 month after the second dose (ie, after the 2-dose infant NeisVac-C series) and 1 month after the toddler dose were analysed to determine antibodies induced by NeisVac-C using an SBA. The immune responses to the diphtheria and tetanus antigens contained in the Infanrix Hexa and Infanrix-IPV+Hib vaccines were to be assessed in blood samples from all subjects drawn 1 month after the 3-dose Infanrix infant series and 1 month after the toddler dose.</p> <p>Local and systemic reactions, use of antipyretic medication, AEs and SAEs.</p>	<p>Most of the adverse events reported were the types of conditions and symptoms expected in infants of this age. During the infant series, the incidence of adverse events was significantly higher among subjects vaccinated with 7vPCV (57.3%) than among those who received 13vPCV (46.3%) ($p = 0.023$). The most frequent types of events were infections and infestations, which were reported more frequently in the 7vPCV group (48.9%) than in the 13vPCV group (39.4%) ($p=0.056$), although there were no clear trends between groups for preferred terms within this System Organ Class (SOC). For both vaccine groups, these events were largely respiratory tract and ear infections and gastroenteritis. Gastrointestinal disorders, including events such as diarrhoea and vomiting, were reported for 8.0% of subjects in the 7vPCV group and for 6.4% of subjects vaccinated with 13vPCV.</p> <p>The difference between groups in the incidence of individual types of AEs was significant only for rash, which occurred in 6 subjects (2.7%) in the 7vPCV group and no subjects vaccinated with 13vPCV ($p = 0.030$). Conjunctivitis approached significance, being experienced by 3 subjects (1.4%) in the 13vPCV group and 11 subjects (4.9%) in the 7vPCV group ($p = 0.054$). These differences are likely chance occurrences and of no clinical significance. Only 3 adverse events were considered related to the test article by the investigator: bronchitis, angioedema, and rash were reported by 1 subject each, all in the 7vPCV group. Severe AEs were reported in 3 subjects vaccinated with 13vPCV (<i>Escherichia</i> urinary tract infection, orchitis, and pneumonia) and in 1 subject in the 7vPCV group (gastroenteritis). All of these severe events were considered serious and resulted in hospitalization. None were considered to be related to the test article. No AEs considered life-threatening were reported during the infant series. No subjects died during the infant series, and no subjects withdrew from the study because of adverse events. Serious AEs occurred in 6 subjects vaccinated with 13vPCV and in 8 subjects vaccinated with 7vPCV. Most of the events were infections and all resulted in hospitalization.</p> <p>None of the SAEs were considered related to the test article.</p>	13vPCV can be given with other vaccines; appears safe

6096A1-3002

This was a multicentre, Phase III, open-label trial evaluating the safety, tolerability, and immunogenicity of 13vPCV in older infants and children, who were naïve to previous vaccination with pneumococcal conjugate vaccine, conducted at nine centres in Poland during 2007. The subjects were enrolled in one of three paediatric age groups:

Group 1: enrolled at 7 to <12 months of age and received 3 doses of 13vPCV

Group 2: enrolled at 12 to <24 months of age and received 2 doses of 13vPCV

Group 3: enrolled at 24 to <72 months of age and received 1 dose of 13vPCV

A total of 354 subjects (99.7%) received dose 1, 90 of 90 subjects in group 1 and 112 of 112 subjects in group 2 received dose 2, and 89 of 90 subjects in group 1 received dose 3. A total of 352 subjects (88 in group 1, 112 in group 2, and 152 in group 3) completed the study (Table 15).

Table 15: Details of Study 0696A1-3002

Design, purpose of study, duration	Parameters studied	Safety	Comments
Assess the PCV response induced by 13vPCV when measured 1 month after the last scheduled dose in each age group.	An enzyme-linked immunosorbent assay (ELISA) was performed to measure concentration of antibodies to the 13 pneumococcal serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. Serum concentrations of anticapsular immunoglobulin G (IgG) were determined in the blood sample collected 1 month after the final vaccination in all groups and in the blood sample collected before vaccination in group 3. Local and systemic reactions, use of antipyretic medication, AEs and SAEs	Vaccination was generally well tolerated in all 3 groups. There was a trend toward greater local reactogenicity (in terms of tenderness, but not erythema or induration) with increasing age and with subsequent dose administration. In contrast, there were fewer systemic reactions in group 3 compared with groups 1 and 2. There were relatively few AEs in all 3 groups, and reported AEs were within the expected spectrum of incidental illness for each age group. The majority of local reactions were mild in severity in all groups. No subjects reported severe induration or severe erythema. Most cases of fever were mild to moderate in severity in the groups. The incidence of moderate fever did not exceed 2.3% in either group after any dose, and severe fever was not reported in any subject. The AEs characterized as infections and infestations (range 13.3% to 46.4%) or as gastrointestinal disorders (range 1.1% to 11.6%) were reported most frequently. The percentages of related AEs reported in groups 1 and 2 were low (range 2.2% to 2.7%). No related AEs were reported in group 1 (dose 3) or in group 3. No subjects withdrew from the study because of an AE. In general, most SAEs were characterized as infections and infestations or as gastrointestinal disorders. No related SAEs were reported in this study, and no subjects withdrew from the study because of an SAE. No deaths or clinically important AEs were reported in this study.	13vPCV appears safe and there is good immunogenicity

The immunogenicity analysis was based on results of assays performed on blood samples obtained 1 month after the final dose. The major results were as follows: For all serotypes, the proportion of responders in groups 1 and 2 ranged from 92.7% to 100.0%. In group 3, the proportion of responders was greater than 98.0%, with the exception of serotype 14, for which the proportion was 88.1%. The IgG GMCs across all serotypes ranged from 1.94 µg/mL to 8.04 µg/mL in group 1, 1.86 µg/mL to 6.45 µg/mL in group 2, and 1.42 µg/mL to 6.03 µg/mL in group 3. The individual serotype IgG GMCs were similar for the 3 age groups.

The GMFRs for group 3 from before vaccination to after vaccination were ≥ 1.95 for all serotypes.

Safety

The total safety database includes primarily data from two Phase I/II studies, two pivotal studies (includes infant and toddler series) and seven supporting studies examining the safety and immunogenicity of 13vPCV, co-administered with other paediatric vaccines, were evaluated. Almost all of these studies included 7vPCV as an active comparator. Each of the studies was conducted in a single country, and vaccination schedules varied across the studies, according to national recommendations for the paediatric immunisation program in each country. It was anticipated that safety profile of 13vPCV would be similar to 7vPCV, as the main difference was the additional six pneumococcal serotypes.

For the pivotal clinical efficacy studies, there appeared to be a very good completion rate of subjects. Most local and systemic reactions are considered mild. Local reactions from the various studies are summarised in Table 16 and systemic reactions are summarised in Table 17. Few

withdrawals appeared to be due to adverse events (AEs) or serious adverse events (SAEs) from the study vaccinations. SAEs are summarised from the various studies in Tables 18 and 19.

Table 16: Subjects Reporting Local Reactions: Infant and Toddler Doses (All 12 Infant Studies)

	Dose 1 ^a			Dose 2 ^a			Dose 3 ^a			Toddler ^b		
	13vPnC n (%)	7vPnC n (%)	p-value ^c	13vPnC n (%)	7vPnC n (%)	p-value ^c	13vPnC n (%)	7vPnC n (%)	p-value ^c	13vPnC n (%)	7vPnC n (%)	p-value ^c
Tenderness												
N	3878	2148		3388	1824		2809	1364		1198	791	
Any	1816 (46.8)	964 (44.9)	0.562	1513 (44.7)	801 (43.9)	0.349	1151 (41.0)	539 (39.5)	0.791	624 (52.1)	443 (56.0)	0.842
Significant ^d	292 (8.3)	183 (9.3)	0.962	184 (6.3)	139 (8.6)	0.038	145 (6.0)	69 (5.9)	0.451	59 (6.2)	47 (8.1)	0.896
Induration												
N	3601	2025		3087	1699		2603	1245		1049	654	
Any	828 (23.0)	444 (21.9)	0.096	865 (28.0)	491 (28.9)	0.987	784 (30.1)	377 (30.3)	0.940 ^f	342 (32.6)	219 (33.5)	0.569
Mild ^e	710 (19.8)	403 (20.0)	0.346	787 (25.6)	447 (26.5)	0.973	713 (27.6)	344 (27.9)	0.908 ^f	308 (29.8)	187 (29.4)	0.813
Moderate ^e	240 (6.9)	91 (4.7)	0.013	203 (7.0)	97 (6.1)	0.612	194 (8.0)	83 (7.2)	0.565	115 (12.0)	62 (10.5)	0.618
Severe ^e	0	0		2 (0.1)	0	0.543 ^f	0	0		0	0	
Erythema												
N	3623	2049		3155	1762		2684	1292		1099	691	
Any	954 (26.3)	569 (27.8)	0.249 ^f	1114 (35.3)	619 (35.1)	0.578	1027 (38.3)	478 (37.0)	0.338	479 (43.6)	302 (43.7)	0.267
Mild ^e	893 (24.7)	547 (26.8)	0.109	1063 (33.9)	594 (33.9)	0.378	974 (36.5)	452 (35.3)	0.293	427 (39.4)	271 (40.0)	0.356
Moderate ^e	92 (2.7)	35 (1.8)	0.007	88 (3.0)	49 (3.1)	0.730	120 (5.0)	61 (5.3)	0.394	113 (11.8)	68 (11.7)	0.235
Severe ^e	0	0		2 (0.1)	0	0.543 ^f	1 (0.0)	0	>0.999 ^f	1 (0.1)	1 (0.2)	0.725

Follow-up time = 4 days following each dose for all studies except studies 003 (stage 1 = 15 days; stage 2 = 8 days), 004 (7 days), and 3005 (7 days).

a. Infant dose data are included for all 12 infant studies in this submission.

b. Toddler dose data are included for the 6 infant studies with toddler dose data in this submission: studies 003, 004, 006, 009, 500, and 501.

c. Mixed model used to calculate difference between vaccine groups in percentages of subjects reporting an event (random effect for protocol).

d. Significant = present and interfered with limb movement.

e. Intensity of induration and erythema are rated by the diameter of the affected area: 0.5-2.0 cm = mild; 2.5-7.0 cm = moderate; >7.0 cm = severe.

f. Fisher exact test, 2-sided, used to calculate difference between vaccine groups in percentages of subjects reporting an event.

Table 17: Subjects Reporting Systemic Events, Fever and Antipyretic Medications: Infant and Toddler Doses (All 12 Infant Studies)

	Dose 1 ^a			Dose 2 ^a			Dose 3 ^a			Toddler ^b		
	13vPnC n (%)	7vPnC n (%)	p-value ^c	13vPnC n (%)	7vPnC n (%)	p-value ^c	13vPnC n (%)	7vPnC n (%)	p-value ^c	13vPnC n (%)	7vPnC n (%)	p-value ^c
Decreased Appetite												
N	3767	2094		3261	1782		2710	1303		1132	747	
	1446 (38.4)	778 (37.2)	0.354 ^d	1233 (37.8)	731 (41.0)	0.697	992 (36.6)	497 (38.1)	0.924	478 (42.2)	375 (50.2)	0.387
Irritability												
N	4022	2215		3606	1969		3024	1480		1283	873	
	2782 (69.2)	1415 (63.9)	0.114	2480 (68.8)	1341 (68.1)	0.443	1873 (61.9)	897 (60.6)	0.249	814 (63.4)	608 (69.6)	0.217
Increased Sleep												
N	3959	2188		3379	1852		2731	1323		1114	748	
	2334 (59.0)	1257 (57.4)	0.918	1719 (50.9)	946 (51.1)	0.729	1125 (41.2)	539 (40.7)	0.605	476 (42.7)	391 (52.3)	0.508
Decreased Sleep												
N	3709	2068		3222	1754		2698	1282		1073	666	
	1351 (36.4)	693 (33.5)	0.027 ^d	1138 (35.3)	613 (34.9)	0.658	916 (34.0)	420 (32.8)	0.496	323 (30.1)	221 (33.2)	0.870
Fever												
N	3594	1998		3110	1718		2580	1253		1103	721	
Any ^e	897 (25.0)	487 (24.4)	0.013	1002 (32.2)	659 (38.4)	0.370	717 (27.8)	406 (32.4)	0.359	474 (43.0)	359 (49.8)	0.472
≥38°C but ≤39°C	863 (24.1)	470 (23.5)	0.029	951 (30.7)	637 (37.3)	0.173	687 (26.8)	391 (31.3)	0.401	448 (41.1)	343 (48.2)	0.602
>39°C but ≤40°C	50 (1.5)	24 (1.2)	0.626 ^d	85 (3.0)	46 (2.9)	0.181	70 (2.9)	30 (2.6)	0.452	62 (6.6)	48 (8.3)	0.895
>40°C	1 (0.0)	4 (0.2)	0.002	3 (0.1)	2 (0.1)	0.987	4 (0.2)	2 (0.2)	0.959	3 (0.3)	1 (0.2)	0.605
Antipyretic Medications												
N	3983	2159		3579	1934		2998	1448		1191	827	
Treat	1758 (45.9)	967 (45.9)	0.345	1683 (49.8)	1025 (55.3)	0.408	1308 (46.1)	720 (51.9)	0.054	490 (43.0)	390 (50.4)	0.553
Prevent	1805 (46.5)	971 (46.0)	0.428	1686 (48.9)	944 (50.9)	0.252	1347 (47.1)	708 (51.1)	0.134	404 (36.1)	353 (46.5)	0.244

Follow-up time 4 days following each dose for all studies except studies 003 (stage 1 = 15 days; stage 2 = 8 days), 004 (7 days), and 3005 (7 days).

a. Infant dose data are included for all 12 infant studies in this submission.

b. Toddler dose data are included for the 6 infant studies with toddler dose data in this submission: studies 003, 004, 006, 009, 500, and 501.

c. Mixed model used to calculate difference between vaccine groups in percentages of subjects reporting an event (random effect for protocol).

d. Fisher exact test, 2-sided, used to calculate difference between vaccine groups in percentages of subjects reporting an event. (For analyses in which the mixed model would not produce a p-value, the Fisher exact test was used to compare vaccine groups if the models did not converge.)

e. "Any" fever = subjects with any temperature ≥38°C; for subcategories of fever by degree of temperature, subjects may be included in more than 1 row.

Table 18: Serious Adverse Events-Death (All 12 Infant Studies)

Table 2-10: Listing of Adverse Events Resulting in Death (All 12 Infant Studies)

Study	Site	Subject	Adverse Event MedDRA		Vaccine Administered	Last Dose	Days Since Last Dose	Related to Study Vaccine ^a
			Term	Adverse Event Verbatim Term				
60963005	002	000107	Sudden infant death syndrome	Infant death cause unknown	7vPnC	Vaccination 1	13	Yes ^b
60963005	004	000320	Sudden infant death syndrome	Sudden unexplained infant death	13vPnC	Vaccination 1	14	No
60963005	079	007651	Sudden infant death syndrome	Asphyxia due to SIDS	13vPnC	Vaccination 2	3	No
6096501	009	000452	Sudden infant death syndrome	Sudden unexpected death in infancy	13vPnC	Vaccination 3	76	No

Narratives for each subject are in the respective study reports in [Section 5.3.5.1](#), [study 3005-infant](#), and [study 501-infant and toddler](#).

a. Based on investigator assessment.

b. Before the cause of death was determined, the investigator wanted to take the most conservative approach in assessing the potential causality of the death. However, when the autopsy later revealed that the cause of death was sudden infant death syndrome (SIDS), the investigator changed his assessment of causality, determining that the death was not related to study vaccine.

Table 19: Serious Adverse Events- (All 12 Infant Studies)

Table 2-11: Number (%) of Subjects With Serious Adverse Events: MedDRA System Organ Classes Reported Most Frequently - Infant Series, Between Infant Series and Toddler Dose, Toddler Dose, and 6-Month Follow-up (All 12 Infant Studies)

System Organ Class/ Preferred Term	Infant Series		Between Infant Series and Toddler Dose ^a		Toddler Dose ^a		6-Month Follow-up ^b	
	13vPnC	7vPnC	13vPnC	7vPnC	13vPnC	7vPnC	13vPnC	7vPnC
	N = 4423 N = 2451		N = 1863		N = 1701 N = 1210		N = 950 N = 455	
Any event	168 (3.8)	92 (3.8)	83 (4.5)	45 (3.3)	18 (1.1)	10 (0.8)	39 (4.1)	6 (1.3)
Infections and infestations	132 (3.0)	71 (2.9)	52 (2.8)	29 (2.1)	8 (0.5)	5 (0.4)	24 (2.5)	3 (0.7)
Gastrointestinal disorders	10 (0.2)	7 (0.3)	12 (0.6)	3 (0.2)	4 (0.2)	1 (0.1)	7 (0.7)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	19 (0.4)	3 (0.1)	4 (0.2)	4 (0.3)	2 (0.1)	2 (0.2)	3 (0.3)	4 (0.9)
Nervous system disorders	5 (0.1)	5 (0.2)	9 (0.5)	4 (0.3)	2 (0.1)	2 (0.2)	4 (0.4)	0 (0.0)
Injury, poisoning and procedural complications	3 (0.1)	2 (0.1)	12 (0.6)	6 (0.4)	2 (0.1)	0 (0.0)	3 (0.3)	0 (0.0)
General disorders and administration site conditions	10 (0.2)	9 (0.4)	3 (0.2)	2 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)
Metabolism and nutrition disorders	6 (0.1)	4 (0.2)	5 (0.3)	2 (0.1)	3 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)

Infant series = from dose 1 through postinfant series blood draw.

Between infant series and toddler dose = from the postinfant series blood draw through the toddler dose.

Toddler dose = from the toddler dose through the posttoddler dose blood draw.

6-month follow-up = from posttoddler dose blood draw to 6-month follow-up contact.

a. Postinfant series data are available for 6 studies: 003, 004, 006, 009, 500, and 501.

b. 6-Month follow-up data are available for 3 studies: 003, 004, and 009.

6096A1-002

The results demonstrated that 13vPCV was generally safe and well tolerated compared with 23vPPV. Although a greater percentage of 13vPCV subjects reported significant tenderness compared with 23vPPV subjects, this tenderness resolved within five days. The total number of AEs reported was small and of the type and severity that appear not pose a safety concern at this time.

During the 15-day post-vaccination observation period, more subjects in the 13vPCV group than in the 23vPPV group reported tenderness at the injection site. This tenderness interfered with arm movement in 10 of the 13vPCV recipients compared with four of the 23vPPV recipients. All tenderness resolved within five days in the 13vPCV group and within four days in the 23vPPV group. No subjects reported fever ≥ 38 degrees C within seven days after vaccination.

Five subjects (two 13vPCV recipients and three 23vPPV recipients) reported six adverse events during the study. The investigator judged all of them as mild or moderate in severity. None of the events was considered by the investigator at least possibly related to vaccination. No severe or life-threatening AEs, SAEs, or deaths were reported during the trial.

6096A1-003

Infant series

Overall, the percentages of subjects with reports of induration or erythema or any tenderness were similar when comparing the 13vPCV and 7vPCV groups after each of the three doses of the infant series. The p-values for vaccine group (13vPCV or 7vPCV) differences in rates of individual reactions were all greater than 0.05 except for significant tenderness after dose 2, which was reported more frequently in 7vPCV recipients (n=10/118, 8.5%) than in the 13vPCV recipients (n=2/110, 1.8%; p=0.035). No cases of severe induration or erythema were reported after administration of any dose. No statistically significant differences between vaccine groups were noted in the number of subjects with reports of systemic events after dose 1, dose 2, or dose 3 (all p \geq 0.074). All instances of fever after each of the three doses of infant series were mild ($\geq 38^{\circ}\text{C}$ and $\leq 39^{\circ}\text{C}$) or moderate ($> 39^{\circ}\text{C}$ and $\leq 40^{\circ}\text{C}$), and frequencies were not statistically different between the 2 vaccine groups (all p \geq 0.201). No severe ($> 40^{\circ}\text{C}$) cases of fever were reported after any dose. Antipyretic use to prevent and treat symptoms was common and did not differ between the two vaccine groups. There were no statistically significant differences between 13vPCV (N=120) and 7vPCV (N=126) groups for any AEs reported in subjects vaccinated during the infant series (all p \geq 0.053).

Twenty-three SAEs were reported in nine 13vPCV recipients and 13 SAEs were reported in nine 7vPCV recipients. The SAEs reported in the 13vPCV group were three cases of bronchiolitis and dehydration; two cases of irritability and otitis media; and one case each of leukocytosis, lymphadenitis, Arnold-Chiari malformation, vomiting, pyrexia, gastroenteritis, RSV bronchiolitis, cystitis, staphylococcal skin infection, hypoglycaemia, febrile convulsion, sensory integrative disorder, and tethered cord syndrome. Among 7vPCV recipients, there were three cases of bronchiolitis; two cases of pneumonia and dehydration; and one case each of pyrexia, gastroenteritis, RSV bronchiolitis, pneumococcal meningitis, urinary tract infection, and viral diarrhoea.

Toddler Dose

After the toddler dose, the percentage of subjects for whom a parent/legal guardian reported local reactions did not differ between the 13vPCV group and the 7vPCV group. None of the observed differences between study groups reached statistical significance. No severe induration or erythema was reported. After vaccination with 13vPCV or 7vPCV at 12 to 15 months, significantly more subjects in the 7vPCV group than in the 13vPCV group had reports of increased sleep (7vPCV n=44/101, 43.6% and 13vPCV n=24/86, 27.9%; p=0.033) and use of medication to prevent symptoms (7vPCV n=36/102, 35.3% and 13vPCV n=15/85, 17.6%; p=0.008). All instances of fever after the toddler dose were mild ($\geq 38^{\circ}\text{C}$ and $\leq 39^{\circ}\text{C}$) or moderate ($> 39^{\circ}\text{C}$ and $\leq 40^{\circ}\text{C}$), and frequencies were not statistically different between the two vaccine groups (all p \geq 0.201). No severe ($> 40^{\circ}\text{C}$) cases of fever were reported. Antipyretic use to prevent and treat symptoms was common and did not differ between the two vaccine groups. There were fewer reports of fever after the toddler dose than after each of the three doses in the infant series.

Within one month after the toddler dose, 55 AEs were reported in 30 subjects vaccinated with 13vPCV (34.9%) and 104 AEs were reported in 51 subjects (49.5%) vaccinated with 7vPCV ($p=0.055$). There were three SAEs reported in one 13vPCV recipient, and no SAEs were reported in the 7vPCV group. This difference between groups is not statistically significant ($p=0.455$). The SAEs reported in the 13vPCV subject were viral conjunctivitis, viral respiratory tract infection (RTI), and status asthmaticus.

Six-Month Follow-Up

There were no statistically significant differences between 13vPCV ($N=86$) and 7vPCV ($N=103$) groups for any AEs reported at the toddler dose 6-month follow-up telephone contact after the toddler dose (all $p \geq 0.127$). SAEs were reported in more subjects in the 13vPCV group (4.7%) than in the 7vPCV group (1%); however, this difference was not statistically significant ($p=0.179$). There were no SAEs that differed significantly between the two vaccine groups (all $p \geq 0.206$). Overall, SAEs were uncommon. No deaths occurred during the study.

6096A1-004 (Pivotal study)

The safety analysis of infant series and toddler data showed that most local and systemic events, including fever, were mild in severity. The AEs observed were characteristic of infants of this age. There were few statistically significant differences between vaccine groups in incidences of individual events and no statistically significant differences between vaccine groups for any related AE.¹⁴ One subject vaccinated with 13vPCV had related SAEs of febrile convulsion and pyrexia after dose 2 of the infant series. These results indicate that the safety profile of 13vPCV is similar to that of 7vPCV.

The majority of local reactions were mild in severity. Significant local tenderness was reported by fewer than 16% of subjects in either vaccine group within seven days of any dose in the infant series or the toddler dose. No subject in either vaccine group experienced severe induration or severe erythema at the injection site after any dose in the infant series or after the toddler dose. There were no statistically significant differences between the two vaccine groups in incidence of local reactions within seven days of vaccination after any dose in the infant series or after the toddler dose. There was no statistically significant difference between the two vaccine groups in the incidence of mild or severe fever within seven days of vaccination, after any dose in the infant series or after the toddler dose. The incidence of moderate fever was significantly higher in the 13vPCV group than the 7vPCV group after dose 1 ($p\text{-value}=0.026$). The percentage of subjects reporting mild fever did not exceed 43.2% in the 13vPCV group and 40.4% in the 7vPCV group, and moderate fever did not exceed 8.5% in 13vPCV recipients and 4.9% in 7vPCV recipients across the three doses in the infant series. Severe fever was reported in only two subjects receiving 7vPCV vaccine: one case occurred after dose 2 and one case after dose 3 of the infant series. For the toddler dose, the percentage of subjects reporting mild fever did not exceed 53.5% in the 13vPCV group and 51.3% in the 7vPCV group, moderate fever did not exceed 6.6% in 13vPCV recipients and 12.5% in 7vPCV recipients; severe fever was reported in only one (1.7%) subject vaccinated with 13vPCV. One case of hives was confirmed out of 18 reports of suspected hives in 17 subjects recorded on e-diaries during the infant series or toddler dose. Of the remaining reports, seven were determined by the investigator to be inconsistent with hives and 10 were neither confirmed nor determined to be inconsistent with hives.

In both vaccine groups, AEs categorized as infections and infestations were the most frequently reported AEs during the infant series as a whole (67.8% and 66.5% of subjects in the 13vPCV group and 7vPCV group, respectively), after each dose in the infant series (range 28.6% to 47.2%), and after the toddler dose (22.8% and 26.4% of subjects in the 13vPCV group and 7vPCV group,

¹⁴ Related AEs are those AEs considered by the investigator to be related to the vaccine.

respectively). The individual events reported most often in the two vaccine groups during the infant series were upper respiratory tract infection (39.5% and 39.6% in the 13vPCV group and 7vPCV group, respectively), otitis media (28.3% and 23.6%), and bronchiolitis (16.9% and 16.3%), and after the toddler dose were upper respiratory tract infection (7.9% and 9.3%) and otitis media (8.6% and 8.9%). The only statistically significant differences between vaccine groups were noted for gastroesophageal reflux disease (GORD; higher incidence in the 7vPCV group, $p=0.036$) and seborrheic dermatitis (higher incidence in the 7vPCV group, $p=0.039$) in the infant series. There were no statistically significant differences between the vaccine groups in incidence of AEs after the toddler dose. Most of the AEs were the types of conditions and symptoms expected in infants of this age. In the infant series, the most frequent types of events related to infections (67.8% and 66.5% in the 13vPCV and 7vPCV groups, respectively), most commonly associated with the respiratory tract or the inner ear; gastrointestinal disorders (25.3% and 26.0% in the 13vPCV and 7vPCV groups, respectively), most commonly diarrhoea and vomiting; and skin disorders (25.6% and 27.8% in the 13vPCV and 7vPCV groups, respectively), most commonly eczema and diaper rash. In the toddler dose, the most frequent types of events related to infections (22.8% and 26.4% in the 13vPCV and 7vPCV groups, respectively), most commonly associated with the respiratory tract or the inner ear; gastrointestinal disorders (5.6% and 6.2% in the 13vPCV and 7vPCV groups, respectively), most commonly diarrhoea; and general disorders and administration site conditions (4.5% and 5.0% in the 13vPCV and 7vPCV groups, respectively), most commonly pyrexia or events related to the injection site. No statistically significant differences between the 13vPCV and 7vPCV groups were noted for AEs assessed as related to study vaccine (that is, pneumococcal or concomitant vaccines).

The most frequent related AEs in the infant series were categorised as gastrointestinal disorders (2.1% and 1.2% in the 13vPCV group and 7vPCV group, respectively), particularly vomiting (1.8% and 0.9%) and diarrhoea (1.2% and 0.3%). After the toddler dose, a total of eight related AEs (six in the 13vPCV group and two in the 7vPCV group) were reported, each in one subject, that included general disorders and administration site conditions (injection site erythema, induration, swelling, and pyrexia), skin conditions (rashes), and respiratory conditions (wheezing). Not all AEs between the post-infant series visit (visit 4) and the toddler dose (visit 5) and during 6-month long-term follow-up were to be recorded. AE reports received during these time periods were consistent with the rest of the study: the most frequently reported AEs were those categorized as infections and infestations.

During the infant series, SAEs were reported for 17 subjects vaccinated with 13vPCV and 16 subjects vaccinated with 7vPCV. Most of the SAEs were infections and were not considered related to the test article. One subject vaccinated with 13vPCV dose 2, experienced SAEs (pyrexia, febrile convulsions) that were considered related to the test article. One subject vaccinated with 13vPCV experienced a life-threatening SAE (near drowning). After the infant series and before the toddler dose, SAEs were reported for 12 subjects (5 in the 13vPCV group and seven in the 7vPCV group), one of which (nephroblastoma in the 7vPCV group) was life-threatening and considered related to the test article by the investigator but not by the study medical monitor. During the toddler dose period, SAEs were reported for three subjects in the 13vPCV group and four subjects in the 7vPCV group, all were of moderate severity, and none were considered related to the test article. At the 6-month follow-up, SAEs were reported for nine subjects in the 13vPCV group and five subjects in the 7vPCV group. The majority of SAEs were related to infections and infestations. There were no deaths reported during the course of this study. There were seven discontinuations from the study or from treatment during or after the infant series because of AEs, four in the 13vPCV group and three in the 7vPCV group. In the 13vPCV group, these AEs included near drowning, thrombocytopenia, convulsion, and febrile convulsion, none of which were considered by the investigator to be related to the test article. In the 7vPCV group, these AEs included muscular weakness, nephroblastoma,

and varicella, of which only nephroblastoma was considered by the investigator (but not by the sponsor) to be related to the test article.

6096A1-006 (Pivotal study)

Infants

The safety analysis of infant series data showed that most local and systemic events, including fever, were mild in severity. No statistically significant differences between vaccine groups were noted for any individual AE or related AE. In addition no related SAEs or deaths were reported in the infant series. These results indicate that the safety profile of 13vPCV is similar to that of 7vPCV.

Across the three doses, 27.1% to 33.0% of 13vPCV recipients experienced tenderness at the injection site, compared with 21.3% to 32.6% in the 7vPCV group. The incidences of any induration ranged from 26.1% to 28.2% and from 20.5% to 35.1% in the 13vPCV and 7vPCV groups, respectively. Incidences of any erythema ranged from 28.2% to 34.9% and from 36.4% to 46.8% in the two vaccine groups, respectively. At least one local reaction was reported in 49.8% to 52.2% of subjects receiving 13vPCV compared with 50.4% to 57.4% in the 7vPCV group. The majority of local reactions were mild in severity. Significant local tenderness was reported in less than 8% of subjects in either vaccine group after each dose. Less than 8% of subjects experienced moderate induration or erythema after each dose. No subject in the infant series of this study experienced severe induration or severe erythema at the injection site after any dose. No statistically significant differences between vaccine groups were noted for injection site tenderness. Significant differences were noted for induration and erythema, but only after dose 1 and dose 2. After dose 1, any induration was reported in 28.2% of 13vPCV recipients and 20.5% of 7vPCV recipients ($p=0.043$). The incidence of any erythema after dose 1 was 28.2% in the 13vPCV group and 36.4% in the 7vPCV group ($p=0.043$), and the incidence of mild erythema was 27.2% and 36.2%, respectively ($p=0.026$). After dose 2, statistically significant differences between vaccine groups were observed for any induration, mild induration, any erythema, and mild erythema. In the 13vPCV and 7vPCV groups, 26.6% and 35.1% of subjects, respectively, experienced any induration ($p=0.050$), and 24.3% and 33.5%, respectively, had mild induration ($p=0.027$). Any erythema was noted in 34.4% of subjects receiving 13vPCV and 46.8% of 7vPCV recipients ($p=0.006$); mild erythema was reported in 33.6% and 45.6%, respectively ($p=0.008$). No statistically significant differences in local reactions were noted after dose 3.

Systemic events may have been associated with pneumococcal vaccine and Infanrix Hexa administration. Most cases of fever were mild in severity (≥ 38.0 degrees C but ≤ 39.0 degrees C) in each vaccine group. The percentage of subjects reporting mild fever ranged from 43.5% to 46.8% in the 13vPCV group and from 36.6% to 48.4% in the 7vPCV group across the three doses. Subjects reporting moderate fever (≥ 39.0 degrees C but ≤ 40.0 degrees C) ranged from 3.7% to 8.8% in 13vPCV recipients and from 1.4% to 4.4% in 7vPCV recipients. Severe fever ($>40^{\circ}\text{C}$) was reported in only two subjects (0.9%), both in the 13vPCV group ($p=0.499$); each case occurred after dose 3. A statistically significant difference was noted after dose 3 for the incidence of mild fever, which was reported in 46.3% of subjects in the 13vPCV group and in 36.6% of subjects in the 7vPCV group ($p=0.040$). Parent(s) or legal guardian(s) administered antipyretic medications to prevent fever in 8.8% to 10.1% in the 13vPCV group and 9.5% to 15.4% in the 7vPCV group. However, 20.2% to 28.3% of 13vPCV recipients and 19.1% to 27.2% of 7vPCV recipients were administered antipyretic medication to treat fever. The percentage of subjects reporting other systemic events was generally similar in the two vaccine groups after each dose. Across the three doses, increased sleep was reported in 49.6% to 61.6% of subjects receiving 13vPCV and in 49.4% to 66.8% of 7vPCV recipients; irritability was noted in 42.5% to 47.2% of 13vPCV recipients and in 45.1% to 55.2% of 7vPCV recipients; decreased appetite was reported in 33.1% to 33.7% of 13vPCV recipients and in

30.2% to 34.3% of the 7vPCV group; and decreased sleep was noted in 20.9% and 25.2% of 13vPCV recipients and in 23.1% to 26.1% of 7vPCV recipients. Overall the percentage of subjects reporting one or more systemic events ranged from 82.7% to 87.1% in the 13vPCV group and from 80.5% to 88.2% in the 7vPCV group (all $p \geq 0.507$). Other than mild fever, the only statistically significant difference noted after any dose was increased sleep, which was reported after dose 2 in 53.9% of 13vPCV recipients and in 66.8% of 7vPCV recipients ($p=0.003$).

In both vaccine groups, AEs categorized as infections and infestations were reported most frequently during the infant series as a whole (range 55.9% to 56.7%) and after each dose (range 22.1% to 32.8%). The individual events reported most often in the two vaccine groups after each dose were upper respiratory tract infection (range, 7.3% to 11.3%) and bronchitis (range, 4.0 to 7.8%). No statistically significant differences between vaccine groups were noted for individual AEs in the infant series or after any dose. The only statistically significant differences were noted for the categories of: respiratory, thoracic, and mediastinal disorders after the infant series and after dose 1 (higher incidence in the 13vPCV group, $p \leq 0.032$); and of congenital, familial, and genetic disorders (higher incidence in the 7vPCV group, $p=0.015$) after dose 3. Furthermore, no statistically significant differences between the 13vPCV and 7vPCV groups were noted for AEs assessed as related to study vaccines, that is, pneumococcal vaccines or Infanrix Hexa. The most frequent related AEs were categorized as general disorders and administration site conditions (5.7% to 6.7%), and pyrexia (3.7% to 4.0%) and crying (2.7% to 3.3%) were reported most often. Fevers occurring within the 4-day reactogenicity period were to be entered into the e-diary, while fevers extending beyond the 4-days may have been reported as AEs (pyrexia) related to study product (that is, either pneumococcal vaccine or Infanrix Hexa). The related injection site reaction AEs, noted in 0.3% to 1.3% of 13vPCV or 7vPCV recipients, were attributed to Infanrix Hexa administration, as injection site reactions for the pneumococcal vaccines were captured in the e-diary. Verbatim text in the database and queries to the site confirmed the relationship to Infanrix Hexa.

Toddlers

The safety analysis of toddler dose data showed that most local and systemic events, including fever, were mild in severity. There was a single statistically significant difference between vaccine groups for an individual AE (pyrexia). There was one report of a related SAE, febrile convulsion, in a subject who had an underlying infection. No deaths were reported after the infant series or during the toddler dose. These results indicate that the safety profile of 13vPCV is similar to that of 7vPCV.

At least one local reaction was reported in 70.4% and 72.4% of 13vPCV and 7vPCV recipients, respectively. The majority of local reactions were mild in severity. Some degree of tenderness was reported in 53.4% and 51.9% of 13vPCV and 7vPCV recipients, respectively, and significant tenderness in 10.8% and 12.7%, respectively. Any induration occurred in 36.8% to 43.8% of subjects, respectively, and moderate induration in 12.1% and 12.7%, respectively. Severe induration was not reported. Any erythema occurred in 47.4% and 56.0% of 13vPCV and 7vPCV recipients, respectively, and moderate erythema in 11.6% and 15.2%, respectively. Severe erythema was reported in one (0.7%) subject in the 7vPCV group. The incidence of tenderness was highest on day 1; the mean duration was 1.8 and 2.2 days in the 13vPCV and 7vPCV groups, respectively. The incidence of induration was highest on day 2, with wide ranges in duration: 1 to 21 days in the 13vPCV group (mean, 3.4 days) and 1 to 10 days in the 7vPCV group (mean, 2.9 days). The incidence of erythema was highest on day 2; the mean duration of erythema was 2.0 and 2.4 days in the 13vPCV and 7vPCV groups, respectively. No statistically significant differences were noted between the vaccine groups for the proportions of subjects with any local reactions or for the severity of tenderness, induration, or erythema.

The percentage of subjects having one or more systemic events, excluding the use of antipyretic medications, was 87.1% in the 13vPCV group and 87.4% in the 7vPCV group. Most systemic

events were mild in severity, including cases of fever. The percentage of subjects with mild fever was 58.7% and 62.0%, respectively, and the percentage with moderate fever was 8.9% and 12.6%, respectively. Severe fever was reported in one subject (0.6%) in the 13vPCV group. Approximately equal percentages of subjects in the two vaccine groups received antipyretic medication to treat symptoms (32.1% to 33.0%) and to prevent symptoms (18.0% to 18.6%). The occurrence of other systemic events was generally similar in the two groups. Irritability was reported in 55.4% and 61.0% of 13vPCV and 7vPCV recipients, respectively, and increased sleep in 56.4% and 54.8%, respectively. Decreased appetite was observed in 43.6% and 46.4% of 13vPCV and 7vPCV recipients, respectively, and decreased sleep was reported in 31.8% and 28.8%, respectively. Most systemic events occurred on the first two days. Mean duration did not exceed 2.7 days after vaccination with 13vPCV or 2.6 days after vaccination with 7vPCV. There were no significant differences between the vaccine groups in the incidence of individual systemic events or for having any systemic event.

AEs after the infant series occurred in 9.7% and 12.3% of 13vPCV and 7vPCV recipients, respectively. The most frequent AEs (5.0% to 6.0%) were in the category of infections and infestations. Severe AEs were reported in 2.7% of subjects per group. One (1; 0.3%) subject from the 13vPCV group had an AE (mastocytosis) assessed by the investigator as related to the test article. There were no significant differences between groups. Sixteen (16) subjects from each vaccine group had a total of 45 SAEs after the infant series. In addition, one SAE (gastroenteritis) was reported in a subject who received a vaccination other than with the randomly assigned vaccine. None of the SAEs were considered related to the vaccine. AEs during the Toddler Dose were reported in 53 (52.9%) 13vPCV recipients and 145 (51.1%) 7vPCV recipients. AEs were also reported in two subjects who received a vaccination other than randomly assigned vaccine. The most frequent AEs were in the category of infections and infestations; the most common were upper respiratory tract infection (11.6% and 13.8% of 13vPCV and 7vPCV recipients, respectively) and bronchitis (6.9% and 7.0%). Statistically significant ($p=0.036$) differences in AEs between groups were observed in two categories. In the category of general disorders and administration site conditions, 7.3% of 13vPCV recipients had 30 AEs and 12.7% of 7vPCV recipients had 48 AEs. Significantly ($p=0.025$) more subjects in the 7vPCV group had pyrexia than in the 13vPCV group (9.9% versus 4.8%). AEs in the category of nervous system disorders occurred in 0.3% of 13vPCV recipients versus 2.5% of 7vPCV recipients. One (1; 0.7%) subject in the 7vPCV group had a febrile convulsion. Severe AEs occurred in nine subjects: 5 (1.7%) 13vPCV recipients and four (1.7%) 7vPCV recipients; none was life threatening. No statistically significant differences in SAEs between groups were noted.

Related AEs were reported in 5.9% and 9.5% of subjects in the 13vPCV and 7vPCV groups, respectively. The most frequent related AE was pyrexia, which was reported in 2.8% of 13vPCV recipients and 4.2% of 7vPCV recipients. The next most frequent related AEs were injection site erythema (1.4% in each vaccine group) and injection site swelling (1.0% and 1.8%, respectively), each of which included incidents at the site of the Infanrix Hexa injection. No statistically significant differences between vaccine groups were noted. Altogether, seven subjects had nine SAEs during the toddler dose, including three (1.0%) subjects with four SAEs in the 13vPCV group and four (1.4%) subjects with five SAEs in the 7vPCV group. One (1) SAE was assessed as related; the subject, who had an underlying infection, had a moderately severe febrile convulsion on day 1 after receiving 7vPCV and Infanrix Hexa. There was no statistically significant difference between groups. No deaths occurred.

6096A1-007

Local reactions were common in both vaccine groups, but were mostly mild to moderate. No subject experienced severe induration or severe erythema during the infant series and significant tenderness was reported in only 1.7% to 6.6% of subjects. The only statistically significant

difference between vaccine groups was noted for any and mild erythema after dose 1 where significantly fewer subjects in the 13vPCV group had any and mild erythema than subjects in the 7vPCV group. No difference was seen between vaccine groups in the incidence of systemic events after dose 1 or dose 2. Fever was uncommon (<7%) after either dose in either vaccine group. The use of medication to prevent or treat symptoms after vaccination was common (40.3% to 54.5%) but did not differ between the two groups. Other systemic events were common but did not differ between the two groups.

Adverse events were reported for 80.4% of subjects in the 13vPCV group and 76.3% of subjects in the 7vPCV group. The most common AEs in both groups were respiratory, that is, rhinitis, upper respiratory tract infection, nasopharyngitis and gastrointestinal such as diarrhoea, vomiting and teething. The only significant difference between vaccine groups was the incidence of cough for the infant series, but this difference between groups was accounted for by the significant difference at the 3-month visit, when subjects received only Pediacel. The most common vaccine-related AEs in both groups were gastrointestinal, that is, diarrhoea and vomiting. There were no significant differences between the two vaccine groups in the incidence of vaccine-related AEs. Serious AEs were reported for one subject in the 13vPCV group (bronchiolitis) and three subjects (reporting four events) in the 7vPCV group (gastroesophageal reflux disease, cellulitis, lower respiratory tract infection, and breath holding).

The safety analysis of infant series data showed that most local and systemic events were mild and no clinically important differences between vaccine groups were noted for these prompted symptoms or unsolicited adverse events. These results indicate that the safety profile of 13vPCV is similar to that of 7vPCV.

6096A1-008

The analysis of safety presented no notable safety concerns for subjects receiving 13vPCV. Although more than 65% of subjects in each vaccine group reported local reactions, the majority of these were mild in severity and the profile of the 13vPCV vaccine was very similar to that of 7vPCV. Fewer than 7% of subjects reported significant tenderness in either vaccine group; no cases of severe induration or severe erythema were reported during the infant series. A statistically significantly higher percentage of 13vPCV recipients than 7vPCV recipients reported moderate erythema after dose 1, but there were no differences at other time points and for other reactions. Most cases of fever were mild in severity and 13vPCV recipients reported the use of antipyretic medication to prevent symptoms significantly less often than did 7vPCV recipients after dose 3 (28.4% vs 37.6%, respectively, $p=0.048$). Over the entire infant series, severe fever (>40 degrees C) was reported in one subject after a third dose of 13vPCV.

A significantly lower percentage of 13vPCV recipients compared with 7vPCV recipients reported at least one AE ($p=0.043$). This appears to be primarily due to a larger percentage of 7vPCV subjects experiencing infections and infestations. The only event that was significantly more common in the 13vPCV group was bronchiolitis. Bronchitis was more common in the 7vPCV group (not significantly different), and there was no difference in the proportion of subjects reporting respiratory disorders including cough, asthma, or wheezing. No 13vPCV recipients reported allergic respiratory disease or wheezing, versus 0.6% and 0.3%, respectively, for 7vPCV recipients.

The incidences of related AEs were not significantly different for the two vaccine groups. No deaths or related SAEs were reported in the infant phase of this study. As noted, one subject was withdrawn from the study because of the AE of urticaria, assessed as not related to the test article, one subject reported the clinically important AE of meningitis, and one subject reported the clinically important AE of anaphylactic reaction (SAE of allergic reaction [ingestion of bananas]). Overall, there do not appear to be clinically significant differences in the AE profiles of 13vPCV and 7vPCV.

The safety analysis of infant series data showed that most local and systemic events, including fever, were mild in severity and no statistically significant differences between vaccine groups were noted for any related AE or the percentage of subjects experiencing one or more AE after each dose. In addition, no related SAEs were reported in the infant series. These results indicate that the safety profile of 13vPCV is similar to that of 7vPCV.

6096A1-011

Overall, the safety profile of 13vPCV was similar to that of 7vPCV. The safety analysis of infant series data showed that most local reactions and systemic events, including fever, were mild in severity; there were no differences between 7vPCV and 13vPCV. The incidences of significant local tenderness were higher than usually observed in clinical studies and ranged from 29.8% to 46.5% and from 26.5% to 43.6% in the 13vPCV and 7vPCV groups, respectively; the incidences were highest after dose 1. The consensus opinion noted by the investigators was that the high rate of reported significant tenderness was most likely due to parental perceptions and not due to reactogenicity of the vaccine.

There were no statistically significant differences between vaccine groups for any individual AE, except for injection site nodule (at the site of concomitant vaccine injection and higher for 7vPCV than for 13vPCV), for severe AEs, or for related AEs. In addition, no related SAEs were reported in the infant series.

6096A1-500

Overall, the safety profile of 13vPCV was similar to that of 7vPCV. Few statistically significant differences were noted for local reactions, systemic events, or AEs after any infant or toddler dose, or after the infant series as a whole. The safety analysis of infant series data showed that most local and systemic events, including fever, were mild in severity. Significant tenderness was reported in $\leq 5\%$ of subjects in each vaccine group after each dose in the infant series and in $\leq 8.5\%$ of subjects in each vaccine group after the toddler dose. The only significant differences between vaccine groups for systemic events were for irritability with dose 1 and mild fever after the toddler dose (both higher with 13vPCV).

No statistically significant differences between vaccine groups were noted for related AEs at any time during the study or for any AE during the infant series; a significant difference between the groups after the toddler dose was noted only for pharyngitis. In addition, no related SAEs were reported in the infant series or after the toddler dose; one related SAE was reported after the infant series.

6096A1-501

Overall, the safety profile of 13vPCV was similar to that of 7vPCV. The safety analysis of the infant series and toddler dose data showed that most local reactions and fever were mild in severity. There was a statistically significant difference in moderate induration reported after dose 1 (12 subjects [4.9%] in the 13vPCV group compared with four subjects [1.6%] in the 7vPCV group; $p=0.045$). There was also a statistically significant difference in significant tenderness noted after dose 3 (11 subjects [6.1%] in the 13vPCV group versus 0 subjects in the 7vPCV group; $p<.001$). The percentage of subjects reporting other systemic events was generally similar in the two vaccine groups after all doses.

The AEs observed were characteristic of infants of this age. There were few statistically significant differences between vaccine groups in incidences of individual events and no statistically significant differences between groups for any related AE. Only two SAEs were considered related to the test article; one subject vaccinated with 7vPCV (dose 3) reported high fever and another subject vaccinated with 7vPCV (dose 3) experienced a febrile convulsion. Statistically significant

differences between the two vaccine groups in incidence of individual AEs after each dose of the infant series were infrequent. After dose 1, a statistically significant difference was observed in the category of general disorders and administrative site conditions (3.2% versus 0.7% in the 13vPCV and 7vPCV groups, respectively, $p=0.037$).

6096A1-3007

Most of the adverse events reported were the types of conditions and symptoms expected in infants of this age. During the infant series, the incidence of adverse events was significantly higher among subjects vaccinated with 7vPCV (57.3%) than among those who received 13vPCV (46.3%) ($p = 0.023$). The most frequent types of events were infections and infestations, which were reported more frequently in the 7vPCV group (48.9%) than in the 13vPCV group (39.4%) ($p=0.056$), although there were no clear trends between groups for preferred terms within this System Organ Class (SOC). For both vaccine groups, these events were largely respiratory tract and ear infections and gastroenteritis. Gastrointestinal disorders, including events such as diarrhoea and vomiting, were reported for 8.0% of subjects in the 7vPCV group and for 6.4% of subjects vaccinated with 13vPCV.

The difference between groups in the incidence of individual types of AEs was significant only for rash, which occurred in six subjects (2.7%) in the 7vPCV group and no subjects vaccinated with 13vPCV ($p = 0.030$). Conjunctivitis approached significance, being experienced by three subjects (1.4%) in the 13vPCV group and 11 subjects (4.9%) in the 7vPCV group ($p = 0.054$). These differences are likely chance occurrences and of no clinical significance.

Only three adverse events were considered related to the test article by the investigator: bronchitis, angioedema, and rash were reported by one subject each, all in the 7vPCV group. Severe AEs were reported in three subjects vaccinated with 13vPCV (*Escherichia* urinary tract infection, orchitis, and pneumonia) and in one subject in the 7vPCV group (gastroenteritis). All of these severe events were considered serious and resulted in hospitalization. None were considered to be related to the test article. No AEs considered life-threatening were reported during the infant series.

No subjects died during the infant series, and no subjects withdrew from the study because of adverse events. Serious AEs occurred in six subjects vaccinated with 13vPCV and in eight subjects vaccinated with 7vPCV. Most of the events were infections and all resulted in hospitalization. None of the SAEs were considered related to the vaccine.

6096A1-3002

Vaccination was generally well tolerated in all three groups. There was a trend toward greater local reactogenicity (in terms of tenderness, but not erythema or induration) with increasing age and with subsequent dose administration. In contrast, there were fewer systemic reactions in group 3 compared with groups 1 and 2. There were relatively few AEs in all three groups, and reported AEs were within the expected spectrum of incidental illness for each age group.

The majority of local reactions were mild in severity in all groups. No subjects reported severe induration or severe erythema. Most cases of fever were mild to moderate in severity in the groups. The incidence of moderate fever did not exceed 2.3% in either group after any dose, and severe fever was not reported in any subject. The AEs characterized as infections and infestations (range 13.3% to 46.4%) or as gastrointestinal disorders (range 1.1% to 11.6%) were reported most frequently. The percentages of related AEs reported in groups 1 and 2 were low (range 2.2% to 2.7%). No related AEs were reported in group 1 (dose 3) or in group 3. No subjects withdrew from the study because of an AE. In general, most SAEs were characterized as infections and infestations or as gastrointestinal disorders. No related SAEs were reported in this study, and no subjects withdrew from the study because of an SAE. No deaths or clinically important AEs were reported in this study.

Summary of safety

The safety database reveals a comparable safety profile for 13vPCV and Prevenar (7vPCV). As Prevenar has an extensive safety database (approximately 285 million doses have been distributed according to the sponsor) and almost all of the 13vPCV studies performed to date have Prevenar as a comparator, this provides added confidence as to the safety profile of 13vPCV. In the studies examined in this submission, in general, clinical studies reported no major differences between local and systemic reactions, adverse events (AEs) and serious adverse events (SAEs) between Prevenar 13 and Prevenar. Most of the reactions reported were mild to moderate. The common local reactions for both vaccines were tenderness, induration and erythema. The common systemic reactions included decreased appetite, irritability, increased sleep and decreased sleep. Fever and use of antipyretic medication was also similar in both 7vPCV and 13vPCV groups. Almost all AEs and SAEs were not thought to be related to either vaccine. In addition to the regular post-marketing pharmacovigilance activity, the plans to monitor adverse events in a post approval study as described in the sponsor's Risk Management Plan (RMP) are reassuring.

Clinical Summary and Conclusions

Pneumococcal disease is a major cause of morbidity and mortality worldwide, particularly as a result of IPD. In Australia, two pneumococcal vaccinations are available (see Table 1), including a 7vPCV and a 23vPPV.

Although the present pneumococcal vaccines have been effective, there have been concerns regarding IPD due to non-7vPCV serotypes, especially amongst infants.

PCVs tend to be more immunogenic amongst infants.

Several pneumococcal vaccines are approved in Australia, as indicated, including a 7vPCV, and the sponsor is proposing to extend the number of serotypes covered by six serotypes (1, 3, 5, 6A, 7F and 19A) in use the same general vaccination formula for IM injection, in order to produce a 13vPCV and to provide better protection for adults.

There were two pivotal clinical studies of the target group covering more than 1200 subjects comparing 13vPCV with 7vPCV, and seven supporting studies examining various facets of 13vPCV tolerance, immunogenicity and safety.

In these studies, there were a few occasions where the 7vPCV common serotypes in 13vPCV did not meet the primary non-inferiority criterion (WHO, 2008), but the differences appeared to be small. In addition, for the six additional serotypes in 13vPCV, there was good evidence that the vaccine is likely to be effective for these.

Concerns have been raised concerning the impact of the additional vaccine components on the components already been shown to be effective, which is hard to gauge from this study. It is reassuring that further surveillance of pneumococcal diseases in five European countries, as per the RMP.

The recommendation of a 3 +1 immunisation schedule for 13vPCV appears to be justified, although differing schedules for Prevenar are used elsewhere.

As expected, the safety profiles of 13vPCV and 7vPCV were similar with a similar rate of local and systemic reactions and use of antipyretic medication. There were no differences in the rates and nature of SAEs and other AEs between the two groups.

Conclusions and recommendation

Data appears adequate to support the use of Prevenar 13 (13vPCV) for the prophylaxis of pneumococcal diseases due to IPD, AOM and pneumonia, as in Prevenar (7vPCV) in children aged

two months to five years, as discussed in the NHMRC (2008) recommendations for pneumococcal vaccination.

Prevenar 13 (13vPCV) is well placed to become an alternative and then replace Prevenar (7vPCV), once incorporated in NHMRC NIS as appropriate, and if ongoing surveillance confirms immunogenicity and non-inferiority to 7vPCV.

It is recommended that the use of Prevenar 13 be closely regulated and that the product should only be available on the prescription of a registered medical practitioner.

There is no conclusive evidence at present that a course of pneumococcal vaccination started using 7vPCV and completed using 13vPCV would provide adequate immunogenicity for the six additional serotypes in 13vPCV, as data evaluating this is not yet available.

The use of the product in older children and adults, including the elderly, pregnant or lactating women is not recommended, as it has not been evaluated for this group.

The use of the product in infants less than six weeks or children greater than five years is not recommended, as it has not been evaluated for groups in this age range.

Post-marketing surveillance should closely monitor the use of Prevenar 13. This was recommended by the sponsor as part of the RMP.

The epidemiology of pneumococcal diseases will also need to be continually monitored for emergence of non-13vPCV serotypes underlying pneumococcal diseases, including IPD, AOM and pneumonia, as part of ongoing surveillance.

If Prevenar 13 is to be added to the vaccine prophylaxis armamentarium, then a strategy will need to be rolled out with a view to ensuring that vaccinators are familiarised with the vaccine. In addition, the relevant clinical recommendations for pneumococcal vaccination produced by the NHMRC (2008) in Australia would also need to be updated.

V. Pharmacovigilance Findings

There was a Risk Management Plan submitted with this application but it was not formally evaluated as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are 13 drug substances, corresponding to the polysaccharide-CRM₁₉₇ conjugates. The manufacturing process for the drug substances consists of

1. polysaccharide production (13 serotypes)
2. polysaccharide activation (13 serotypes)
3. CRM₁₉₇ production
4. conjugation 13PS-CRM₁₉₇ conjugates

Evaluation questions have been satisfactorily resolved.

Nonclinical

Immunogenicity and repeat-dose toxicity studies were conducted with Prevenar 13, in rats, rabbits and cynomolgus monkeys. There are no nonclinical concerns on the capacity for Prevenar 13 to induce appropriate multi-valent antibody responses in the tested species. There are no concerns on systemic toxicity in animals. Nodule/granuloma formation was found consistently after subcutaneous injection in all animal species, and was likely associated with the aluminium

phosphate adjuvant. Local nodule formation at injection site is a possible concern after multiple vaccinations.

Clinical

Following recommendations for inclusion of 7-valent pneumococcal conjugate vaccine (7vPCV) in the childhood immunisation schedule in many countries, it is not feasible to conduct placebo controlled efficacy studies of subsequent pneumococcal conjugate vaccines. Immunogenicity endpoints to support licensure of subsequent PCVs were developed by US FDA and WHO. The clinical evaluation report p5 describes immunogenicity endpoints used in the development of 13vPCV. An IgG antibody concentration measured by ELISA, with a pre-adsorption step, of 0.35 µg/mL at one month after three infant doses has been used as a correlate for efficacy of all vaccine serotypes. This correlate is based on pooled efficacy estimates in prevention of IPD in 3 efficacy studies of Prevenar (or 9vPCV). Opsonophagocytic antibody, as a functional antibody assessment, has also been assessed with a threshold $\geq 1:8$ correlated with serotype specific IPD efficacy.

Two Phase III studies have been identified as pivotal by the Sponsor. Study 6096A1-004 is a randomised, double blind comparison of 13vPCV and 7vPCV given at 2-, 4-, 6- and 12-15 months of age with concurrent routine paediatric vaccines conducted in USA. Study 6096A1-006 is a randomised, double blind comparison of 13vPCV and 7vPCV given at 2-, 3-, 4- and 11-12 months of age with routine paediatric vaccines conducted in Germany. Study 6096A1-3005, a Phase III, randomised, double blind, lot consistency study, with 7vPCV comparator, conducted in USA with a 2-,4-,6- and 12 month schedule is also a pivotal study with commercial formulation and manufacture scale relevant to the Australian immunisation schedule and concomitant vaccines.

The primary objectives of **Study 6096A1-004** were to demonstrate that the immune response to the 7 common pneumococcal serotypes by 13vPCV was non-inferior to the immune response induced by 7vPCV 1 month after the third dose, and to demonstrate that the immune response to the 6 additional pneumococcal serotypes induced by 13vPCV was non-inferior to the lowest immune responses elicited by a pneumococcal serotype contained in 7vPCV. Other objectives included assessment of non-inferiority of GMCs after the fourth dose, assessment of responses to concomitant DTPa, HBV, IPV, PRP-T (PRP conjugated to tetanus) or PRP-OMP (PRP conjugated to meningococcus), and mumps measles rubella vaccine (MMRV) antigens, and assessment of opsonophagocytic activity after third and fourth doses in a subset. A total of 666 subjects were randomised to 13vPCV or 7vPCV. 663 subjects received the first vaccine dose and 584 subjects (87.7%) completed the infant series. Demographic characteristics were well balanced between treatment groups.

For the 13vPCV arm, 10 of the 13 serotypes demonstrated non-inferiority pneumococcal IgG antibody concentration ≥ 0.35 µg/mL after the third dose. Serotypes 6B and 9V responses to 13vPCV did not meet non-inferiority criteria and the additional serotype 3 showed a lower proportion achieving ≥ 0.35 µg/mL in the 13vPCV group than the 7vPCV group.

After the toddler dose a high proportion (>98%) achieved ≥ 0.35 µg/mL in the 13vPCV arm - the exception was the additional serotype 3. In comparison of GMCs after the toddler dose, 12 of the 13 serotypes met the non-inferiority criterion - the exception was serotype 3.

Functional OPA seroresponse $\geq 1:8$ was observed in a high proportion of subjects (>90%) for all serotypes in the 13vPCV group after dose 3 whereas a substantial proportion achieved OPA seroresponse $\geq 1:8$ only for the additional serotypes 6A and 7F in the 7vPCV group. Functional OPA seroresponse $\geq 1:8$ after dose 4 were achieved in more than 96.7% for all serogroups in the 13vPCV group and showed a modest increase from dose 3 proportions only for serotype 6A and 19A in the 7vPCV group.

Concomitantly administered vaccines Pediarix (DTPa-Hepatitis B [HepB]-IPV [GSK]), ActHIB (PRP-T), PedvaxHIB (PRP-OMP), Proquad (MMRV) and VAQTA (Hepatitis A [HepA]) showed

AusPAR Prevenar 13 pneumococcal polysaccharide conjugate vaccine Wyeth Australia Pty Ltd PM-2009-00110-3-2 Final 13 May 2010

non-inferiority of antibody responses when concomitantly administered with 13vPCV compared to 7vPCV.

Study 6096A1-006 was conducted in Germany with a 2-, 3-, 4- and 11-12 month schedule which does not reflect the Australian schedule for 7vPCV. Infanrix-Hexa (DTPa-HepB-IPV–PRP-T) was administered concomitantly with PCV. A total of 604 subjects were enrolled and 586 subjects completed the primary series.

For the 13vPCV arm, 12 of the 13 serotypes demonstrated non-inferiority of the pneumococcal IgG antibody concentration ≥ 0.35 $\mu\text{g/mL}$ after third dose. The exception was serotype 6B. After dose 4, a seroresponse ≥ 0.35 $\mu\text{g/mL}$ was achieved by a high proportion ($>98\%$) in the 13vPCV group, except for serotype 3, and the non-inferiority criterion was met for GMCs for 12 of the 13 serotypes (serotype 3 was the exception). Functional OPA seroresponse $\geq 1:8$ was observed for all serotypes in a high proportion of subjects in the 13vPCV group after dose 3 and dose 4. Concomitantly administered vaccines showed non-inferiority of antibody responses.

Study 6096A1-3005 is a randomised, double blind 7vPCV controlled study evaluating 3 lots of 13vPCV in a 2, 4, 6 and 12 month schedule, in healthy infants given routine paediatric vaccines in USA. The 13vPCV lots were two lots at pilot scale and 1 lot at manufacture scale. The routine vaccines were Pediarix (DTPa-HBV-IPV), ActHIB (PRP-T), Proquad (MMRV) and VAQTA (HepA).

The objective was to demonstrate that IgG GMC ratio among the 3 lots was equivalent 1 month after the third dose. The equivalence criterion was the ratio of GMCs for any two lots did not exceed a 2-fold difference (log transformed geometric mean response for each serotype among the 3 lots <0.693 and >0.693). Other objectives related to IgG antibody concentration ≥ 0.35 $\mu\text{g/mL}$, post-dose 4 antibody concentrations and antibody response to concomitantly administered vaccines. The study is briefly described in CER p18. 1600 subjects were enrolled, 450 to each of the 13vPCV groups and 250 to the 7vPCV group. Each of the 13 serotypes met the equivalence criterion.

Study 6096A1-3002 is a study in older infants and children naive to PCV to support catch-up dosage regimens and **Study 6096A1-008** included assessment of 7vPCV/13vPCV regimens relevant to proposed statements that vaccination with 7vPCV can be switched to 13vPCV. Further data are pending and conclusive evidence on the adequacy of immunogenicity for the six new serotypes when switching from 7vPCV to 13vPCV during the course of immunisation is not yet available.

Safety

Safety data were available from 12 clinical studies in infants, reflecting exposure of 4423 subjects to at least 1 dose of 13vPCV and 2451 subjects to at least 1 dose of 7vPCV. Nearly all clinical studies compared 13vPCV with 7vPCV, and with co-administration of paediatric vaccines in these studies in infants and children. Table 16 presents local adverse events and Table 17 presents systemic combined for infant studies in which AE were reported in more than 3000 subjects who received 13vPCV and more than 2000 subjects who received 7vPCV. The incidence of local events, tenderness, induration, and fever (any and significant) and the systemic events, decreased appetite, irritability, decreased sleep and fever and use of antipyretic medication, was generally closely comparable in 13vPCV and 7vPCV groups and generally similar across doses 1 to 4. Serious adverse events are shown in Table 19. The incidence of any types of SAE was 3.9% for 13vPCV and 3.8% for 7vPCV in the infant studies and 1.1% for 13vPCV and 0.8% for 7vPCV after the toddler dose. There were no notable differences in types or frequencies of SAE between 13vPCV and 7vPCV groups. A total of 4 deaths (3 after 13vPCV and 1 after 7vPCV) occurred in all 13vPCV studies as shown in Table 13A, attributed to SIDS between 3 days and 75 days after vaccination.

The clinical evaluator concluded the safety profile was comparable for 13vPCV and for 7vPCV in clinical studies. 7vPCV has an extensive postmarketing safety database compiled from the distribution of more than 200 million doses, and this provides confidence regarding the safety profile of 13vPCV.

Conclusion of Clinical Evaluator

The evaluator concluded that the proposed 3+1 schedule for 13vPCV is justified. The safety profile of 13vPCV and 7vPCV was similar with regard to local and systemic adverse events and use of antipyretics. There were no differences in the nature or rates of SAE between the two groups.

Risk-Benefit Analysis

The evaluator considered that for the 7 common serotypes on the few occasions when non-inferiority criteria, for pneumococcal antibody concentrations measured by ELISA, were not met that the small differences between 13vPCV and 7vPCV are unlikely to have a biological impact. The evaluator identifies that in Study 6096A1-004 serotype 6B and 9V responses were lower after dose 3 in infants for 13vPCV compared to 7vPCV, but after 4 doses this difference is lost. The additional serotype 3, however, showed low ELISA response both post dose 3 and post dose 4 in the 13vPCV group. OPA response was shown to the 13 vaccine serotypes in this study.

In Study 6096A1-006 serotype 6B response in the 13vPCV after dose 3 was inferior to 7vPCV and after dose 4 serotype 3 GMC response did not meet the non-inferiority criterion.

The Delegate considered that when given in a 3+1 schedule that 13vPCV and 7vPCV show comparable ELISA response for the common serotypes.

There are numbers of uncertainties in interpretation in the immunogenicity endpoints used in the submitted clinical studies. A single IgG antibody concentration measured by ELISA, with a pre-adsorption step, of 0.35 µg/mL at 1 month after three infant doses has been used as a correlate for efficacy of all vaccine serotypes and all geographic areas, which may not be warranted from the results of three studies which were pooled. The correlates were developed based on protection against invasive pneumococcal disease and may differ for estimation of protection against pneumonia and acute otitis media. The sponsor has submitted plans for monitoring of vaccine effectiveness against IPD and AOM to the US FDA.

Long term antibody persistence data are not yet available with 13vPCV.

Substantial reduction of vaccine type IPD has been observed in older age groups after the introduction of 7vPCV programs.

Serotype replacement, especially with serotype 19A, has been observed following the introduction of 7vPCV programs. 13vPCV offers potential benefit in addressing serotype 19A disease but there is potential for emergence of other serotypes not included in 13vPCV.

Concomitant vaccines examined in schedules relevant to Australia have demonstrated non-inferiority when 13vPCV and 7vPCV are administered concomitantly.

The available safety data from over 4,000 infants and children vaccinated with 13vPCV in comparison with 7vPCV have supported a similar safety profile for the two vaccines. The sponsor has provided commitments to US FDA to undertake a post-marketing observational database study in the USA to monitor less common adverse events.

The Delegate proposed to register Prevenar 13 for the indication:

Prevenar 13 is indicated for active immunisation against disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F & 23 (including sepsis, meningitis, pneumonia, bacteraemia, and acute otitis media) in infants and children from 6 weeks up to 5 years of age.

The primary infant series consists of three doses, each of 0.5 mL, given as early as 6 weeks of age and with an interval of at least 1 month between doses. The second dose is recommended at 4 months, the third dose at 6 months and a fourth dose at 12-15 months of age.

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal and recommended the following indication:

Active immunisation for the prevention of disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (including invasive disease, pneumonia and acute otitis media) in infants and children from 6 weeks up to 5 years of age

The use of PREVENAR 13 should be determined by official recommendations, taking into consideration the impact of invasive pneumococcal disease in different age groups as well as variability of serotype epidemiology in different geographical areas.

In making this recommendation, the ACPM was satisfied that the immunogenicity and safety of Prevenar 13 has been demonstrated. As the application was based on immunogenicity studies rather than disease endpoint studies, the indication for Prevenar and Prevenar 13 should be similar. In its Pre-ACPM response, the sponsor provided additional data from clinical trials utilising a number of switching strategies, to support the recommendation that infants and children who have begun immunisation with Prevenar may complete immunisation by switching to Prevenar 13 at any point in the schedule and the Committee endorsed this recommendation. Furthermore, the Committee noted that the proposed dosage regimen would simplify any strategy involving transition to the 13 valent agent for Australian use.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Prevenar13 pneumococcal polysaccharide conjugate vaccine, 13 valent adsorbed, 0.5mL, syringe containing 2.2 µg of pneumococcal purified capsular polysaccharides for serotype 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23 F and 4.4 µg of pneumococcal purified capsular polysaccharides for serotype 6B for

Active immunisation for the prevention of disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (including invasive disease, pneumonia and acute otitis media) in infants and children from 6 weeks up to 5 years of age.

The use of Prevenar 13 should be determined by official recommendations, taking into consideration the impact of invasive pneumococcal disease in different age groups as well as variability of serotype epidemiology in different geographical areas.

Attachment 1. Product Information

PRODUCT INFORMATION

Prevenar 13[®]

NAME OF THE MEDICINE

Prevenar 13

Pneumococcal polysaccharide conjugate vaccine, 13-valent adsorbed

DESCRIPTION

The vaccine is a ready to use homogeneous white suspension for intramuscular injection, supplied as a pre-filled syringe.

Active ingredients

Each 0.5 mL dose contains:

2.2 µg of pneumococcal purified capsular polysaccharides for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F

4.4 µg of pneumococcal purified capsular polysaccharides for serotype 6B.

Each serotype is individually conjugated to non-toxic diphtheria CRM₁₉₇ protein and adsorbed on aluminium phosphate (0.565 mg).

Excipients

Succinic acid, polysorbate 80, aluminium phosphate, sodium chloride in water for injections.

PHARMACOLOGY

Streptococcus pneumoniae is an important cause of morbidity and mortality in persons of all ages worldwide. It is a leading cause of death and illness in infants, among the elderly, and in persons who have certain underlying medical conditions. The organism causes invasive infections, including bacteraemia and meningitis, pneumonia and other lower respiratory tract infections, and upper respiratory tract infections including otitis media and sinusitis.

Based on serotype surveillance performed before the introduction of Prevenar, Prevenar 13 is estimated to cover 93.3% of serotypes causing IPD (Invasive Pneumococcal Disease) among children less than 5 years of age in Australia (Watson M. et al., *Communicable Disease Intelligence* 2004; 28(4): 455-464) and 92.8 % in New Zealand (Heffernan H.M., et al., *Epidemiology of Infections* 2007; 1-8.)

Prevenar 13 is estimated to cover over 90% of serotypes causing antibiotic resistant IPD.

Pharmacodynamics

Pharmacotherapeutic group: pneumococcal vaccines.

Pharmacokinetics

Evaluation of pharmacokinetic properties is not available for vaccines.

CLINICAL TRIALS

Prevenar 13 immunogenicity clinical trials

The World Health Organization (WHO) has recommended a serum anti-capsular polysaccharide IgG antibody concentration of 0.35 µg/mL using an enzyme-linked immunosorbent assay, measured one month after the primary infant series as a single antibody reference concentration to estimate the efficacy of new pneumococcal conjugate vaccines against IPD. This recommendation is largely based upon the observed correlation between immunogenicity and IPD efficacy from three placebo-controlled trials with either Prevenar or the investigational 9-valent CRM₁₉₇ conjugate polysaccharide vaccine. This reference concentration is only applicable on a population basis and cannot be used to predict protection against IPD on an individual basis.

Immune responses following a three-dose primary infant series

Clinical trials have been conducted in a number of European countries and the US using a range of primary vaccination schedules. The percentage of infants achieving pneumococcal anti-capsular polysaccharide IgG antibody concentrations ≥ 0.35 µg/mL and opsonophagocytic activity (OPA) antibody titers $\geq 1:8$, one month after a three-dose primary series (at 2, 4 and 6 months) and after booster dosing, from representative studies are presented below (Table 1):

Table 1: Percentage of subjects with Pneumococcal Anti-capsular Polysaccharide IgG Antibody concentrations ≥ 0.35 µg/mL and OPA Antibody Titer $\geq 1:8$ following Prevenar 13 administration in a 2, 4, 6 month primary schedule

Serotype		Primary Schedule (2, 4, 6 months)	Booster
		IgG (N=897-924) OPA (N=91-94)	IgG (N=458-479) OPA (N=88-92)
1	IgG ≥ 0.35 µg/mL	95.6-99.3%	98.7-100.0%
	OPA Antibody $\geq 1:8$	98.9%	98.9%
3	IgG ≥ 0.35 µg/mL	63.5-90.3%	90.5-92.2%
	OPA Antibody $\geq 1:8$	96.8%	97.8%
4	IgG ≥ 0.35 µg/mL	94.4-98.9%	99.1-99.2%
	OPA Antibody $\geq 1:8$	97.8%	98.9%
5	IgG ≥ 0.35 µg/mL	89.7-97.3%	99.1-99.6%
	OPA Antibody $\geq 1:8$	92.3%	98.9%
6A	IgG ≥ 0.35 µg/mL	96.0-98.2%	99.1-100.0%
	OPA Antibody $\geq 1:8$	100.0%	98.9%
6B	IgG ≥ 0.35 µg/mL	87.3-98.5%	99.6%
	OPA Antibody $\geq 1:8$	98.9%	98.9%
7F	IgG ≥ 0.35 µg/mL	98.4-100.0%	98.8-99.6%
	OPA Antibody $\geq 1:8$	100.0%	100.0%
9V	IgG ≥ 0.35 µg/mL	90.5-99.3%	99.1-100.0%
	OPA Antibody $\geq 1:8$	100.0%	98.9%
14	IgG ≥ 0.35 µg/mL	97.4-98.2%	98.7-100.0%
	OPA Antibody $\geq 1:8$	100.0%	100.0%
18C	IgG ≥ 0.35 µg/mL	96.8-98.1%	98.7-99.6%
	OPA Antibody $\geq 1:8$	100.0%	98.9%
19A	IgG ≥ 0.35 µg/mL	98.4-99.6%	100.0%
	OPA Antibody $\geq 1:8$	100.0%	97.8%
19F	IgG ≥ 0.35 µg/mL	98.0-99.3%	99.6-100.0%
	OPA Antibody $\geq 1:8$	90.4%	96.7%
23F	IgG ≥ 0.35 µg/mL	87.2-94.6%	99.1-99.6%
	OPA Antibody $\geq 1:8$	98.9%	98.9%

In Prevenar 13 recipients, antipolysaccharide binding antibody for each of the 13 serotypes has been demonstrated to be correlated with functional antibacterial opsonophagocytic activity (biologically active antibody).

Immune responses following a two-dose primary series

The immunogenicity after two doses in infants has been documented in four studies. The proportion of infants achieving a pneumococcal anti-capsular polysaccharide IgG concentration ≥ 0.35 $\mu\text{g/mL}$ one month after the second dose ranged from 79.6% to 98.5% across 11 of the 13 vaccine serotypes. Smaller proportions of infants achieved this antibody concentration threshold for serotype 6B (27.9% to 58.4%) and 23F (55.8% to 68.6%). Compared to a three-dose infant series, pneumococcal anti-capsular polysaccharide IgG GMCs were lower after a two-dose infant series for most serotypes.

Booster responses following two-dose and three-dose primary series

Post-booster antibody concentrations were higher for 12 serotypes than those achieved after the infant primary series, which is consistent with adequate priming (the induction of immunologic memory). For serotype 3, antibody concentrations following the infant primary series and booster dose were similar. Antibody responses to booster doses following two-dose or three-dose infant primary series were comparable for all 13 vaccine serotypes.

For children aged from 7 months to 5 years, age appropriate catch-up immunisation schedules result in levels of anti-capsular polysaccharide IgG antibody responses to each of the 13 serotypes that are at least comparable to those of a three-dose primary series in infants.

Prevenar protective efficacy

The efficacy of Prevenar (7-valent) was evaluated in two major trials – the Northern California Kaiser Permanente (NCKP) trial and the Finnish Otitis Media trial (FinOM). Both trials were randomised, double-blind, active-control trials in which infants were randomised to receive either Prevenar (7-valent) or control vaccine (NCKP, meningococcal serogroup C CRM-conjugate [MnCC] vaccine; FinOM, hepatitis B vaccine) in a four-dose series at 2, 4, 6, and 12 - 15 months of age. The various efficacy results from these trials (for invasive pneumococcal disease, pneumonia, and acute otitis media) are presented below (Table 2).

Table 2: Summary of Efficacy of Prevenar (7-valent)

Test	Study	N	VE [*]	95% CI
Invasive Pneumococcal Disease (IPD)				
Per-protocol	NCKP	30,258	97%	85, 100
Intent-to-treat		37,866	94%	81, 99
Pneumonia (Per-protocol)				
<i>With bacteraemia</i>			87.5%	7, 99
<i>Clinical pneumonia with abnormal chest X-ray</i>			20.5%	4.4, 34.0
Acute Otitis Media (AOM)				
Per-protocol (reduction of)	NCKP	37,868		
<i>Total episodes</i>			7%	4, 10
<i>Recurrent AOM</i> <i>(3 episodes in 6 mo. or 4 episodes in 1 yr.)</i>			9%	3, 15
<i>Recurrent AOM</i> <i>(5 episodes in 6 mo. or 6 episodes in 1 yr.)</i>			23%	7, 36
<i>Tympanostomy tube placement</i>			20%	2, 35

Per-protocol (reduction of)	FinOM	1662		
<i>Total episodes</i>			6%	-4, 16
<i>All pneumococcal AOM</i>			34%	21, 45
<i>Vaccine-serotype AOM</i>			57%	44, 67
Intent-to-treat				
<i>Vaccine-serotype AOM</i>			54%	41, 64

* Vaccine efficacy

Prevenar effectiveness

The effectiveness of Prevenar (7-valent) against pneumococcal disease (comprising the protection afforded by vaccination and from herd immunity due to reduced transmission of vaccine serotypes in the population) has been evaluated in routine paediatric immunisation programmes that employ either three-dose or two-dose primary infant series, each with booster doses. This surveillance will continue with Prevenar 13.

Data from several countries is summarised in Table 3. It is important to note that as countries continually update the data from their surveillance systems, values included in this table may change over time.

Table 3. Summary of Effectiveness of Prevenar (7-valent) for Invasive Pneumococcal Disease				
Country	Year of Introduction	Recommended Schedule	Disease Reduction, %	95% CI
USA	2000	2, 4, 6, 12 - 15 months		
<i>Children <5^a</i>			Vaccine serotypes: 98% All serotypes: 77%	97, 99% 73, 79%
<i>Persons ≥65^b</i>			Vaccine serotypes: 76.2% All serotypes: 38.2%	NA
Canada (Quebec) ^c	2004	2, 4 and 12 months	All serotypes: 72.5%	NA
UK (England and Wales) ^d	2006	2, 4 and 13 months	Two doses under age 1: 85%	49, 95%
Australia ^e	2002	2, 4 and 6 months	Vaccine serotypes: 89.6%	NA

^a 2005 data.

^b 2004 data.

^c Children < 5 years of age. 2006 data.

^d Children <2 years of age. Calculated vaccine effectiveness as of May 2008 (Broome method). Complete effectiveness for routine 2+1 schedule not yet available.

^e Roche et al., *Communicable Disease Intelligence*. 2008; 32:18-30 (*incl in Mod 1.3.1*).

Effectiveness of Prevenar (7-valent) in a 3+1 schedule has also been observed against acute otitis media and pneumonia since its introduction in a national immunisation programme. In a retrospective evaluation of a large US insurance database, AOM visits were reduced by 42.7%, and prescriptions for AOM by 41.9%, in children younger than 2 years of age, compared with a pre-licensure baseline (2004 vs. 1997 - 99). In a similar analysis, hospitalisations and ambulatory visits for all-cause pneumonia were reduced by 52.4% and 41.1%, respectively. For those events specifically identified as pneumococcal pneumonia, the observed reductions in hospitalisations and ambulatory visits were 57.6% and 46.9%, respectively, in children younger than 2 years of age, compared with a pre-licensure baseline (2004 vs. 1997 - 99).

While direct cause-and-effect cannot be inferred from observational analyses of this type, these findings suggest that Prevenar (7-valent) plays an important role in reducing the burden of mucosal disease (AOM and pneumonia) in the target population.

Children with sickle cell disease

The immunogenicity of Prevenar (7-valent) has been investigated in an open-label, multicentre study in 49 infants with sickle cell disease. Children were vaccinated with Prevenar (3 doses one month apart from the age of 2 months), and 46 of these children also received a 23-valent pneumococcal polysaccharide vaccine at the age of 15 - 18 months. After primary immunisation, 95.6% of the subjects had antibody levels of at least 0.35 µg/mL for all seven serotypes found in Prevenar. A significant increase was seen in the concentrations of antibodies against the seven serotypes after the polysaccharide vaccination, suggesting that immunological memory was well established.

INDICATIONS

Active immunisation for the prevention of disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (including invasive disease, pneumonia and acute otitis media) in infants and children from 6 weeks up to 5 years of age.

The use of Prevenar 13 should be determined by official recommendations, taking into consideration the impact of invasive pneumococcal disease in different age groups as well as variability of serotype epidemiology in different geographical areas.

CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients, or to diphtheria toxoid
- Allergic reaction or anaphylactic reaction following prior administration of Prevenar.

PRECAUTIONS

Do not administer Prevenar 13 intravenously. Do not administer Prevenar 13 intravascularly. Take care to avoid injecting into or near nerves and blood vessels. The vaccine should not be injected in the gluteal area (see DOSAGE AND ADMINISTRATION).

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

As with other vaccines, the administration of Prevenar 13 should be postponed in subjects suffering from acute moderate or severe febrile illness.

Disease coverage

Prevenar 13 will not protect against *Streptococcus pneumoniae* serotypes other than those included in the vaccine nor other micro-organisms that cause invasive disease, pneumonia, or otitis media. As with any vaccine, Prevenar 13 may not protect all individuals receiving the vaccine from pneumococcal disease.

Children with blood disorders

This vaccine should not be given to infants or children with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

Children with impaired immune response

Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunisation.

Vaccination in high-risk groups

Limited data have demonstrated that Prevenar (three dose primary series) induces an acceptable immune response in infants with sickle cell disease with a safety profile similar to that observed in non-high-risk groups. Safety and immunogenicity data are not yet available for children in other specific high-risk groups for invasive pneumococcal disease (e.g. children with another congenital or acquired splenic dysfunction, HIV-infected, malignancy, nephrotic syndrome). Vaccination in high-risk groups should be considered on an individual basis. Specific data are not yet available for Prevenar 13.

Children below 2 years old should receive the appropriate-for-age Prevenar 13 vaccination series. The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccines in children ≥ 24 months of age with conditions (such as sickle cell disease, asplenia, HIV infection, chronic illness or who are immunocompromised) placing them at higher risk for invasive disease due to *Streptococcus pneumoniae*. Whenever recommended, children at risk who are ≥ 24 months of age and already primed with Prevenar 13 should receive 23-valent pneumococcal polysaccharide vaccine. The interval between the 13-valent pneumococcal conjugate vaccine (Prevenar 13) and the 23-valent pneumococcal polysaccharide vaccine should not be less than 8 weeks. There are no data available to indicate whether the administration of 23-valent pneumococcal polysaccharide vaccine to unprimed children or to children primed with Prevenar 13 might result in hyporesponsiveness to further doses of Prevenar 13.

Risk of apnoea

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Prophylactic antipyretics

Antipyretic treatment should be initiated according to local treatment guidelines.

Prophylactic antipyretic medication is recommended:

- for all children receiving Prevenar 13 simultaneously with vaccines containing whole cell pertussis because of higher rate of febrile reactions
- for children with seizure disorders or with a prior history of febrile seizures.

Carcinogenicity and mutagenicity

Prevenar 13 has not been evaluated for any carcinogenic or mutagenic potential, or impairment of fertility.

Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and local tolerance studies.

Use in pregnancy

Category B2

Prevenar 13 is not indicated or recommended for use in pregnant women and has not been evaluated for potential harmful effects during pregnancy in animals or humans.

Use in lactation

Safety during lactation has not been established. It is not known whether vaccine antigens or antibodies are excreted in breast milk.

Geriatric use

The safety and effectiveness of Prevenar 13 in geriatric populations have not been established.

Interactions with other medicines

Different injectable vaccines should always be given at different injection sites.

Prevenar 13 can be given with any of the following vaccine antigens, either as monovalent or combination vaccines: diphtheria, tetanus, acellular or whole cell pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, hepatitis B, meningococcal serogroup C, measles, mumps, rubella and varicella. Clinical trials demonstrated that the immune responses and the safety profiles of the administered vaccines were unaffected.

Previously, trials with Prevenar and rotavirus vaccines have demonstrated that the immune responses of the seven pneumococcal serotypes in Prevenar and the rotavirus vaccine were unaffected. It is not expected that any differences in immune response for the six additional serotypes or the rotavirus vaccine will be observed if Prevenar 13 is used. In clinical trials, where there was concomitant administration of Prevenar 13 and rotavirus vaccine, no change in the safety profiles of these vaccines was observed.

Effects on ability to drive and operate machinery

Not relevant.

ADVERSE EFFECTS

Adverse reaction frequencies are listed below in CIOMS frequency categories:

Very common: $\geq 10\%$

Common: $\geq 1\%$ and $< 10\%$

Uncommon: $\geq 0.1\%$ and $< 1\%$

Rare: $\geq 0.01\%$ and $< 0.1\%$

Very rare: $< 0.01\%$

These data are from clinical trials in which Prevenar 13 was administered simultaneously with other routine childhood vaccines.

Body as a whole Very common:	Fever; any injection-site erythema, induration/swelling or pain/tenderness; Injection-site erythema or induration/swelling 2.5 cm –7.0 cm (after toddler dose and in older children [age 2 to 5 years]).
Common	Fever greater than 39°C; injection-site erythema or induration/swelling 2.5 cm - 7.0 cm (after infant series); injection-site pain/tenderness interfering with movement
Uncommon	Injection-site induration/swelling or erythema greater than 7.0 cm
Digestive system Common:	Diarrhoea; vomiting
Immune system disorders Rare:	Hypersensitivity reaction including face oedema, dyspnoea, bronchospasm
Metabolic and nutritional disorders Very common:	Decreased appetite
Nervous system Very common:	Drowsiness/increased sleep; restless sleep/decreased sleep
Uncommon:	Seizures (including febrile seizures)
Skin and appendages Common:	Rash
Uncommon:	Urticaria or urticaria-like rash
Psychiatric disorders Very common:	Irritability
Uncommon:	Crying

Table 4. Percentage of Infant and Toddler Subjects Reporting Solicited Local Reactions at the Prevenar 13 or Prevenar (7-valent) Injection Sites

	Dose 1 ^a		Dose 2 ^a		Dose 3 ^a		Dose 4 ^b	
Graded Local Reaction	Prevenar 13 (N ^c =3601-3878)	Prevenar 7 (N ^c =2025-2148)	Prevenar 13 (N ^c =3087-3388)	Prevenar 7 (N ^c =1699-1824)	Prevenar 13 (N ^c =2603-2809)	Prevenar 7 (N ^c =1245-1364)	Prevenar 13 (N ^c =1049-1198)	Prevenar 7 (N ^c =654-791)
Tenderness								
Any	46.8	44.9	44.7	43.9	41.0	39.5	52.1	56.0
Significant ^d	8.3	9.3	6.3	8.6 [*]	6.0	5.9	6.2	8.1
Induration								
Any	23.0	21.9	28.0	28.9	30.1	30.3	32.6	33.5
Mild ^e	19.8	20.0	25.6	26.5	27.6	27.9	29.8	29.4
Moderate ^e	6.9 [*]	4.7	7.0	6.1	8.0	7.2	12.0	10.5
Severe ^e	0	0	0.1	0	0	0	0	0
Erythema								
Any	26.3	27.8	35.3	35.1	38.3	37.0	43.6	43.7
Mild ^e	24.7	26.8	33.9	33.9	36.5	35.3	39.4	40.0
Moderate ^e	2.7 [*]	1.8	3.0	3.1	5.0	5.3	11.8	11.7
Severe ^e	0	0	0.1	0	0	0	0.1	0.2

* Statistically significant difference $p < 0.05$

Follow-up time = 4 days following each dose for most studies. Two studies had a follow-up time of 7 days and one study had a follow-up time of 15 days for stage 1 and 8 days for stage 2.

- Infant dose data are included for 12 infant studies.
- Toddler dose data are included for the 6 infant studies with toddler dose data.
- Number of subjects reporting Yes for at least 1 day or No for all days.
- Significant = present and interfered with limb movement.
- Intensity of induration and erythema are rated by the diameter of the affected area: 0.5-2.0 cm = mild; 2.5-7.0 cm = moderate; >7.0 cm = severe.

Table 5. Percentage of Infant and Toddler Subjects Reporting Solicited Systemic Adverse Reactions, Fever and Antipyretic Medications after Each Vaccination

	Dose 1 ^a		Dose 2 ^a		Dose 3 ^a		Dose 4 ^b	
Graded Systemic Events	Prevenar 13 (N ^c =3594-4022)	Prevenar 7 (N ^c =1998-2215)	Prevenar 13 (N ^c =3110-3606)	Prevenar 7 (N ^c =1718-1969)	Prevenar 13 (N ^c =2580-3024)	Prevenar 7 (N ^c =1253-1480)	Prevenar 13 (N ^c =1073-1283)	Prevenar 7 (N ^c =666-873)
Decreased Appetite	38.4	37.2	37.8	41.0	36.6	38.1	42.2	50.2
Irritability	69.2	63.9	68.8	68.1	61.9	60.6	63.4	69.6
Increased Sleep	59.0	57.4	50.9	51.1	41.2	40.7	42.7	52.3
Decreased Sleep	36.4*	33.5	35.3	34.9	34.0	32.8	30.1	33.2
Fever^d								
Any	25.0*	24.4	32.2	38.4	27.8	32.4	43.0	49.8
Mild	24.1*	23.5	30.7	37.3	26.8	31.3	41.1	48.2
Moderate	1.5	1.2	3.0	2.9	2.9	2.6	6.6	8.3
Severe	0.0	0.2*	0.1	0.1	0.2	0.2	0.3	0.2
Antipyretic Medications								
Treat	45.9	45.9	49.8	55.3	46.1	51.9	43.0	50.4
Prevent	46.5	46.0	48.9	50.9	47.1	51.1	36.1	46.5

* Statistically significant difference $p < 0.05$

Follow-up time = 4 days following each dose for most studies. Two studies had a follow-up time of 7 days and one study had a follow-up time of 15 days for stage 1 and 8 days for stage 2.

- Infant dose data are included for 12 infant studies.
- Toddler dose data are included for the 6 infant studies with toddler dose data.
- Number of subjects reporting Yes for at least 1 day or No for all days.
- "Any" fever = subjects with any temperature $\geq 38^{\circ}\text{C}$; for subcategories of fever by grading, subjects may be included in more than 1 row. Fever grading: mild $\geq 38^{\circ}\text{C}$ but $\leq 39^{\circ}\text{C}$, moderate $> 39^{\circ}\text{C}$ but $\leq 40^{\circ}\text{C}$, severe $> 40^{\circ}\text{C}$.

Additional adverse reactions from Prevenar (7-valent)

Although the following adverse drug reactions were not observed in the clinical trials for Prevenar 13, they are considered adverse drug reactions for pneumococcal 7-valent conjugate vaccine and are considered adverse drug reactions for Prevenar 13 as well. These reactions are listed as follows with the frequency seen with pneumococcal 7-valent conjugate vaccine.

Adverse reactions from Prevenar (7-valent) clinical trials

Nervous system

Rare: Hypotonic-hyporesponsive episode

Adverse reactions from Prevenar (7-valent) post-marketing experience

These frequencies are based on spontaneous reporting rates for pneumococcal 7-valent conjugate vaccine and have been calculated using number of reports and number of doses distributed.

General disorders and administration site conditions

Very rare: Injection-site dermatitis; injection-site urticaria, injection-site pruritus

Blood and lymphatic system disorders

Very rare: Lymphadenopathy localized to the region of the injection-site

Immune system disorders

Very rare: Anaphylactic/anaphylactoid reaction including shock

Skin and subcutaneous tissue disorders

Very rare: Angioneurotic oedema; erythema multiforme

DOSAGE AND ADMINISTRATION

The dose of Prevenar 13 is 0.5 mL given intramuscularly only, with care to avoid injection into or near nerves and blood vessels. The preferred sites are anterolateral aspect of the thigh (vastus lateralis muscle) in infants or the deltoid muscle of the upper arm in young children.

Do not administer Prevenar 13 intravascularly or into the gluteal area. Do not administer Prevenar 13 intravenously, subcutaneously or intradermally, since the safety and immunogenicity of these routes have not been evaluated.

Upon storage, a white deposit and clear supernatant can be observed. The vaccine should be well shaken to obtain a homogeneous white suspension and be inspected visually for any particulate matter and/or variation of physical aspect prior to administration. Do not use if the content appears otherwise. Prevenar 13 is a suspension containing an adjuvant. The vaccine must not be used if it cannot be uniformly suspended.

Prevenar 13 is not to be mixed with other vaccines or products in the same syringe. Prevenar 13 is for single-use in one patient only. The suspension contains no antimicrobial agent. Discard any residue.

Immunisation schedules

Data on the interchangeability of Prevenar or Prevenar 13 with other pneumococcal conjugate vaccines containing a protein carrier different from CRM₁₉₇ are not available.

It is recommended that infants who receive a first dose of Prevenar 13 complete the vaccination course with Prevenar 13.

The immunisation schedules for Prevenar 13 should be based on official recommendations.

Infants aged 6 weeks - 6 months

The primary infant series consists of three doses, each of 0.5 ml, with the first dose usually given at 6 weeks of age and with an interval of at least 1 month between doses. The first dose may be given as early as six weeks of age. A fourth (booster) dose is recommended after 12 months of age, and at least 2 months after the third dose.

Vaccination schedule for infants (6 weeks – 6 months of age)				
Dose:	Dose 1	Dose 2	Dose 3	Dose 4
Age at Dose:	6 weeks	4 months	6 months	12-15 months

Infants and children previously vaccinated with Prevenar

Prevenar 13 contains the same 7 serotypes contained in Prevenar and is manufactured based on the same conjugate technology using the same carrier protein CRM₁₉₇.

Infants and children who have begun immunisation with Prevenar may complete immunisation by switching to Prevenar 13 at any point in the schedule. For the seven serotypes in Prevenar, no additional doses are needed after the booster dose. However, clinical studies are ongoing as to whether additional doses of Prevenar 13 are needed for adequate immunogenicity for the six new serotypes.

Vaccination schedule for previously unvaccinated children ≥ 7 months of age		
Age at first dose	Total number of 0.5 mL doses	Duration between doses
7-11 months of age	3	Between dose 1 and 2: At least 1 month Between dose 2 and 3: At least 2 months (3rd dose after 12 months of age)
12-23 months of age	2	At least 2 months
24 months to <72 months of age	1	N/A

Influence of foods, compatibility with drugs/fluids

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

OVERDOSAGE

Overdose with Prevenar 13 is unlikely due to its presentation as a pre-filled syringe. However, there have been reports of overdose with Prevenar 13 defined as subsequent doses administered closer than recommended to the previous dose. In general, adverse events reported with overdose are consistent with those that have been reported with doses given in the recommended schedules of Prevenar 13.

PRESENTATION

Prevenar 13 is presented as a suspension in 0.5 mL pre-filled syringes (Type I glass) in packs of 1 and 10. All syringe components are latex-free.

Storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Discard if the vaccine has been frozen.

POISON SCHEDULE

Prescription Only Medicine (S4)

NAME AND ADDRESS


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