European Medicines Agency
Evaluation of Medicines for Human Use

EMA/798877/2009

ASSESSMENT REPORT

FOR

Prevenar 13

Common Name: **Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)**

Procedure No. EMEA/H/C/001104

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

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TABLE OF CONTENTS

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Wyeth Lederle Vaccines S.A. submitted on 02 December 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Prevenar 13, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The legal basis for this application refers to:
A - Centralised / Article 8(3) / New active substance.
Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier:
composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

The applicant applied for the following 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.

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 27 April 2006 and 19 July 2007. The Scientific Advice pertained to quality and clinical aspects of the dossier.

Licensing status:
A new application was filed in the following countries: USA.
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Bengt Ljungberg** Co-Rapporteur: **Pieter Neels**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 02 December 2008.
- The procedure started on 24 December 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2009.
- During the meeting on 20-23 April 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 April 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 May 2009.
- The summary report of the inspection carried out at the following site: Wyeth Pharmaceuticals, Division of Wyeth Holdings Corporatio 401 N. Middletown Road Pearl River, NY 10965 USA on 27-31 October 2008 was issued in February 2009. The summary report of the inspection carried out at the following site: Wyeth BioParma One Burtt Road Andover, MA 01810 USA on 20-24 April 2009 was issued in May 2009
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 July 2009.
- During the CHMP meeting on 20-23 July 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.

- The applicant submitted the responses to the CHMP consolidated List of Outstanding issues on 24 August 2009 and on 8 September 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 18 September 2009.
- During the meeting on 21-24 September 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Prevenar 13 on 24 September 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 23 September 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Streptococcus pneumoniae is a gram-positive encapsulated diplococcus and a major cause of mortality and morbidity worldwide with the highest incidence in infants under 2 years of age and in the elderly over 60 years of age. *S. pneumoniae* has been estimated to cause ~16 million deaths every year, including up to one million in children below 5 years of age. The highest morbidity and mortality rates have been reported from developing countries. The spectrum of disease encompasses invasive pneumococcal disease (IPD), such as sepsis and meningitis, lower respiratory infections, such as bacterial pneumonia and upper respiratory infections, such as acute otitis media (AOM). The relative incidences of the various disease entities are estimated to be that for 1 case of IPD there are 100 cases of pneumonia and 1000 cases of otitis media. Extrapolation of data on hospitalizations due to IPD from England and Wales (Melegaro, 2006) (prior to introduction of 7-valent Prevenar to the EU paediatric population <5 years of age indicate that there would be 6500 IPD (meningitis and sepsis) cases and 61,000 pneumonia cases (50% hospitalized) annually.

Acute otitis media is most prevalent in early childhood, with the peak attack-rate occurring from 6 to 18 months of age and with ~60% of children having had at least one episode of AOM by 1 year of age. A study from England and Wales (Melegaro 2004) estimated that 270,000 AOM cases would occur annually in children <5 years of age, which would correspond to 2.1 million AOM cases in the EU. Bacteria are isolated in ~70% of middle ear fluid samples from children with otitis media; with *S. pneumoniae* and *H. influenzae* being the most commonly identified pathogens.

Despite the availability of antibiotic therapies the mortality of pneumococcal disease remains high. The continuing emergence of penicillin-resistant and multidrug-resistant pneumococcal strains is an increasing global threat posing serious therapeutic challenges. Although the resistance patterns vary between countries, the predominance of certain serotypes (i.e. 6A/B, 9V, 14, 19A/F, and 23F) among the resistant organisms is shared. Another important aspect of *S. pneumoniae* epidemiology is the nasopharyngeal (NP) carriage of the pathogen occurring in virtually all children at some time. The relationship between the acquisition of carriage of individual serotypes and their likelihood of causing IPD is not known. However, NP carriage plays an important role in the transmission of pneumococcal strains and in particular, of antibiotic-resistant strains.

There are 91 distinct pneumococcal serotypes, which can be grouped by immunological relatedness into 46 serogroups. However, only 10 to 15 serotypes cause the vast majority of invasive disease worldwide. Serotypes differ in invasiveness with types 1 and 5 frequently mentioned among those with the highest invasive potential. The global epidemiology of pneumococcal serotypes and their role in disease differ between continents. The prevalence of individual serotypes may also vary regionally, between different age groups and over time. Serotype 14 and serogroup 6 predominate worldwide, serotypes 1 and 5 being more common in the developing world, whereas serogroup 18 is more common in the industrialised countries. The epidemiology in Europe differs from that in the US; before the introduction of Prevenar (7-valent pneumococcal conjugate vaccine), the 7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) targeted by the vaccine were responsible for almost 90% of cases of IPD in young children in the US and for more than 60% of cases in Europe.

Vaccine impact on invasive pneumococcal disease

Since 2000, when universal mass vaccination with Prevenar was implemented in the US, the number of IPD cases among children aged below 5 years has fallen substantially, in 2001 the incidence of IPD in children less than 5 years of age had declined by 56% and in 2004 by 76%, with a 96% decline in IPD caused by vaccine serotypes. A significant decline in IPD caused by penicillin-resistant strains has also been seen. In addition, substantial decreases in IPD in other, non-immunized age groups have been documented, and the number of cases prevented through this indirect (herd) protection is approximately double that attributed to direct protection alone. However, over subsequent years an increase has been observed for IPD caused by the vaccine-related serotype 19A, and to a lesser extent for IPD caused by some other non-vaccine serotypes (serotypes 3, 15, 22F, 33F and 35). It is so far a

relatively small number of cases compared to the overall decline in IPD. Such serotype replacement with 19A has also been observed in the EU (Spain, France), but not in some other countries with universal childhood vaccination, i.e. Australia and Canada. The reason for the rises in serotype 19A is not fully clear and may, in addition to the introduction of Prevenar, be related to antibiotic pressure or emergence of new clones. The experience gained indicates that close long-term monitoring of pneumococcal disease is essential during widespread use of pneumococcal vaccines. Generalised immunisation programmes with Prevenar have been implemented in EU countries in recent years and effectiveness data against IPD are becoming available.

In view of the considerable public health impact of successful vaccines against pneumococcal disease, the WHO has stated that the development of safe, effective vaccines that offer broad protection against pneumococcal disease should be a high priority. There is an unmet medical need for extended valency vaccines beyond the 7 serotypes in Prevenar designed to better cover the global pneumococcal serotype distribution. Of note is that the presence of serotypes 1 and 5 is considered critical by WHO and GAVI, given their important contribution to the burden of disease in developing countries. Therefore, a 10-valent pneumococcal conjugate vaccine has been developed that recently gained a positive CHMP opinion in the EU. The 13 serotypes in the 13-valent pneumococcal conjugate vaccine (7 Prevenar types + 6 additional serotypes (1, 3, 5, 7F. 6A, 7F, 19A)) would further expand coverage and would in Europe cover 80% or more of IPD cases in children less than 5 years of age, as documented by surveillance studies performed before the introduction of 7-valent Prevenar.

Licensure criteria for pneumococcal conjugate vaccines

Over the past years, regulatory agencies and experts in the field have reflected upon the serological criteria for the evaluation and licensure of new pneumococcal conjugate vaccines. It was agreed to follow the same pathway as used for licensure of Hib and MenC conjugate vaccines, and after the demonstration of a high level of invasive pneumococcal disease efficacy in Northern California with Prevenar, to licence future new pneumococcal conjugate vaccines for IPD purely on the basis of immunological data in comparison with the licensed vaccine. A consensus recommendation on criteria for licensure of new pneumococcal conjugate vaccines against IPD was reached at the WHO Expert Committee meeting in 2003 (WHO 2005, Jodar 2004, Lee 2003). The WHO has issued a technical report series (TRS 927, annex 2) with recommendations for the evaluation of new pneumococcal conjugate vaccines that reflect these principles.

The following criteria are recommended for use as the primary end-point for demonstration of non-inferiority against a registered vaccine:

- IgG antibody concentration, as measured by ELISA, in sera collected 4 weeks after a three-dose primary series is considered to be the optimal primary end-point and main licensing parameter.
- A single threshold or reference antibody concentration is recommended for use for all pneumococcal serotypes. A reference antibody concentration of 0.35μg/ml, that has been determined through a pooled analysis of data from the efficacy trials with invasive disease end-points that have been completed to date, is recommended. This threshold does not necessarily predict protection in an individual subject.
- The reference value is defined on the basis of data obtained using ELISA without pre-adsorption with serotype 22F. Antibody concentrations determined using an alternative method will need to be bridged to this method to derive an equivalent threshold concentration. It is recommended that the assay used be calibrated against a reference assay.
- Direct clinical comparison of the registered (established) vaccine with the new one is the preferred method for evaluating new vaccine formulations.
- The percentage of responders (those in whom post-immunization antibody concentration is above the threshold) should be used as the criterion to determine non-inferiority.
- For the serotypes present in a registered vaccine, the percentage of responders to each serotype in the new formulation or combination should be compared with the percentage of responders to the same serotype in the registered vaccine in the same population.

- Non-inferiority to antibody response for each of the serotypes in the registered vaccine is desirable, but not an absolute requirement. Registration of products in which one or more serotypes do not meet non-inferiority criteria would have to be decided on an individual basis.
- Serotypes not contained in a registered formulation may be evaluated for non-inferiority to the aggregate response to the serotypes in the registered vaccine. Failure of one or more new serotypes to meet this criterion may be considered on an individual basis.

Additional criteria that must be met to support registration:

- In addition to showing non-inferiority with respect to the primary end-point, additional data to demonstrate the functional capacity of the antibody and induction of immunological memory in a subset of the sera are required for registration.

Functional antibodies

- Opsonophagocytic activity (OPA) as measured by opsonophagocytic assay after a three-dose priming series is required to demonstrate the functionality of antibodies.
- The method used to demonstrate OPA should be comparable to the reference assay.

Immunological memory

- Evidence of memory should be demonstrated. One possible method is to administer a booster dose of pneumococcal polysaccharide vaccine and to compare concentrations between age-matched unprimed and primed individuals; data from non-concurrent controls may be sufficient for the purposes of comparison.
- A full dose of polysaccharide vaccine should be used at this stage because the use of a reduced dose of the polysaccharide vaccine as a booster has not been sufficiently tested.
- Avidity of antibodies is also a useful marker for immunological memory.

In follow-up of WHO 2003 meeting, a WHO workshop took place in January 2007 with the objective to formulate a plan for the standardisation of the pneumococcal OPA assay (WHO 2007).

Product development rationale

The Applicant has developed the 13-valent pneumococcal conjugate vaccine (Prevenar 13), as a successor to the currently registered vaccine, Prevenar, for use in infants and young children to prevent pneumococcal disease (invasive pneumococcal disease (IPD), pneumonia, and acute otitis media (AOM), caused by the 13 pneumococcal serotypes contained in the vaccine. Prevenar is a 7-valent vaccine that contains serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. In addition to these serotypes, Prevenar 13 contains serotypes 1, 3, 5, 6A, 7F, and 19A. As in Prevenar, each of the polysaccharides is covalently conjugated to the diphtheria toxoid cross-reactive material 197 (CRM_{197}) protein, which acts as an immunologic carrier.

Rationale for the 6 additional serotypes in the 13-valent vaccine

Serotypes 1 and 5 are encountered more frequently in the developing world. In Europe, serotype 1 causes around 6% of childhood IPD, but the majority of infections occur in children after the 2nd year of life. Recent data from the UK, after the introduction of Prevenar, have shown that serotype 1 is responsible for 14.6% of IPD cases in children <5 years. Serotype 1 has been associated with complicated pneumonia, such as parapneumonic empyema (PPE). IPD cases by serotype 5 are unusual in Europe, but recent reports from Spain underscore the increasing importance with 5% of IPD in children <5 years caused by this serotype in 2007. An increase in the proportion of serotype 5 isolates from 0.2% to 4.2% of IPD cases has also been recently reported from England and Wales (2007 to 2008), predominately due to an outbreak.

Serotype 3 IPD in young EU children is less common; the mean proportion of all cases is 2.5%. The frequency of type 3 IPD from recent years, as documented in countries that have introduced Prevenar, is 6.5% in Germany and 5.9% in the UK in the age group <5 years. Invasive infections by serotype 3 are more commonly seen in older children and have shown an association with severe pneumonia.

Serotype 6A is an important serotype in Europe responsible for a mean proportion of 4.9% of IPD cases and has also been shown to be associated with diminished antibiotic susceptibility. The highest proportion of cases is reported from Germany (mean 9.8% of cases, peaking to 14% in 2006 to 2007). Due to cross-reactivity with 6B, Prevenar have been shown to significantly reduce the incidence of 6A

IPD in vaccinated children in the US, but less so with regard to 6A NP carriage. Despite high vaccination rates in the US no reduction of 6A-specific IPD cases in adults through herd immunity as was seen with each of the 7 serotypes in the vaccine.
Serotype 7F is responsible for a substantial IPD burden in Europe and the mean proportion of paediatric IPD is 5.5%. In the UK, an increase in the numbers of cases since 2006 has been observed, with 7F accounting for 12.5 % of all IPD cases in 2007-08. In a recent publication from Germany (Rückinger, 2009) 7F was found to account for a higher risk of severe IPD and fatal outcome than other serotypes.
Serotype 19A is responsible for a significant proportion of IPD in Europe, with the highest rates reported in Belgium (9.6%), France (16%) and Spain (21%) in children below 5 years. Prevenar does not provide protection against 19A, instead an increase in IPD due to this serotype has been reported in the US after the introduction of Prevenar, which has also been reported from some EU countries. Of concern, the prevalence of IPD due to penicillin-resistant and often multiply antibiotic resistant 19A isolates increased from 6.7% to 35% in the US. In addition to ineffectiveness of Prevenar against 19A, antibiotic resistance, clonal expansion and emergence, and capsular switching may have each contributed to the genetic diversity of 19A and to its emergence as the predominant invasive pneumococcal serotype in the United States.

2.2 Quality aspects

Introduction
The Applicant has developed the 13-valent pneumococcal conjugate vaccine (Prevenar 13), as a successor to the currently registered vaccine, Prevenar, for use in infants and young children to prevent pneumococcal disease (invasive pneumococcal disease (IPD), pneumonia, and acute otitis media (AOM), caused by the 13 pneumococcal serotypes contained in the vaccine. Prevenar is a 7-valent vaccine that contains serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.

Prevenar 13 is a sterile liquid formulation of pneumococcal capsular polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, individually conjugated to diphtheria toxoid CRM_{197} protein, as in Prevenar. Succinate buffer is also included in the Prevenar 13 formulation to improve process control and to provide further pH control following the addition of aluminum phosphate. In addition, 0.02% Polysorbate 80 (P80) is included in the final vaccine formulation to improve the robustness of the manufacturing process.

Composition of Prevenar 13

Names of Ingredients	Unit Formula (0.5 mL dose)	Function
Active ingredients:	**Nominal Composition**	
Thirteen pneumococcal conjugates (saccharides conjugated to CRM_{197})		
Polysaccharide Serotype 1	2.2 µg	Antigen
Polysaccharide Serotype 3	2.2 µg	Antigen
Polysaccharide Serotype 4	2.2 µg	Antigen
Polysaccharide Serotype 5	2.2 µg	Antigen
Polysaccharide Serotype 6A	2.2 µg	Antigen
Polysaccharide Serotype 6B	4.4 µg	Antigen
Polysaccharide Serotype 7F	2.2 µg	Antigen
Polysaccharide Serotype 9V	2.2 µg	Antigen
Polysaccharide Serotype 14	2.2 µg	Antigen
Oligosaccharide Serotype 18C	2.2 µg	Antigen
Polysaccharide Serotype 19A	2.2 µg	Antigen
Polysaccharide Serotype 19F	2.2 µg	Antigen
Polysaccharide Serotype 23F	2.2 µg	Antigen
CRM_{197} protein	~ 32 µg [a]	Carrier protein
Adjuvant:		
Aluminum Phosphate	0.125 mg Al	Adjuvant
Other Ingredients:		
Sodium Chloride	4.25 mg	Excipient
Succinic Acid	0.295 mg	Excipient
Polysorbate 80	0.1 mg	Excipient
Water-for-Injection	qs to 0.5 mL	Excipient

Drug Substance (to be changed in the EPAR to "Active Substance")

Intermediates:

- Manufacture

Production and control of starting materials/intermediates

The manufacture of Pneumococcal Polysaccharide consists of a three-stage process: (1) fermentation and harvest, (2) purification, and (3) dispensing, storage and shipping.

Fermentation and Harvesting of Pneumococcal Polysaccharide

The production scheme at both manufacturing sites is a four-stage fermentation process followed by inactivation plus a harvest step.
Purified polysaccharide is filtered and dispensed into 50 L stainless steel drums using a closed system and stored frozen at -20 ± 5°C.

The polysaccharides of the 13 serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23 F are produced separately by similar processes. A working seed is thawed and expanded in Soy media complemented with Dextrose/Magnesium Sulfate. The culture is terminated by lysing the cells with the addition of Sodium Deoxycholate solution (DOC). The polysaccharides are then purified using

precipitation, diafiltration and a chromatography step. The purified polysaccharides are filtered and stored in stainless steel drums.

Activation/ conjugation

The activation of the polysaccharides is accomplished by partial oxidation of adjacent (vicinal) hydroxyl groups in the carbohydrate repeat units using sodium periodate or periodic acid. The conjugation reaction is performed in non-aqueous DMSO and in an aqueous medium. Prior to dispensing into flexible containers, the bulk conjugate is diluted to a target saccharide concentration.

The conjugation reaction is initiated by adding sodium cyanoborohydride solution to the mixture.

The manufacturing of the different serotypes is well described and follows what is already accepted for Prevenar 7.

The description of the establishment and testing of the MCB is acceptable.
The working cell banks (WCB) are manufactured and stored at a Wyeth Facility. WCB are derived from the MCB and are used to manufacture fermentation batches.

The *Streptococcus pneumoniae* strains used for the production of pneumococcal polysaccharide have not been genetically modified.

All polysaccharide master cell banks (MCB) and working cell banks (WCB) are stored in two locations. Future WCB batches will be prepared according to the procedure documented.

Establishment and testing of the cell banks follow standard requirements for this type of product.

The raw materials are in line with what is currently accepted for Prevenar.

In-process tests are performed to monitor processing.

The Pneumococcal Polysaccharides and Activated Saccharides are in compliance with the Ph.Eur. monograph for Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (2150). The justification of specifications is based upon compendial requirements, clinical trial experience, and data obtained from manufacturing runs.

The manufacturing of the different serotypes and their conjugation are well described and follows what is already accepted for Prevenar.

Specifications:

Polysaccharide

The release and stability specifications and justification for the specifications are provided for Pneumococcal Polysaccharide. The specifications were selected to ensure the identity, purity, potency, safety, and quality of the intermediate.

A summary of the procedures and validations used for pneumococcal polysaccharide is provided.

Compared to Prevenar 7 method revisions and improvements have been implemented for polysaccharides. The methods and validation has been acceptably described.

Activated saccharide:

The release and stability specifications and a summary of the rationale for the specifications are provided. A summary of the procedures and validations used for activated saccharide is provided.

The specifications resemble those of Prevenar 7.

Activated saccharides are filled into glass bottles, lyophilized and closed with a gray butyl stopper. The stopper is secured with a non-product contact cap. These container closure systems are used for purified polysaccharides and activated saccharides resp. for all thirteen serotypes. The materials of construction for all contact components have been demonstrated to be compatible with the

pneumococcal polysaccharides and activated saccharides through stability studies. This material is identical to what is used for Prevenar 7.

Stability

Polysaccharides
Formal stability studies have been conducted on the different Pneumococcal Polysaccharides to demonstrate that they will remain within specifications through the defined expiry period when stored under the recommended storage condition.

Demonstration of potency, identity, purity, quality, and safety of the intermediate supports long-term storage at -20 ± 5°C and for some serotypes 2-8°C.

Following review of the submitted data the proposed storage periods can be accepted.

Activated polysaccharides
Activated Saccharide Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F used in Prevenar has a recommended storage condition of -25 ± 5 °C. Activated Saccharide Serotype 4, 6B, 9V, 14, 18C, and 23F used in Prevenar 13 has recommended storage conditions of both -25 ± 5°C and -20 ± 5°C. New commercial stability studies (for all 13 serotypes) are being conducted at -20 ± 5°C.

Process validation and evaluation

Polysaccharide

The scope of the process validation strategy applies to the polysaccharide fermentation, clarification and purification processes. These processes perform reliably and produce Purified Pneumococcal Polysaccharide that meets pre-determined specifications and quality characteristics. Process validation was performed on a minimum of three, successful, consecutive production batches for each site supporting the manufacture of Pneumococcal Polysaccharide Serotypes.

Activation and Conjugation
Process validation was performed on a minimum of three successful, consecutive production batches for both the activation process and conjugation process.

Manufacturing Process Development

Changes to the polysaccharide, activated saccharide and conjugate production processes improved manufacturing robustness and optimized the yield.

Prevenar polysaccharide manufacturing processes have undergone re-validation to ensure robust manufacturing capability.

The Applicant has presented a comprehensive validation programme and has well documented the basis for the choices when setting up the process and the development of the manufacturing process.

- Characterisation

The chemical structure as well as the chemical designation of the repeating units is given. The predicted monoisotopic molecular weight has been given for all serotypes as well as the measured molecular weight as determined by SEC-MALLS. NMR analyses verifies the predicted structure.

Results from analysis of molecular weights, concentration of O-acetyl remaining after de-O-acetylation and activation results in an approximate degree of oxidation are tested batch wise and fulfils the specifications.

Chemical analyses using the polysaccharide specific and protein assays indicate the presence of both specific polysaccharide structures (uronic acid, hexoses etc) and protein in the conjugate as expected. By amino acid analyses of the conjugate, approximate number of lysine residues in CRM_{197} found to be modified during the conjugation process presumably by attachment to the Polysaccharide is given. The apparent size of the conjugate based on SEC is tested.

Biological and Immunological Characterization
The conjugate elicits a positive response to a polysaccharide type-specific antibody and to an anti-CRM197 antibody in the slot blot assay. Results from Nephelometry analysis of the MBC using type-specific polyclonal antisera are reported.

The characterization of the serotypes is acceptably described.

Characterisation of the polysaccharides and conjugates is in line with what is expected and follows what is tested in the batch analyses and what is required by the Ph Eur. Potential impurities has been sufficiently described and are in line with what was accepted for Prevenar 7.

The tests applied in the batch testing of the conjugates follows those of Ph Eur. The batch data indicates that the process is reproducible and gives rise to batches testing inside the proposed limits.

- Impurities

Pneumococcal Polysaccharide
The main impurities arising from the fermentation and purification of Pneumococcal Polysaccharide are *Streptococcus pneumoniae* cellular proteins, nucleic acids and C-polysaccharide as well as other process related impurities.

Activated Saccharide and Conjugate
The main impurity arising from the activation of pneumococcal polysaccharides are residues of the oxidizing reagent which is removed with ultrafiltration.

The main impurities arising from the conjugation of purified activated pneumococcal polysaccharide and Diphtheria CRM_{197} carrier protein are residues of the conjugation reagents and incompletely reacted free protein and free saccharide.

The impurities are common to all serotypes and do not differ from what has been used in Prevenar 7.

- Specifications

The release and stability specifications and a summary of the rationale of for the specification are provided for Pneumococcal Saccharide-CRM_{197} Conjugate. Pneumococcal Saccharide-CRM_{197} Conjugate is in compliance with the Ph.Eur. monograph for Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (2150).

A summary of the analytical procedures used for Pneumococcal polysaccharide, activated saccharide and MBC is provided. The methods listed are used for all serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F), unless stated otherwise.

Endotoxin, pH, moisture and sterility methods were verified based on compendial requirements.

Non-compendial methods were validated in accordance with the International Conference on Harmonization guidelines (ICH Q2 (R1)) through execution of a validation protocol with pre-determined acceptance criteria.

Batch Analyses
Batch analyses are provided. The data from all batches, including process validation batches, were within the release specifications and demonstrate consistency across the drug substance batches produced.

Justification of Specifications
Justifications of the specifications for Pneumococcal Saccharide-CRM_{197} Conjugates are based upon compendial requirements, clinical trial experience, and data obtained from manufacturing runs. The specifications were selected to ensure the identity, purity, potency, safety, and quality of the drug substance.

Batches of Pneumococcal Saccharide-CRM197 Conjugate were evaluated to establish commercial specifications, and data are provided.

- Stability

Conjugate Stability and Storage
The stabilities of Monovalent Bulk Conjugates (MBC) were determined based on formal stability studies using material from manufacturing scale batches and process validation batches. Primary stability data includes stability data from studies at 2°C-8°C (long term storage condition) and 25°C ± 2 °C/60% ± 5% RH (accelerated storage condition). The stability data available to date demonstrate that all MBC's test parameters remain with specification during storage at the recommended long-term storage conditions of 2°C-8°C .

Stability data from thermal cycling and stress testing are presented. A photostability study confirmed that the MBCs are not photolabile. Thermal cycling studies (three freeze-thaw cycles) and stability data on samples stored at the stress conditions support short-term temperature excursions.

CRM197
Manufacture
CRM 197 is produced in the same manner as now is the case for Prevenar 7. The CRM197 protein is produced from the same clone and with the same process as is already currently approved for Prevenar. It is this strain that will be licensed for use in Prevenar 13. This is currently used in commercial production of Prevenar 7.
The manufacture of CRM197 consists of a three-stage process: (1) fermentation and harvest, (2) purification by ultrafiltrations and DEAE chromatography, and (3) dispensing, storage and shipping. The production scheme is a four stage fermentation process plus a harvest step. CRM can be stored either lyophilized or in a liquid frozen form. Testing of the cell banks and intermediates follows that of the current process and is acceptable.

Batch results indicate a reproducible production. Data support the proposed storage period for the liquid and lyophilized forms have been provided.

The production of the CRM197 protein has been described in sufficient detail.

Molecular characterization was performed on the master cell bank. The original DNA sequence analysis of the CRM_{197} gene on the plasmid from the master seed was demonstrated to be in alignment with the published sequence of the diphtheria toxin (dtox)(1) and the predicted amino acid sequence for CRM_{197} protein.

The source and generation of the master seed is the same as for Prevenar and has been acceptably described.

The production of the seed lot system has been acceptably described. Stability data has been submitted for the primary WCB.

Acceptable specifications have been submitted for raw materials. Appropriate specifications for CRM_{197} are provided and on file.

The IPC methods and their validation has been satisfactorily described.

The manufacturing process including the changes has been validated.

Characterisation

The release specifications ensure adequate removal of these impurities by the manufacturing process. Process validation and evaluation has demonstrated the ability to control the levels of these impurities.

The combination of diafiltration, precipitation and ion exchange chromatography produces a CRM_{197} preparation that is substantially free of contaminating substances.

The characterization of the product and its potential impurities is sufficiently described.

Stability

Data from process validation and commercial batches demonstrate there have been no significant changes in liquid (frozen) Diphtheria CRM197 carrier protein batches when stored at the recommended storage condition of -75 ± 5 °C.

A thermal stress study at 25 ± 2 °C / 60 ± 5% Relative Humidity is being conducted to demonstrate the effect of temperature excursions during storage and shipping. All the available results demonstrate that liquid (frozen) Diphtheria CRM197 carrier protein remains stable throughout the course of evaluation.

The data support the proposed expiry period for liquid (frozen) CRM197 when stored at -75 ± 5°C and expiry period for lyophilized CRM197 carrier protein when stored at -25 ± 5°C or -20 ± 5°C.

Drug Product (To be changed in the EPAR to "Medicinal Product")

13-Valent Pneumococcal Conjugate (Prevenar 13) vaccine is a sterile liquid suspension 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 CRM_{197} protein. The vaccine contains 2.2 µg/dose of each of the serotypes, except for serotype 6B at 4.4 µg/dose. The vaccine is formulated in 5 mM succinate buffer containing 0.85% NaCl and 0.02% polysorbate 80, at pH 5.8, and contains aluminum phosphate at 0.125 mg/dose aluminum, as an adjuvant. Each 1 mL syringe contains a single 0.5 mL dose of vaccine for parenteral administration, with no preservative.

Compared to Prevenar 7 succinate and polysorbate 80 is added to the formulation. The succinate/saline buffer was added to the formulation to provide pH control and suitable osmolality. Succinate was chosen based on its ability to provide adequate buffering capacity with minimal impact to the binding of the conjugates to the aluminium phosphate.

- Pharmaceutical Development

Prevenar 13 consists of the thirteen pneumococcal conjugates (Drug Substances) in 5 mM succinate, 0.85% NaCl buffer, pH 5.8, with 0.02% polysorbate 80 and aluminum phosphate at 0.25 mg/mL aluminum.

The succinate/saline buffer was added to the formulation to provide pH control and suitable osmolality. Succinate was chosen based on its ability to provide adequate buffering capacity with minimal impact to the binding of the conjugates to the aluminum phosphate.

Aluminum phosphate was added as an adjuvant to enhance immunogenicity.

The constituents of the product and their concentration has been satisfactorily justified.

The Prevenar 13 formulation was developed based on the licensed 7-valent Prevenar vaccine. Compared to the Prevenar vaccine, Prevenar 13 was formulated with 5 mM succinate, 0.85% NaCl buffer, pH 5.8, to provide enhanced pH control, and with 0.02% polysorbate 80, to enhance the solubility of the conjugates.

There are no overages in the Prevenar 13 vaccine.

Sterility establishes the safety of the product, and antigenicity is a measure of the potency of the vaccine.

The antigenicity of the vaccine is tightly controlled to a target value for each conjugate of 4.4 µg/mL for all serotypes except 6B for which the target value is 8.8 µg/mL.

The manufacturing process development work has been extensively described and supports the proposed process.

- Adventitious Agents

13-Valent Pneumococcal Conjugate Vaccine (Prevenar 13) is composed of components derived from bacterial fermentation, and is not a viral product.

Although ingredients of animal origin are used in the preparation of the vaccine component the main theoretical risk associated with these ingredients is a contamination of the product by Transmissible Spongiform Encephalopathy (TSE) agents.

The animal derived ingredients used in Prevenar 13 production are excluded from the scope of the October 2003 revision to the TSE guideline. Nevertheless, Wyeth has been vigilant in assuring proper use and control of animal derived materials.

The Adventitious Agents Safety Evaluation presented is considered acceptable.

- Manufacture of the Product

The 13 conjugates are added to a mixture of Succinate/Sodium chloride buffer and polysorbate 80 and then sterile filtered. The solution is then mixed with Aluminium phosphate suspension and stirred. The adsorbed vaccine is then filled in prefilled syringes. The manufacture of 5.5 mM succinate, 0.85% NaCl buffer, pH 5.8 (succinate/saline buffer) and 1% polysorbate 80 in succinate/saline buffer includes routine monitoring of established operating parameters, and in-process control testing.

The formulation of Prevenar 13 bulk vaccine includes routine monitoring of established operating parameters, and in-process control testing. The controls performed during formulation and filling is acceptably described.

Three process validation runs were performed at the commercial scale to validate the formulation and filling process for Prevenar 13 bulk vaccine into the syringes. These results validate the formulation process, demonstrating that the process produced Prevenar 13 that meets its pre-determined quality attributes.

All three batches met the pre-determined acceptance criteria and release specifications for aluminum, antigenicity, appearance, endotoxin, pH, polysorbate 80, protein (total and bound), sterility and extractable volume. All tests met acceptance criteria.

A thorough validation program has been performed and shows that the process is well under control.

- Product Specification

The release and stability tests and specifications for Prevenar 13 drug product are presented. The specifications were selected to ensure the identity, purity, potency, safety, and the quality of the Prevenar 13 drug product. Prevenar 13 drug product complies with the Ph.Eur. monograph for Pneumococcal Polysaccharide Conjugate Vaccine (adsorbed) (2150). Endotoxin, pH, sterility and extractable volume methods were verified based on compendial requirements.

The aluminum, antigenicity, identity, polysorbate 80 and protein assays were validated in accordance with the International Conference on Harmonization guidelines (ICH Q2 (R1)) through execution of a validation protocol with pre-determined acceptance criteria.

Batch analyses are provided in Module 3.

Prevenar 13 process-related impurities are predominantly derived from the manufacture of the thirteen pneumococcal conjugates. There are no known process-related impurities associated with Prevenar 13 formulation and filling.

Prevenar 13 Drug Product-related impurities would result from degradation of the conjugates to release protein and saccharide breakdown products.

Justification of the specifications for Prevenar 13 is based upon compendia requirements, clinical trial experiences, and data obtained from manufacturing runs. A summary of the specifications is provided.

Prevenar 13 drug product complies with the Ph.Eur. monograph for Pneumococcal Polysaccharide Conjugate Vaccine (adsorbed) (2150).

- Stability of the Product

The formal stability studies completed to date demonstrate that Prevenar 13 quality attributes met acceptance criteria during storage of Prevenar 13 syringes at the recommended long-term storage conditions of 2 - 8 °C.

Similarly, the data demonstrate that Prevenar 13 quality attributes met acceptance criteria during storage of Prevenar 13 syringes at the accelerated conditions of 25 ± 2 °C for up to 6 months.

The constituents of the product and their concentration have been satisfactorily justified. Batch results indicate a reproducible production. The applicant claim 24 months shelf life when stored at 2-8°C.

2.3 Non-clinical aspects

Introduction

The non-clinical study program of Prevenar 13 consists of a series of repeat-dose toxicity studies, including assessment of immunogenicity, a series of safety pharmacology studies and a local tolerance study in rabbits. There are no non-clinical studies addressing protection against disease.
The immunogenicity, safety pharmacology, and nonclinical toxicity studies were conducted under GLP regulations.

Pharmacology

- Primary pharmacodynamics

There were no separate nonclinical pharmacodynamic studies conducted with Prevenar 13; however, immunogenicity of Prevenar 13 was evaluated as part of the nonclinical repeat-dose toxicity studies with 13vPnC in rats, rabbits, and cynomolgus monkeys.

Adult Rats, First 13-Week (1 Dose/2 Weeks) Study *(Study ID RPT-59899*)
In the first 13-week toxicity study, adjuvanted 13vPnC was administered SC two weeks apart Sprague-Dawley rats at a dose volume of 0.5 mL/injection followed by a 4-week dose-free recovery period. The control group received 0.5 mL sterile 0.9% sodium chloride for injection. Analysis of IgG antibody titers specific for Pneumococcal polysaccharide (PnPs) serotype 18C in 13vPnC was performed.
None of the animals in the saline control group had a detectable increase in anti PnPs-18C IgG antibodies, while all animals administered 13vPnC mounted a positive serum IgG antibody response against the PnPs-18C.

Adult Rats, Second 13-Week (1 Dose/2 Weeks) Study (*Study ID RPT-66951*)
In the second 13-week toxicity study, adjuvanted 13vPnC and adjuvanted 7vPnC were administered SC to S-D rats at a dose volume of 0.5 mL/injection followed by a 4-week dose-free recovery period.
Analysis of IgG antibody titers specific for each serotype in 13vPnC and 7vPnC determined by qualified ELISAs using serotype specific capsular PnPs as coating antigens were performed.
An increase in anti-13vPnC and anti-7vPnC IgG antibodies against each of the serotypes in the respective vaccines was detected after administration of 13vPnC or 7vPnC, respectively. No response was observed in the saline or $AlPO_4$ vehicle control groups.

Day 87 serotype-specific IgG titers (geometric means) for the serotypes common for 13vPnC and 7vPnC:

	4	6B	9V	14	18C	19F	23F
13vPnC	49052	39487	36472	5294	93608	11003	77758
7vPnC	253976	89015	146457	9850	315808	63324	300750

Juvenile Rats, 8-Week (1 Dose/2 Weeks) Study (*Study ID RPT-59901*)
In an 8-week toxicity study with adjuvanted 13vPnC in S-D juvenile rats was administered SC 2 weeks apart to male and female S-D juvenile at a dose volume of approximately 0.15 mL/injection on post natal day 7 and 0.5 mL/injection on subsequent occasions. The control group received injections of 0.15 mL sterile 0.9% sodium chloride and 0.5 mL at all subsequent doses.
IgG responses determined from the ELISA indicated that none of the saline control animals seroconverted and the animals given 13vPnC had a positive serum IgG antibody response to all serotypes in 13vPnC after 5 doses.

Rabbits, 5-Cycle (1 Dose/3 Weeks) Study (*Study ID RPT-72055*)
In the 5-cycle toxicity study, New Zealand White (NZW) rabbits were given adjuvanted 13vPnC intramuscularly at a dose volume of 0.5 mL/injection, 3 weeks apart. A saline control group and an $AlPO_4$ vehicle control group were also included in the study. Selected animals underwent a 4-week dose free recovery period after the last injection.
IgG responses measured in the multiplex serological assay indicated that the saline control group and $AlPO_4$ vehicle control group animals did not mount an immune response to any serotype in 13vPnC after 4 doses and that the animals administered 13vPnC made a positive serum IgG antibody response to each serotype in 13vPnC after 4 doses.

Cynomolgus Monkeys, 13-Week (1 Dose/2 Weeks) Study (*Study ID RPT 59900*)
In the 13-week toxicity study, cynomolgus monkeys were given adjuvanted 13vPnC SC at a dose volume of 0.5 mL/injection, two weeks apart. The control group received approximately 0.5 mL sterile 0.9% sodium chloride for injection.
IgG levels and titers indicated that none of the saline control animals and all of the animals administered 13vPnC mounted a positive serum IgG antibody response to all serotypes in 13vPnC and to diphtheria toxoid.

- Secondary pharmacodynamics

These studies are not required for vaccines.

- Safety pharmacology programme

Safety pharmacology studies are summarised in the following table

Organ Systems Evaluated Study ID	Species/ Strain	Duration Method of Administration	Dose (µg/mL)	N/ Gender/ Group	Noteworthy Findings
Central Nervous System RPT-64576	Rats/S-D	Single-Dose SC	0 61.6 µg polysaccharide, 58 µg CRM_{197}, and 0.25 mg $AlPO_4$	8 M	• There were no unscheduled deaths and no clinical signs. • There were no effects of 13vPnC on the CNS as measured during this study.
Respiratory RPT-64577	Rats/S-D	Single-Dose SC	0 61.6 µg polysaccharide, 58 µg CRM_{197}, and 0.25 mg $AlPO_4$	8 M	• There were no unscheduled deaths and no clinical signs. • There were no effects of 13vPnC on the tidal volume, respiratory rate, or minute volume as measured during this study.
Cardiovascular RPT-6457	Monkeys/ Cynomolgus	Single-Dose SC	0 61.6 µg polysaccharide, 58 µg CRM_{197}, and 0.25 mg $AlPO_4$	4 M 4 F	• All animals survived to study completion and no 13vPnC-related clinical signs occurred. • There were no 13vPnC-related effects noted for the mean blood pressure (arterial, systolic, diastolic) pulse pressure, or ECGs measured in this study. There was no evidence of QTc prolongation, morphologic changes, or abnormal atrial or ventricular arrhythmias in any of the ECGs examined. PR, QRS, and QTc intervals were similar to those in the control group.

- Pharmacodynamic drug interactions

These studies are not required for vaccines.

Pharmacokinetics

Pharmacokinetics testing is not required for vaccines.

Toxicology

- Single dose toxicity

Single dose toxicity was evaluated after administration of the first dose in the repeat-dose toxicity studies (see below).

- Repeat dose toxicity (with toxicokinetics)

Repeat-dose toxicity was studied in rats, dogs and rabbits.

Adult Rats, First 13-Week (1 Dose/2 Weeks) Study (*Study ID RPT-59899*)
The study was performed to evaluate the toxicity of adjuvanted 13vPnC administered SC in rats, two weeks apart. There were no 13vPnC-related deaths during the study. There were no 13vPnC-related effects on clinical signs, body weight, food consumption, ophthalmoscopic observations, or organ weight data. The only effects detected in this study were injection-site related and associated with the AlPO4 adjuvant after the SC injection of 13vPnC. Nodules were observed at the injection sites in male and female rats in the 13vPnC-treated group, starting with the second dose. Clinical pathology changes consisting of increases in fibrinogen and absolute neutrophil counts, as well as increased globulin with concurrently decreased albumin values, were seen in 13vPnC-treated rats. There was evidence of recovery in the clinical pathological changes. There was no evidence of systemic toxicity in this study.

Adult Rats, Second 13-Week (1 Dose/2 Weeks) Study (*Study ID RPT-66951*)
This study was conducted to allow comparisons between saline control, AlPO4 vehicle control, adjuvanted 13vPnC, and adjuvanted 7vPn which were administered SC to S-D rats at a dose of 0.5 mL/injection, 2 weeks apart. Selected animals underwent a 4-week dose free recovery period after the last injection to assess possible immune response, delayed effects, and/or recovery/reversibility of AlPO4 vehicle control-, 13vPnC-, and 7vPnC-related effects.
There were no saline-, AlPO4 vehicle control-, 13vPnC-, or 7vPnC-related deaths during the study. 13vPnC and 7vPnC did not produce clinical signs of toxicity or an effect on body weight, food consumption, ophthalmoscopy findings, or organ weights during the dosing or recovery phases. There were no biologically meaningful differences between the saline control and vehicle controls for these parameters. The only clinical signs observed during the study were at the injection sites. Transient edema and erythema, which were generally slight in magnitude, were observed at the injection sites of animals given 13vPnC and 7vPnC during the dosing phase. During the recovery phase, no edema or erythema was observed with the exception of 1 female from the 13vPnC group that had very slight erythema only at the end of the recovery phase. Small masses (nodules) were observed at the injection sites of animals given the AlPO4 vehicle control, 13vPnC, and 7vPnC during the dosing phase. In the 13vPnC and 7vPnC groups, the nodules were still present during recovery; however, the incidence and/or size of the nodules decreased over time indicating resolution over the recovery period. The nodules correlated with thickened injection sites at necropsy and inflammation at the injection sites observed microscopically. In the 13vPnC and 7vPnC groups, they also correlated with clinical pathology effects (statistically significant [$p \leq 0.05$] increases in neutrophil and monocyte counts, and fibrinogen levels; and decreases in albumin, increases in globulin, and decreases in albumin/globulin ratio) consistent with a minor inflammatory or immune response during the dosing phase.

Rabbits, 5-Cycle (1 Dose/3 Weeks) Study (*Study ID RPT-72055*)
This study was performed to assess the toxicity of adjuvanted 13vPnC administered intramuscularly at a dose of 0.5 mL/injection.
There were no unscheduled deaths in the study. There were no AlPO4 vehicle control- or 13vPnC-related clinical signs, effects on body weight, food consumption, ophthalmology parameters, injection site irritation, body temperature, or clinical pathology. In addition, there were no 13vPnC-related organ weight, macroscopic, or microscopic changes. At the end of the dosing period, the only microscopic changes were localized chronic inflammation and degeneration/necrosis at the injection site in both AlPO4 vehicle control- and 13vPnC-dosed animals. At the end of the observation period, the microscopic degeneration/necrosis at the injection site completely reversed and the chronic inflammation partially reversed (slight in both AlPO4 vehicle control- and 13vPnC-dosed animals based on average severity) with complete reversibility of injection site changes expected if the study had been extended.

Cynomolgus Monkeys, 13-Week (1 Dose/2 Weeks) Study (*Study ID RPT 59900*)
A 13-week study were cynomolgus monkeys were given adjuvanted 13vPnC SC at a dose 0.5 mL/injection two weeks apart was submitted.
There were no deaths during the study. There were no effects on clinical signs, body weight, food consumption, body temperature, ophthalmoscopic observations, hematology, serum chemistry, or organ weight data. The only effects detected in this study were injection-site related and associated with the AlPO4 adjuvant after the SC injection of 13vPnC. Nodules (small circumscribed SC solid

lumps) were observed in male and female monkeys from the 13vPnC-treated group, starting with the second dose. These effects were detected in the in-life observations, and macroscopic and microscopic evaluations. There was no evidence of systemic toxicity in this study.

- Genotoxicity and Carcinogenicity

These studies are not required for vaccines.

- Reproduction Toxicity

Prevenar 13 is intended for the vaccination of infants. No studies of fertility, embryo-fetal development, and peri- postnatal development toxicity have been conducted. A juvenile toxicity study was conducted in rats to support SC dosing of infants.

- Local tolerance

A study was conducted to evaluate the irritation potential of 13vPnC, with and without the AlPO4 adjuvant, in male NZW rabbits after a single IM injection *(Study ID RPT-62420)*. 13vPnC (30.8 µg polysaccharide, 29 µg CRM_{197}, and 0.125 mg AlPO4) and 13vPnC without the AlPO4 adjuvant (30.8 µg polysaccharide and 29 µg CRM_{197}) were administered as a single IM injection into the left vastus lateralis (thigh muscle), at a dose volume of 0.5 mL/injection, to 3 male rabbits/group. A control group (3 males) received 0.5 mL sterile 0.9% sodium chloride for injection.

All animals survived to scheduled termination. There were no clinical signs, injection site irritation, effects on body weight or food consumption, or macroscopic or microscopic lesions related to 13vPnC, with or without the AlPO4 adjuvant.

- Other toxicity studies

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

Juvenile Rats, 8-Week (1 Dose/2 Weeks) Study (*Study ID RPT-59901*)
In an 8-week toxicity study with adjuvanted 13vPnC in S-D juvenile rats was administered SC 2 weeks apart to male and female S-D juvenile at a dose volume of approximately 0.15 mL/injection on post natal day 7 and 0.5 mL/injection on subsequent occasions. The control group received injections of 0.15 mL sterile 0.9% sodium chloride and 0.5 mL at all subsequent doses.

All animals survived to scheduled termination. There were no effects on viability index, clinical signs, body weight, food consumption, or clinical pathology; there were no adverse organ weights during the study. The only effects in this study were injection-site related and associated with the AlPO4 adjuvant after the SC injection of 13vPnC. These effects were detected in the in-life observations, and macroscopic and microscopic evaluations. There was no evidence of systemic toxicity in this study.

Ecotoxicity/environmental risk assessment
In accordance with EMEA "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00) which specifies that vaccines are exempt due to the nature of their constituents, no additional information has been performed.

Discussion on the non-clinical aspects

There were no separate nonclinical pharmacodynamic studies conducted with Prevenar 13; however, immunogenicity of 13vPnC was evaluated as part of the nonclinical repeat-dose toxicity studies with 13vPnC in rats, rabbits, and cynomolgus monkeys.

In the repeat-dose toxicity studies animals were given a clinical dose every 2^{nd} or 3^{rd} week with a total of 5-7 injections. Antibody titres were determined using ELISA or Luminex technology. In all studies, vaccination with 13vPnC resulted in a robust antibody response to all tested serotypes. These data

demonstrate that the toxicity studies are all relevant for addressing safety concerns, related to the generation of an immune response.

Issues of concern in the clinical evaluation of the vaccine are the consequence of the increased number of serotypes on the immune response and the importance of the introduction of polysorbate 80 in the vaccine formulation which took place during the clinical development. In one of the rat studies (RPT-66951) a comparison was made between the previous 7-valent vaccine (without polysorbate 80) and the new 13-valent vaccine (with polysorbate 80). The immune response to the common serotypes was consistently higher with the 7-valent vaccine. While immunogenicity data from the animal studies is of no direct importance for the clinical evaluation of the vaccine, which should be based on human immunogenicity data, these findings indicate a potential difference in immunogenicity between the vaccine formulations. This issue is further discussed in the Clinical part.

Safety pharmacology studies addressing CNS and respiratory effects were performed in rats. A safety pharmacology study addressing cardiovascular effects was performed in monkeys. There were no important findings.

Repeat dose toxicity studies were performed in rats, rabbits and monkeys. The animals were given a clinical dose every 2nd or 3rd week with a total of 5-7 injections. The only finding in these studies was injection site reactions which were observed in rats and monkeys receiving SC injections but not in rabbits receiving IM injections. Injection site reactions are also observed in the clinic.

No studies on genotoxicity or carcinogenicity have been performed. This is in agreement with applicable guidelines. Reproductive and developmental toxicity have not been studied. This is acceptable since the vaccine is intended for vaccination of infants. A juvenile toxicity study was performed in rats. There were no findings which differed from those seen in adult animals.

2.4 Clinical aspects

Introduction

The initial indication proposed at the time of the application was:
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 sepsis, meningitis, bacteraemia, pneumonia and acute otitis media) in infants and children from 2 months to 5 years of age.

The approved indication is:
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.

This submission included immunogenicity results from a total of **14 clinical trials**, including a formulation study in Poland (009), 2 pivotal non-inferiority trials in Germany (006) and in US (004). The study design and main objectives of the 14 studies are described in Table 1-1 below as well as in the section describing the individual study.
The application includes safety and immunogenicity data obtained from **4429 infants**, who received at least 1 dose of Prevenar 13 and from **354 older infants and young children**.

There are no efficacy studies with the 13-valent pneumococcal conjugate vaccine (Prevenar 13). The overall objective of the clinical development program was to evaluate the immunogenicity, safety and clinical consistency of Prevenar 13 in the target population. Non-inferiority of the immune response compared with licensed 7-valent Prevenar was specifically evaluated. Studies were designed to evaluate the immunogenicity and safety of the vaccine when used for primary, catch-up and booster vaccination; and to evaluate the presence of immune memory through administration of a booster dose. Additionally, co-administration of Prevenar 13 with commonly administered paediatric vaccines was evaluated. Switching from 7-valent Prevenar to Prevenar 13 in Prevenar-primed subjects will be evaluated post-approval; data on 1 dose of Prevenar 13 to Prevenar-primed subjects in study 008 have been submitted during the procedure.

Table 1-1: Overview of the Prevenar 13 Clinical Studies

Study	Country	Study Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	N Vaccinated per Group (as Randomized)
Formulation Bridging Trial					
6096A1-009	Poland	Demonstrate that the immune response to 13 serotypes after administration of Prevenar 13+P80 is non-inferior relative to Prevenar 13-P80 measured 1 month after the infant series.	Prevenar 13+P80 or Prevenar 13-P80 (2, 3, 4, 12)	Pentaxim (2, 3, 4) Engerix-B (2) Priorix (12)	Prevenar 13+P80: 250 Prevenar 13-P80: 250
Pivotal Pneumococcal Non-inferiority Trials					
6096A1-004	United States	Demonstrate that the PnC serotype-specific IgG responses (proportion of responders at ≥0.35 µg/mL) induced by Prevenar 13 are non-inferior to those induced by Prevenar or Prevenar reference[a] measured 1 month after the infant series. Demonstrate that the serotype-specific geometric mean IgG concentrations induced by Prevenar 13 are non-inferior to those induced by Prevenar or Prevenar reference[a] measured 1 month after the toddler dose. Assess the non-inferiority of antigen-specific response (Dip, PT, FHA, PRN, Hib) 1 month after dose 3 of PnC and concomitant vaccine in the Prevenar 13 group relative to the Prevenar group.	Prevenar 13 or Prevenar (2, 4, 6, 12-15)	Pediarix (2, 4, 6) ActHIB (2, 4, 6) PedvaxHIB (12-15) ProQuad (12-15) VAQTA (12-15)	Prevenar 13: 332 Prevenar: 331

Study	Country	Study Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	N Vaccinated per Group (as Randomized)
6096A1-006	Germany	Demonstrate that the PnC serotype-specific IgG responses induced by Prevenar 13 are non-inferior to those induced by Prevenar or Prevenar reference[a] measured 1 month after the infant series. Assess the non-inferiority of antigen-specific response (Dip, HBV, Hib) 1 month after dose 3 of PnC and concomitant vaccine in the Prevenar 13 group relative to the Prevenar group.	Prevenar 13 or Prevenar (2, 3, 4, 11-12)	Infanrix hexa (2, 3, 4, 11-12)	Prevenar 13: 300 Prevenar: 303
Manufacturing Scale Bridging Trials					
6096A1-3000	Poland	Assess the PnC response induced by manufacturing scale Prevenar 13 relative to pilot scale Prevenar 13 measured 1 month after the infant series.	Prevenar 13 pilot lot or Prevenar 13 man lot (2, 3, 4, 12)	Pentaxim (2, 3, 4) Engerix-B (2) Priorix (12)	Prevenar 13 pilot: 134 Prevenar 13 man: 134
6096A1-3005	United States	Demonstrate that the immune responses induced by 3 lots of Prevenar 13 are equivalent at 1 month after the infant series. Demonstrate the non-inferiority of immune response induced by Pediarix given with Prevenar 13 relative to Pediarix given with Prevenar 1 month after the infant series (antigens assessed: Tet; polio types 1, 2, 3; HBV).	Prevenar 13 pilot lot 1, Prevenar 13 pilot lot 2, or Prevenar 13 man lot or Prevenar (2, 4, 6, 12)	Pediarix (2, 4, 6) ActHIB (2, 4, 6) MMR II and Varivax (12) Havrix (12)	Prevenar 13 pilot 1: 486 Prevenar 13 pilot 2: 484 Prevenar 13 man: 485 Prevenar: 244

Study	Country	Study Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	N Vaccinated per Group (as Randomized)
Additional Vaccine Schedules and Concomitant Vaccine Immunogenicity Trials					
6096A1-007	United Kingdom	Evaluate the immune response after NeisVac-C (MnC using SBA) and Prevenar 13 relative to NeisVac-C and Prevenar measured 1 month after the infant series. Evaluate the immune response after Pediacel (antigens assessed: PT, FHA, PRN, FIM, Hib) and Prevenar 13 relative to Pediacel and Prevenar measured 1 month after the infant series. Assess the immune responses to Prevenar 13 measured 1 month after the infant series.	Prevenar 13 or Prevenar (2, 4, 12)	NeisVac-C (2, 4) Pediacel (2, 3, 4) Menitorix (12)	Prevenar 13: 139 Prevenar: 139
6096A1-008	France	Demonstrate that the immune responses after Pentavac (antigens assessed: PT, FHA, Hib, Dip, Tet, polio types 1, 2, 3) and Prevenar 13 are non-inferior to the response after Pentavac and Prevenar measured 1 month after the infant series. Assess the immune responses to Prevenar 13 measured 1 month after the infant series.	Prevenar 13 or Prevenar (2, 3, 4, 12)	Pentavac (2, 3, 4, 12)	Prevenar 13: 302 Prevenar: 309
6096A1-011	India	Assess the PnC immune response after Prevenar 13 relative to Prevenar measured 1 month after the infant series. Assess the immune response after Easyfive, ie, DTP-Hib-HBV vaccine (antigens assessed: PT, FHA, PRN) and Prevenar 13 relative to DTP-Hib-HBV and Prevenar measured 1 month after the infant series.	Prevenar 13 or Prevenar (6, 10, 14 weeks, 12 months)	Easyfive (6, 10, 14 weeks) Biopolio (6, 10, 14 weeks)	Prevenar 13: 178 Prevenar:175
6096A1-500	Italy	Demonstrate that the immune response after Infanrix hexa (antigen assessed: HBV) and Prevenar 13 is non-inferior to the response after Infanrix hexa and Prevenar measured 1 month after the toddler dose. Assess the immune response to Prevenar 13 measured 1 month after the infant series and just before the toddler dose.	Prevenar 13 or Prevenar (3, 5, 11)	Infanrix hexa (3, 5, 11)	Prevenar 13: 302 Prevenar: 302

Study	Country	Study Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	N Vaccinated per Group (as Randomized)
		Assess the immune responses induced by Prevenar 13 relative to Prevenar measured 1 month after the toddler dose.			
6096A1-501	Spain	Demonstrate that the immune response after Meningitec (antigen assessed: MnC by SBA) and Prevenar 13 is non-inferior to response after Meningitec and Prevenar 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 Prevenar 13 relative to Infanrix hexa and Prevenar. Assess the immune responses to Prevenar 13 measured 1 month after dose 2 and 1 month after dose 3 of the infant series and 1 month after the toddler dose.	Prevenar 13 or Prevenar (2, 4, 6, 15)	Infanrix hexa (2, 4, 6) Meningitec (2, 4, 15) Infanrix-IPV+Hib (15) MMR II (12)	Prevenar 13: 314 Prevenar: 302
6096A1-3007	Spain	Demonstrate the non-inferiority of immune response after NeisVac-C and Prevenar 13 relative to NeisVac-C (antigen: MnC using SBA) and Prevenar measured 1 month after a 2-dose NeisVac-C infant series. Demonstrate the non-inferiority of immune response after Infanrix hexa and Prevenar 13 relative to Infanrix hexa (antigens assessed: Dip, Tet) and Prevenar measured 1 month after a 3-dose infant series. Assess the immune responses to Prevenar 13 measured 1 month after dose 2 and 1 month after dose 3 of the infant series.	Prevenar 13 or Prevenar (2, 4, 6, 15)	Infanrix hexa (2, 4, 6) NeisVac-C (2, 4, 15) Priorix (12) Infanrix-IPV+Hib (15)	Prevenar 13: 218 Prevenar: 226
Trial in Older Infants and Young Children					
6096A1-3002	Poland	Assess the PnC response induced by Prevenar 13 when measured 1 month after the last scheduled dose in each age group.	Prevenar 13: Group 1: (3 doses) 7 to <12 months, 1 month later, and 12-16 months Group 2: (2 doses) 12 to <24	NA	Group 1: 90 Group 2: 112 Group 3: 152

Study	Country	Study Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	N Vaccinated per Group (as Randomized)
			months and 56 to 70 days later Group 3: (1 dose) 24 to <72 months		
Phase 1-2 Trials					
6096A1-002	United States	(NOTE: Immunogenicity was a secondary objective in this study.) Assess the postvaccination responses to the 13 pneumococcal serotypes in Prevenar 13. Obtain sera to be used as reagents for further development, validation, and standardization of pneumococcal assays.	Single dose of Prevenar 13 or 23vPS	NA	23vPS: 15 Prevenar 13: 15
6096A1-003	United States	Compare the percentages of subjects achieving a predefined antibody level to each of the 7 common serotypes after 3 doses of Prevenar 13 relative to 3 doses of Prevenar.	Prevenar 13 or Prevenar (2, 4, 6, 12-15)	Pediarix (2, 4, 6) ActHIB (2, 4, 6, 12-15)	Prevenar 13: 121 Prevenar: 126

Abbreviations: Prevenar 13+P80 = Prevenar 13 formulated with polysorbate 80; Prevenar 13-P80 = Prevenar 13 formulated without polysorbate 80; 23vPS = 23-valent pneumococcal polysaccharide vaccine; Dip = diphtheria; FHA = filamentous hemagglutinin; FIM = fimbrial agglutinogens; HBV = hepatitis B virus vaccine; Hib = *Haemophilus influenzae* type b; man = manufacturing; MnC = meningococcal C vaccine; NA = not applicable; PnC = pneumococcal conjugate vaccine; polio types 1, 2, 3 = poliovirus vaccine type 1, type 2, and type 3; PRN = pertactin; PT = pertussis toxoid; SBA = serum bactericidal assay; Tet = tetanus.

Components of vaccines by trade name: ActHIB = Hib; Biopolio = OPV; Easyfive = DTP, Hib, and HBV; Engerix-B = HBV; Havrix = HAV; Infanrix hexa = DTaP, Hib, HBV, and IPV; Infanrix-IPV+Hib = DTaP, IPV, and Hib; Meningitec = meningococcal C vaccine; Menitorix = Hib and meningococcal C vaccine; MMR II = measles, mumps, and rubella vaccine; NeisVac-C = meningococcal C vaccine; Pediacel = DTP, Hib, and IPV; Pediarix = DTaP, HBV, and IPV; PedvaxHIB = Hib; Pentavac = DTaP, Hib, and IPV; Pentaxim = DTaP, Hib, and IPV; Priorix = MMR; ProQuad = MMR and varicella vaccine; VAQTA = HAV; Varivax = varicella vaccine.

a. In studies 004 and 006, values for the additional serotypes in the Prevenar 13 group are compared with the Prevenar reference value, defined as the lowest value among the 7 common serotypes in the Prevenar group.

Ongoing trials

For clinical studies 3000, 3005, 007, 008, and 3007, only primary series data were included in the application dossier. Booster data for study 007 and study 008 were submitted with the responses to the D120 LoQ. Study 008 provides important information concerning the effect of a toddler dose of Prevenar 13 following a primary vaccination series with Prevenar. Two further studies (6096A1-3010 and 6096A1-3011) are underway to demonstrate the safety of a 2nd dose of Prevenar 13 (equivalent of a 5th or 6th dose of a CRM conjugated vaccine) and will provide the safety data to support the use of two Prevenar 13 doses in toddlers previously immunized with Prevenar.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

In January 2009 a request was adopted for a routine GCP inspection on Prevenar 13. The MAH notified EMEA in March 2009 that the Drugs Controller General India (DCGI) had placed the ongoing study 6096A-011 on hold. The review by DCGI has been completed and re-corrective actions implemented and the clinical hold has been lifted for all sites according to a notification by the MAH to EMEA.
The CHMP requested a GCP inspection of the pivotal studies 004 (US) and 006 (Germany). The inspection team concluded that the data presented in the report are accurately described and hence the data can be accepted for evaluation.

Pharmacokinetics

Pharmacokinetic studies were not performed in accordance with the note for guidance on clinical evaluation of new vaccines (CPMP/EWP/463/97).

Pharmacodynamics

As generally done with vaccines, pharmacodynamic studies are essentially comprised by the immunogenicity studies that characterise the immune response to vaccines. The detailed characterisation of the immunological response is discussed below.

Clinical efficacy and immunogenicity

- Assays

Serological assays

The serological methods used for assessing vaccine induced immune responses included a 22F-pre-absorption ELISA for measurement of total anti-pneumococcal IgG concentrations and an opsonophagocytic (OPA) assay for measurement of functional antibody response. Both assays were validated in accordance with ICH guidelines.
The ELISA is designed to measure binding IgG concentrations through the use of an established antibody standard (89S-F reference serum) following guidelines contained in the relevant WHO guidance document. The adsorption step with capsular polysaccharide from serotype 22F was introduced to further enhance the assay's specificity following a well-designed bridging study to the reference ELISA assay. The WHO reference threshold value of 0.35 µg/ml was used as a primary endpoint comparator for the current trials of Prevenar 13.
The OPA assay was a killing-assay using a HL60 cell line. The OPA assays are not standardized to an external standard, as the ELISA. The lowest recordable titer from an actual OPA assay is 8, as the

lowest dilution of sera tested is 1:8, which was used as an endpoint comparator for the current trials of Prevenar 13.

Detailed data were provided on the testing methodology and validation strategy of the company OPA and 22F-ELISA. Each OPA assay was optimized on a serotype-specific basis and had been the subject of several improvements to increase specificity and testing throughput. The company OPA was shown to be in good agreement with the four other OPA assays that were evaluated in a WHO-initiated interlaboratory study. The applicant has committed to continue working on the amelioration of standardisation and validation methods of the serotype-specific OPA assays.

Correlation analyses were performed between IgG ELISA and OPA values, using aggregate data from the Prevenar 13 clinical studies in which OPA responses were determined. A clear association was demonstrated between IgG ELISA responses and OPA responses following vaccination with Prevenar 13 for each of the 6 additional serotypes, as well as for the 7 common serotypes.

All assays used to evaluate the immune response to co-administered vaccine antigens were performed at the Wyeth central laboratory or in a validated laboratory using standardized, validated procedures with adequate controls.

Serological testing in clinical studies

Immunogenicity in terms of pneumococcal antibody response was measured with the 22F-ELISA in all study subjects. Functional antibodies were measured by OPA assay in a subset of subjects in 5 studies (003, 004. 006, 3000 and 500) and constituted an exploratory endpoint. Overall, OPA data are available on a total of 660 subjects (380 subjects in the Prevenar 13 group and 280 in the in the Prevenar group). Supplementary data on functional immune response were also provided from studies 009 and 3005 (using a P80-containing vaccine formulation), study 007 and 008. The Applicant has also included OPA assays in clinical trials 3010 and 3011 as well as in the post-marketing study 3014 to complete the testing program.

- Dose response studies

No dose response studies have been performed with the Prevenar 13 vaccine.
The same dosage as Prevenar was maintained for the common serotypes in Prevenar 13 and the 2.2-µg dosage was selected for the additional serotypes that were added to the Prevenar 13 formulation. The Prevenar 13 clinical program was designed to demonstrate that this dosage is both safe and immunologically non-inferior to the effective Prevenar serotypes.

- Phase I/II studies

The clinical program began with a phase I study in American adults (002, n=30) showing that, compared with 23-valent pneumococcal polysaccharide vaccine (23vPS), Prevenar 13 is well tolerated and immunogenic. This study provided the data required for proceeding to a phase I/II study in healthy infants (003).

In study 003, the immune response and safety of Prevenar 13 was compared with that of Prevenar in 249 US infants receiving 4 doses at 2, 4, 6, and 12 to 15 months of age. The results demonstrated that Prevenar 13 was immunogenic. Immune responses to all 13 pneumococcal serotypes in Prevenar 13 were observed as was shown by the increases in antibody concentrations from pre-vaccination through post-primary series sustained levels through the pre-booster dose; and post-booster dose serum IgG increases (except serotype 3) The ELISA IgG and functional antibody responses to the 7 common serotypes in subjects in the Prevenar 13 and Prevenar groups were similar, although somewhat lower in Prevenar 13 recipients. The data from the phase I/II study supported progression to phase III studies beginning in September 2006.

- Main studies

A total of 12 phase III studies (Table 1-1) were conducted with the 13-valent vaccine. In 8 of the 12 studies licensed 7–valent Prevenar was included as a comparator. The exceptions were the formulation bridging study (009), the manufacturing scale bridging trials (3000 and 3005) and the catch-up study (3002).

The Prevenar 13 clinical program included 2 pivotal non-inferiority trials (study 004 in US infants and study 006 in German infants). The pivotal trials along with other phase III studies were conducted using a formulation of Prevenar 13 that did not contain polysorbate 80 (P80) in contrast to the proposed commercial formulation. While the clinical trial program was initiated, it became apparent that the addition of 0.02% P80 to the final Prevenar 13 formulation was necessary to optimize the manufacturing process. Therefore, a formulation bridging study (study 009) was performed to compare the immune responses elicited to each of the serotypes by Prevenar 13 without P80 and Prevenar 13 with P80 in the final formulation. Based on the results of study 009, it was decided to include P80 in the final formulation. The final formulation including P80 was used in studies 3000 and 3005. Clinical consistency of the manufacturing process was evaluated in these two studies.

The two pivotal trials were designed and powered to assess non-inferiority of immune response relative to licensed 7-valent Prevenar. In additional trials in Europe, the immunogenicity of Prevenar 13 was evaluated using different vaccination schedules. Studies in France (008) and Spain (501, 3007) used a 3-dose infant series, whereas studies in Italy (500) and the UK (007) used a 2-dose infant series. In each of these studies, the serum IgG response to Prevenar 13 was assessed in the Prevenar 13 group only, except for study 500 in which IgG response was evaluated in both the Prevenar 13 and Prevenar groups after the toddler dose. However, some of these studies were powered to allow assessment of Prevenar 13 non-inferiority should questions arise from the pivotal non-inferiority trials. Functional immune response (OPA assays) were performed for a subset of subjects (n=660) in both the Prevenar 13 and Prevenar groups in the phase I/II study (003), in the pivotal non-inferiority trials in Germany (006) and the US (004), and in the pilot-to-manufacturing scale bridging study in Poland (3000). In the Italian study (500), using a 2-dose infant series, OPA responses in the Prevenar 13 group were assessed.

Ten studies in the US, Europe and India evaluated the immune responses to concomitantly administered routine paediatric vaccines. The co-administration of Prevenar 13 vaccine was evaluated with the following monovalent or combination vaccines [including the combination vaccine DTPa-HBV-IPV/Hib]: diphtheria-tetanus, acellular pertussis vaccine (DTPa), hepatitis B vaccine (HBV), inactivated polio vaccine (IPV), Haemophilus influenzae type b vaccine (Hib), measles-mumps-rubella vaccine (MMR), varicella vaccine, meningococcal serogroup C conjugate vaccine and hepatitis A (HAV) vaccine. DTPw co-administration was evaluated in the EPI schedule in India. There are no immunogenicity data on concomitant administration of rotavirus vaccines, HAV vaccine or OPV.

Primary immunisation in all studies started at 2 months of age months of age except in study 500 (3 months) and study 011 (6 weeks). Catch-up vaccination were performed in children aged >6 months up to 5 years. All studies were conducted in healthy infants and toddlers. An important deficiency of the submitted documentation is the lack of data on vaccine immunogenicity in high-risk children, i.e. those with sickle cell disease, asplenia, nephrotic syndrome, immunosuppression, HIV infection, cochlear implant and cerebrospinal leaks which will be addressed in the post-marketing program.

The clinical studies covered most of the primary immunisation schedules used in Europe and included an appreciable number of subjects receiving a booster dose. The EPI-schedule (6-10-14 weeks) was evaluated in a study in India.

The results from the 12 Phase III clinical studies supported the immunogenicity of the 13-valent vaccine. These studies evaluated the following issues:

- **Non-inferiority of immune responses to Prevenar 13 relative to Prevenar** (004 and 006)
- **Formulation** (Prevenar 13+P80 vs.Prevenar 13-P80) (study 009)
- **Clinical consistency of the manufacturing process** (studies 3000 and 3005)

- **3-dose primary vaccination** followed by a booster dose in the second year of life:
  2-3-4 months (studies 006, 008, 009, 3000)
  2-4-6 months (studies 004, 501, 3005, 3007)
  6-10-14 weeks (study 011)
- **2-dose primary vaccination** followed by a booster dose at 11-12 months of age:
  2-4 (-12) months (study 007)
  3-5 (-11) months (study 500)
- **Catch up immunisation schedules** (study 3002)
- **Booster vaccination (**studies 004, 006, 007, 008, 009, 3000, 3005, 501)
- **Immune memory** (same as the booster studies)
- **Co-administered vaccines (**studies 004, 006, 007, 008, 011, 500, 501, 3005, 3007)
- **Switching from Prevenar to Prevenar 13 in infants previously vaccinated with Prevenar** (study 008: infants previously vaccinated with 3 doses of Prevenar were randomized to either Prevenar or Prevenar 13 at 12 months of age - data submitted in the response to D120 LoQ).

Methods (general)

All primary vaccination studies were controlled randomised double-blind trials except for study 3002 (catch-up vaccination), which was open-label.

Objectives

All phase III studies had primary immunogenicity objectives either related to serotype-specific pneumococcal response or to antigen-specific responses in co-administered paediatric vaccines. The formulation bridging trial (study 009) and manufacturing scale bridging studies (studies 3000 and 3005) had specific immunogenicity objectives related to formulation (+/- P80), manufacturing scale Prevenar 13 vs. pilot scale Prevenar 13 and consistency of 3 lots of Prevenar 13, respectively. The toddler immunogenicity study had the objective to determine the immune response to Prevenar 13 in older age groups (7 to <12 months, 12 to <24 months and 2 to <5 years).

Study objectives related to pneumococcal response
The primary objectives of the pivotal studies were to demonstrate that the serotype-specific IgG responses (proportion of responders ≥0.35µg/ml) induced by Prevenar 13 were non-inferior to those induced by Prevenar or Prevenar reference measured 1 month after the primary series.

A co-primary (or secondary) objective was to demonstrate that that the serotype-specific geometric mean IgG concentrations (GMCs) induced by Prevenar 13 were non-inferior to those induced by Prevenar or Prevenar reference measured 1 month after the primary series.

As (primary or) secondary objectives, the immune response 1 month after a booster dose was compared in the same way as after the primary series. Immune memory was evaluated by the ability of the Prevenar 13 antibody response to be boosted using geometric mean fold rise (GMFR) in antibody concentration following the booster dose.

The secondary objectives also included comparison of the vaccine groups at other serotype-specific IgG antibody thresholds, i.e. ≥1.00 µg/ml and ≥0.15 µg/ml and also of the persistence of post-dose 3 immune response until the booster dose.

The explorative objective included to assess the level of OPA produced by Prevenar 13 relative to the level of OPA produced by Prevenar one month after the primary series and one month after the booster dose. Each of the serotype-specific assays was validated, but unlike the IgG ELISA, the OPA

assays are not standardized due to a lack of an external standard. While the IgG concentration values determined by the ELISA can be compared across serotypes, this cannot be done for the OPA assays. According to the Applicant, the values generated by the OPA assays are not biologically equivalent among the different serotypes and therefore can only be compared within a given serotype.

Study objectives related to concomitant vaccine antigens
The primary objectives included to assess non-inferiority of post-dose 3 antigen-specific responses (the following antigens were targeted in different studies: DT, TT, PT, FHA PRN, FIM, Hib, HBV, polio, MenC or MMRV) of pneumococcal and concomitant vaccine in the Prevenar 13 group relative to the Prevenar group. The proportion of subjects in each vaccine group who achieved primary predetermined antibody levels, geometric mean concentrations (GMCs) or geometric mean titers (GMTs), and/or the proportion of subjects achieving alternative antibody concentration threshold were measured. As secondary objectives, the same comparative analyses between the two vaccine groups were performed 1 month after the booster dose.

Non-inferiority criteria and additional immunogenicity criteria

The proportion of subjects achieving an IgG ELISA concentration ≥0.35 µg/ml was calculated for each serotype and for each vaccine group. The difference in proportions (Prevenar 13-Prevenar or Prevenar reference) was then calculated, along with the corresponding 2-sided 95% CI. Non-inferiority for a given serotype was declared if the lower limit of the CI for the difference was greater than -0.10.

The IgG ELISA antibody geometric mean concentrations (GMCs) were determined for each serotype and for each vaccine group. Non-inferiority for a given serotype was declared if the lower limit of the 2-sided, 95% CI for the geometric mean ratio (GMR) (Prevenar 13 relative to Prevenar or Prevenar reference) was greater than 0.5 (i.e. no greater than 2-fold).

Additional criteria were used to evaluate failed serotypes, including use of a lower antibody threshold ≥0.15µg/ml. Functional activity data for each of the 13 serotypes, were expressed as the proportion of study subjects with an OPA titer ≥1:8 as well as the geometric mean of OPA titers (GMTs).

Study 009 - Formulation change (addition of polysorbate 80 (P80))

Method

Study 009 was a randomised, double-blind trial evaluating the immunogenicity of a Prevenar 13 vaccine manufactured with and without P80 in 500 healthy Polish infants given in a 2-3-4- and 12-month schedule. The primary objective was to demonstrate that the immune responses to the 13 pneumococcal serotypes induced by Prevenar 13+P80 were non-inferior to the immune responses induced by Prevenar 13 without P80 when measured 1 month after the primary series.

Results

For the primary series analysis, the percentages of responders were somewhat **lower in Prevenar 13+P80 group** for most of the Prevenar 13 serotypes (Table 1-2). Among the 7 common serotypes the proportion of responders at ≥0.35 µg/ml in the Prevenar 13+P80 group ranged from 60.9% (6B) to 97.9% (18C). The corresponding range in the Prevenar 13-P80 group was 66.4% (6B) to 97.9% (18C). The responses to 6B and 23F were lower than expected, in particular in the 13vPvC+80 group. Among the additional 6 serotypes the proportion at ≥0.35 µg/ml ranged from 86.6% (6A) to 98.7% (19A) in the Prevenar 13+P80 group and from 86.1% (6A) to 100.0% (19A) in the Prevenar 13-P80 group. The non-inferiority criteria were met for **11 of the 13 serotypes. The exceptions were serotypes 6B and 23F;** for these 2 serotypes the lower bound of the 95% CI was -14.2% and -12.1%, respectively. The results in the all-available immunogenicity population were similar to those in the evaluable immunogenicity population.

Table 1-2: Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35µg/mL After Dose 3 of the Infant series – Evaluable Infant Immunogenicity Population

	Vaccine Group (as Randomized)							
	13vPnC+P80 N[a]=238			13vPnC-P80 N[a]=238				
Serotype	n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[c])
7vPnC								
4	222	93.3	(89.3, 96.1)	224	94.1	(90.3, 96.7)	-0.8	(-5.4, 3.7)
6B	145	60.9	(54.4, 67.2)	158	66.4	(60.0, 72.4)	-5.5	(-14.2, 3.3)
9V	231	97.1	(94.0, 98.8)	232	97.5	(94.6, 99.1)	-0.4	(-3.7, 2.8)
14	225	94.5	(90.8, 97.1)	232	97.5	(94.6, 99.1)	-2.9	(-6.9, 0.7)
18C	233	97.9	(95.2, 99.3)	233	97.9	(95.2, 99.3)	0.0	(-3.0, 3.0)
19F	228	95.8	(92.4, 98.0)	234	98.3	(95.8, 99.5)	-2.5	(-6.1, 0.6)
23F	205	86.1	(81.1, 90.3)	220	92.4	(88.3, 95.5)	-6.3	(-12.1, -0.7)
Additional								
1	228	95.8	(92.4, 98.0)	220	92.4	(88.3, 95.5)	3.4	(-0.9, 7.9)
3	233	97.9	(95.2, 99.3)	236	99.2	(97.0, 99.9)	-1.3	(-4.1, 1.1)
5	224	94.1	(90.3, 96.7)	220	92.4	(88.3, 95.5)	1.7	(-3.0, 6.4)
6A	206	86.6	(81.6, 90.6)	205	86.1	(81.1, 90.3)	0.4	(-5.8, 6.7)
7F	235	98.7	(96.4, 99.7)	237	99.6	(97.7, 100.0)	-0.8	(-3.2, 1.2)
19A	235	98.7	(96.4, 99.7)	238	100.0	(98.5, 100.0)	-1.3	(-3.6, 0.3)

All 13 serotypes met the 2-fold non-inferiority criterion for IgG GMCs, defined as a ratio (Prevenar 13+P80 to Prevenar 13-P80) at the lower limit of the 95% CI of >0.5. In general, GMC were lower in the Prevenar 13+P80 group with GMC ratios (GMRs) being below 1 (0.84-0.97) for all serotypes, except 7F.

Both non-inferiority criteria were met in the post-booster dose analysis. The post-primary and post-booster antibody GMCs were, however, lower in the Prevenar 13+P80 group with GMRs for 12 and 10 of the serotypes, respectively, falling below 1 (0.84-0.98).

In the opinion of the Applicant the differences in immunogenicity in the Prevenar 13+P80 data are unlikely to be clinically significant. The decision was made to include P80 in the Prevenar 13 formulation and was based on a more robust manufacturing process and supported by the overall similarity in the immunogenicity responses elicited by the Prevenar 13+P80 compared with Prevenar 13-P80.

Pivotal non-inferiority studies 006 and 004

Method

The phase III clinical program included 2 pivotal non-inferiority trials (study 004 in US infants and study 006 in German infants). Both were double-blind, controlled, randomized trials and involved approximately 300 infants per group with vaccinations given at 2, 3, 4, and 11 to 12 months of age (study 006) and at 2, 4, 6, and 12 to 15 months of age (study 400). The studies were powered to demonstrate the non-inferiority of the pneumococcal IgG antibody responses elicited by Prevenar 13 when compared with those elicited by Prevenar.

The primary objective of the trials was to demonstrate that the immune responses to the 7 common serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) induced by Prevenar 13 were non-inferior to the immune responses induced by Prevenar, and to demonstrate that the immune responses to the 6 additional serotypes (1, 3, 5, 6A, 7F, and 19A) induced by Prevenar 13 were non-inferior to the lowest immune response among the 7 common serotypes induced by Prevenar, when measured 1 month after the primary series.

As an exploratory objective in each non-inferiority trial, functional antibody response was also assessed using opsonophagocytic activity (OPA) assay in a subset of subjects. OPA assay results were useful in evaluating the overall immune response to a given serotype, particularly if the serotype failed

the primary non-inferiority criteria. In addition, OPA results provided a useful method for discriminating functional antibody for serotypes with cross-reactive IgG antibody responses.
Results

➢ **Study 006 (Germany) (n=600)**

Study 006 is the pivotal non-inferiority evaluation of Prevenar 13 compared to Prevenar for European licensure.

ELISA Results
Primary non-inferiority analysis
At the primary pre-specified antibody level of ≥0.35 µg/ml the non-inferiority criteria (a lower limit of the 95% CI for the difference greater than -10%) was met for **12 of 13 pneumococcal serotypes (except serotype 6B).** The difference in proportions of responders to 6B was -9.6%, with a lower limit of the 95% CI of -16% (Table 1-3). For the 6 additional serotypes, the comparison serotype was 6B (87.1%). The proportions of responders in the Prevenar 13 group were all higher than 91.9% and all additional serotypes met the non-inferiority criterion.

Table 1-3: Comparison of subjects achieving IgG antibody concentration ≥0.35 µg/ml post-dose 3 of the primary series - Evaluable infant immunogenicity population

	Vaccine group								Difference	
	Prevenar 13				Prevenar					
Serotype	N	n	%	95%CI	N	n	%	95%CI		95% CI
Common serotypes										
4	285	280	98.2	96.0, 99.4	279	274	98.2	95.9, 99.4	0.0	-2.5, 2.6
6B	**284**	**220**	**77.5**	**72.2, 82.2**	**278**	**242**	**87.1**	**82.5, 90.8**	**-9.6**	**-16.0, -3.3**
9V	285	281	98.6	96.4, 99.6	279	269	96.4	93.5, 98.3	2.2	-0.4, 5.2
14C	284	281	98.9	96.9, 99.8	279	272	97.5	94.9, 99.0	1.5	-0.9, 4.1
18C	285	277	97.2	94.5, 98.8	277	273	98.6	96.3,99.6	-1.4	-4.2, 1.2
19F	284	272	95.8	92.7, 97.8	277	266	96.0	93.0, 98.0	-0.3	-3.8, 3.3
23F	284	252	88.7	84.5, 92.2	277	248	89.5	85.3, 92.9	-0.8	-6.0, 4.5
Additional serotypes										
1	285	274	96.1	93.2, 98.1	278	242	87.1	82.5, 90.8	9.1	4.5. 13.9
3	282	277	98.2	95.9, 99.4	278	242	87.1	82.5, 90.8	11.2	7.0, 15.8
5	284	264	93.0	89.3, 95.6	278	242	87.1	82.5, 90.8	5.9	0.8, 11.1
6A	283	260	91.9	88.1, 94.8	278	242	87.1	82.5, 90.8	4.8	-0.3, 10.1
7F	285	281	98.6	96.4, 99.6	278	242	87.1	82.5, 90.8	11.5	7.4, 16.1
19A	285	283	99.3	97.5, 99.9	278	242	87.1	82.5, 90.8	12.2	8.3, 16.8

Secondary non-inferiority analysis
To address the secondary endpoint, IgG GMCs were calculated and GMCs in the 2 vaccine groups were compared by computation of geometric mean ratios (GMRs, Prevenar 13 to Prevenar reference). For the 6 additional serotypes the GMRs were relative to the GMC value for serotype 23F in the Prevenar group. Results showed that **all 13 pneumococcal serotypes met the 2-fold non-inferiority criterion**, i.e. GMRs were greater than 0.5, including serotype 6B.

OPA Results
Proportions with OPA titre >1:8
For the 7 common serotypes, the proportion of subjects achieving an OPA antibody titer ≥1:8 were similar in the 2 vaccine groups. For each serotype responder rates were ≥96.0% in Prevenar 13 recipients and ≥93.6% in Prevenar recipients. The responder rate for 6B was 96% in the Prevenar 13 group and 98.9% in the Prevenar group. The proportion with OPA titre ≥1:8 to the 6 additional serotypes was 93% (serotype 1) or higher in the Prevenar 13 group. The lower limits of the 95% CIs exceeded 86.1% for each serotype in the Prevenar 13 group and 86.6% for the 7 common serotypes in the Prevenar group.

OPA GMTs
When values were compared (Prevenar 13 to Prevenar), GMRs for the 7 common serotypes ranged from 0.64 (6B and 14) to 1.02 (23F). Five of the 7 common serotypes had GMRs with lower limits of the 95% CIs ≥0.5, except for serotypes 6B and 14, which had lower limits of the CI of 0.44 and 0.42, respectively. For the six additional serotypes GMTs ranged from 50.2 (serotype 1) to 11,544.8 (serotype 7F).

Table 1-4: Comparison post-dose 3 OPA GMTs - evaluable infant immunogenicity population

	Vaccine group							
	Prevenar 13			Prevenar				
Serotype	n	GMT	95%CI	n	GMT	95%CI	Ratio	95%CI
Common serotypes								
4	92	1573.5	1283.0, 1929.2	94	1860.79	1540.0, 2248.4	0.85	0.64, 1.11
6B	100	744.43	556.9, 995.1	94	1160.76	921.5, 1462.2	**0.64**	**0.44**, 0.93
9V	89	4973.84	3614.8, 6745.1	89	5379.5	3935.5, 7353.3	0.92	0.59, 1.42
14	95	2139.65	1570.1, 2915.8	89	3345.19	2473.3, 4524.5	**0.64**	**0.42,** 0.98
18C	100	1509.65	1243.7, 1832.6	94	1780.26	1382.4, 2292.6	0.85	0.62, 1.16
19F	100	**150.12**	116.9, 192.8	94	**165.69**	122.9, 223.2	0.91	0.62, 1.33
23F	100	1089.92	795.2, 1493.9	93	1070.83	785.59, 1457.8	1.02	0.66, 1.58
Additional serotypes								
1	100	**50.21**	39.39, 64.02	92	4.15	3.99, 4.32	12.09	9.37, 15.59
3	100	**250.73**	205.5, 305.9	94	6.13	5.17, 7.28	40.87	31.46, 53.10
5	100	**162.02**	126.3, 207.8	94	4.64	3.96, 5.43	34.95	25.96, 47.05
6A	99	1228.45	883.5, 1708.1	93	**122.40**	74.09, 202.21	10.04	5.57, 18.10
7F	99	11544.75	9364.0, 14233.3	94	**115.45**	75.16, 177.32	100.0	62.69, 159.5
19A	95	**442.48**	360.5, 543.1	94	6.70	5.19, 8.66	66.02	47.69, 91.39

Booster dose

ELISA Results

Non-inferiority analyses

The non-inferiority criterion at the 0.35 µg/ml level was met for 12 of the 13 serotypes after the booster dose**; the exception was serotype 3**. For serotype 3, the difference in proportions of responders was -6% and the lower limit of the 95% CI was **-10.2%.** As regards GMR, the 2-fold non-inferiority criterion was met for 12 of 13 serotypes: the **exception was serotype 3.**

GMFRs

The geometric mean fold rises (GMFRs) of antibody concentrations from pre- to post-boost for the 7 common serotypes ranged from 3.8 (serotype14) to 10.1 (23F) in the Prevenar 13 group and from 4.2 (serotype 14) to 11.0 (23F) in the Prevenar group. For the 6 additional serotypes, the fold rises ranged from 4 (serotype 3) to 8.1 (serotype 1) in the Prevenar 13 group. In the comparison of GMFR the lower limit of the CI for the ratio was at least 0.76, exceeding the 2-fold criterion for all serotypes.

OPA Results

Proportions with OPA titre >1:8

For the 7 common serotypes, the percentage of subjects achieving an OPA antibody titer ≥1:8 was similar in the 2 vaccine groups; at least 97.9% (23F) in Prevenar 13 group and at least 94.8% (19F) in Prevenar group. OPA activity was present for all 6 additional serotypes in the Prevenar 13 group, with at least 98.0% of subjects achieving OPA titer ≥1:8.

OPA GMTs

GMTs for the 7 common serotypes were high in both vaccine groups. The highest GMTs were seen for serotype 9V and the lowest for serotype 19F in both groups.. For the additional serotypes in the Prevenar 13 group, the lowest GMTs were observed for serotype 3, followed by serotypes 1 and 5.

For 4 of the 7 common serotypes, GMRs ranged from 0.86 to 1.30, and the lower bounds of the CIs were ≥0.60, but GMRs for serotypes 14, and 23F were 0.61 and 0.76 and the lower bounds of the CIs were less than 0.5 (0.43 to 0.47, respectively).

➢ **Study 004 (US) (n=666)**

Study 004 is the pivotal non-inferiority evaluation of Prevenar 13 compared to Prevenar for US licensure.

ELISA Results

Primary non-inferiority analysis

The primary non-inferiority criterion was **met for 10 of the 13 serotypes**. The exceptions were **serotypes 6B, 9V and 3,** which had lower limits for the 95% CI of **-10.9%, -12.4%** and **-36.2%,** respectively (Table 1-5). For the 6 additional serotypes, the serotype used as Prevenar reference was 6B (92.8%).

Table 1-5: Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35µg/mL After Dose 3 of the Infant Series – Evaluable Infant Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC				7vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	252	238	94.4	(90.9, 96.9)	251	246	98.0	(95.4, 99.4)	-3.6	(-7.3, -0.1)
6B	252	220	87.3	(82.5, 91.1)	250	232	92.8	(88.9, 95.7)	-5.5	(-10.9, -0.1)
9V	252	228	90.5	(86.2, 93.8)	252	248	98.4	(96.0, 99.6)	-7.9	(-12.4, -4.0)
14	251	245	97.6	(94.9, 99.1)	252	245	97.2	(94.4, 98.9)	0.4	(-2.7, 3.5)
18C	252	244	96.8	(93.8, 98.6)	252	248	98.4	(96.0, 99.6)	-1.6	(-4.7, 1.2)
19F	252	247	98.0	(95.4, 99.4)	251	245	97.6	(94.9, 99.1)	0.4	(-2.4, 3.4)
23F	252	228	90.5	(86.2, 93.8)	252	237	94.0	(90.4, 96.6)	-3.6	(-8.5, 1.2)
Additional										
1	252	241	95.6	(92.3, 97.8)	250	232	92.8	(88.9, 95.7)	2.8	(-1.3, 7.2)
3	249	158	63.5	(57.1, 69.4)	250	232	92.8	(88.9, 95.7)	-29.3	(-36.2, -22.4)
5	252	226	89.7	(85.2, 93.1)	250	232	92.8	(88.9, 95.7)	-3.1	(-8.3, 1.9)
6A	252	242	96.0	(92.8, 98.1)	250	232	92.8	(88.9, 95.7)	3.2	(-0.8, 7.6)
7F	252	248	98.4	(96.0, 99.6)	250	232	92.8	(88.9, 95.7)	5.6	(1.9, 9.7)
19A	251	247	98.4	(96.0, 99.6)	250	232	92.8	(88.9, 95.7)	5.6	(1.9, 9.7)

GMC

Twelve (12) of the 13 serotypes met the GMC ratio non-inferiority criterion (lower limit of the 95% CI for the GMR >0.5), even though all the GMRs were less than 1 (range 0.68 to 0.84). **The exception was serotype 3.** For serotype 3, the GMR was 0.35 (95% CI, 0.30 to 0.41). Results for the all-available population were consistent with those for the evaluable population.

OPA Results

Proportion of subjects achieving OPA GMT >1:8

There were no differences in the proportion of infants exhibiting a OPA titer ≥1:8 for the 7 common serotypes, with response rates of at least 90.4% and 92.6% in the Prevenar 13 and Prevenar groups, respectively. For each of the 6 additional serotypes the proportions with OPA titer ≥1:8 was at least 91.4%.

OPA GMTs

OPA GMTs for the 7 common serotypes ranged from 54.4 (19F) to 4035.4 (9V) in the Prevenar 13 group and from 44.9 (19F) to 3259 (9V) in the Prevenar group after the primary series (Table 1-6). For the additional 6 serotypes, GMTs ranged from 51.8 (serotype 1) to 9493.8 (serotype 7F) in the Prevenar 13 group.

When GMTs were compared GMRs for the 7 common serotypes ranged from 0.67 to 1.24. Of note, the OPA GMRs were 0.70 and 1.24 for serotypes 6B and 9V, respectively, although neither of these serotypes met the primary non-inferiority criterion based on IgG antibody levels. Serotype 4 was the only serotype for which the lower limit of the 95% CI was less than 0.50**.**

Table 1-6: Comparison of Pneumococcal OPA GMTs After Dose 3 of Infant Series – Evaluable Infant Immunogenicity Population

	Vaccine Group (as Randomized)							
	13vPnC			7vPnC				
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])	Ratio[d]	(95% CI[c])
7vPnC								
4	92	359.32	(276.04, 467.72)	92	535.68	(421.13, 681.37)	0.67	(0.47, 0.96)
6B	94	1054.65	(817.34, 1360.87)	94	1513.66	(1206.64, 1898.81)	0.70	(0.50, 0.98)
9V	93	4035.40	(2932.68, 5552.75)	94	3259.01	(2288.43, 4641.25)	1.24	(0.77, 1.99)
14	94	1240.41	(934.93, 1645.69)	94	1480.55	(1133.40, 1934.02)	0.84	(0.57, 1.23)
18C	94	275.59	(210.33, 361.10)	94	375.64	(291.68, 483.75)	0.73	(0.51, 1.06)
19F	94	54.42	(40.20, 73.65)	94	44.92	(33.90, 59.52)	1.21	(0.80, 1.83)
23F	94	791.07	(604.96, 1034.44)	94	923.56	(708.59, 1203.74)	0.86	(0.59, 1.25)
Additional								
1	92	51.83	(38.84, 69.16)	92	4.41	(4.06, 4.80)	11.75	(8.72, 15.83)
3	94	120.67	(92.38, 157.62)	94	6.70	(5.27, 8.52)	18.00	(12.60, 25.72)
5	91	90.86	(67.10, 123.02)	93	4.15	(3.94, 4.38)	21.88	(16.17, 29.61)
6A	94	979.68	(783.04, 1225.71)	94	100.35	(66.22, 152.08)	9.76	(6.11, 15.61)
7F	94	9493.77	(7339.13, 12280.98)	89	128.00	(79.55, 205.97)	74.17	(43.68, 125.93)
19A	93	151.94	(105.16, 219.52)	92	6.53	(5.01, 8.50)	23.28	(14.83, 36.52)

Booster dose

ELISA Results

One month after the booster dose, at least 98.7% of subjects in the 2 vaccine groups achieved antibody concentrations ≥0.35 μg/ml for the 7 common serotypes. Except for serotype 3 (90.5%), the proportion of responders to each of the 6 additional serotypes was at least 99.6% in the Prevenar 13 group. The non-inferiority criterion was met **for 12 of the 13 serotypes. The exception was serotype 3**, the difference between the proportions of responders of 90.5% in the Prevenar 13 group and the comparison serotype (19F, 98.7%) was -8.1% with a lower limit of the 95% CI of -12%. In the co-primary comparison of post-booster IgG GMCs in the 2 vaccine groups, **12 of the 13 serotypes (all except serotype 3)** met the 2-fold non-inferiority criterion. For serotype 3, GMCs were 0.94 μg/ml and 0.07 μg/ml in the Prevenar 13 group and Prevenar group, respectively, but the GMR calculated using the comparison serotype was 0.26 (95% CI, **0.22** to 0.30). GMRs were less than 1 (range 0.68 to 1.18) for all the common serotypes, except serotype 19F.

OPA Results

For each common serotype, proportions of responders (GMT ≥1:8) after the booster dose were ≥96.7% in the Prevenar 13 group and ≥94.8% in the Prevenar group after the booster dose. The proportion of responders to the 6 additional serotypes was 97.8% (serotypes 19A and 3) or higher in the Prevenar 13 group.

When OPA GMTs were compared (Prevenar 13 to Prevenar ratio), GMRs for the 7 common serotypes ranged from 0.55 to 1.19. The lower limits of the 95% CIs ranged from 0.36 to 0.76. The 2-fold non-inferiority criterion was met for 4 of 7 common serotypes. The exceptions were serotypes 9V, 18C and 23F.

Other immunogenicity studies

➢ ***Lot-to-lot consistency***

Different lots of Prevenar 13 produced using the commercial process, all of which contained P80, were tested in 2 separate studies to demonstrate consistency of the manufacturing process and comparability of scale. The first study (3000) assessed the comparative immunogenicity of a pilot lot and a manufacturing lot of vaccine using a 2-, 3-, and 4-month primary series. The data showed that the immune responses elicited by both vaccines were comparable across all serotypes. The second study (3005) was conducted using a 2-, 4-, and 6-month infant series. Two pilot lots and one manufacturing lot were assessed for equivalency of the immune response. In this study, lots were tested by pair-wise comparisons of all 3 lots. To be considered equivalent, the GMCs needed to be

within 2-fold (the lower limit of the 2-sided 95% CI for the GMR greater than 0.5 and the upper limit less than 2.0). Using these criteria equivalent responses were demonstrated across all serotypes irrespective of the specific lot comparisons.

➢ ***3-dose primary vaccination***

Nine primary vaccination studies evaluated immunogenicity of the Prevenar 13 in two different 3-dose schedules used in the EU, 2-3-4 months (studies 006, 008, 009 and 3000) and 2-4-6 months (studies 003, 004,501, 3005 and 3007). In addition, one study in India assessed an EPI-schedule, but due to a clinical hold, this study was not fully representative of a 6-10-14 week schedule and is not further addressed. Only in the 2 pivotal studies 004 and 006 and in 2 other trials (011 and 500 (booster phase)) was the immune response to Prevenar 13 compared with that of Prevenar. The other studies evaluated the immune response of the co-administered vaccine antigens in the Prevenar 13 and Prevenar groups.

The Prevenar 13 vaccine was demonstrated to induce an immune response to all 13 serotypes in all vaccination schedules. The profile was similar to that of Prevenar although overall the 13-valent vaccine was slightly less immunogenic. Between 90.5% to 99% (Prevenar 13) and 97.5% to 98.6% (Prevenar) of subjects achieved an antibody concentration ≥0.35 μg/ml to the 7 common serotypes, except for serotypes 6B and 23F in both vaccine groups. Both these serotypes exhibited delayed responses with significant increase only after the 3rd dose. Across studies and schedules serotype 14 was the most immunogenic serotype by ELISA. The ELISA responses for the additional serotypes appeared to be in the range of those observed for the common serotypes, except for serotype 3 having the lowest proportion of responders (63.5%-99.2%) and GMCs. Schedule had an effect, higher GMCs were measured for almost all serotypes in the 2-4-6 month schedule in comparison with the 2-3-4 month schedule.

As regards the functional immune response induced to the 7 common serotypes, at least 84%-100% of subjects (80-100% for Prevenar) across all schedules achieved OPA titres ≥8. GMTs were somewhat lower in the Prevenar 13 group (with the possible exception of serotype 19F). For both vaccines and across studies the highest OPA GMTs were observed for serotypes 9V and 14 and the lowest were observed for 19F. As regards the additional serotypes, the functional immune response induced to 7F and 6A appear satisfactory whereas the low GMTs observed for serotypes 1, 3 and 5 raise concerns. The OPA response against serotype 19A was modest with 91-100% of subjects attaining OPA titres >1:8, and with GMTs ranging from 152 to 442.

Cross-reactive responses in the Prevenar group

Cross-reactive immune responses were observed by ELISA for serotypes 6A and 19A in the Prevenar group. Increased ELISA reactivity was also seen for serotype 5. However, only the serotype 6A responses were shown to exert functional activity, which has also been confirmed to translate to efficacy of Prevenar against 6A IPD. As regards OPA, substantial responses were demonstrated for serotype 7F in the Prevenar group. This opsonic activity was shown to be due to presence of 7F IgM antibodies, possibly as a result of natural exposure to 7F or cross-reactive 7F PS in bacteria.

➢ ***2-dose primary vaccination and booster response***

Studies with a 2-dose primary series included 007 (2-4 months) and 500 (3-5 months). No comparison of immunogenicity with Prevenar after the primary series was performed in any of the study. Comparative data after a booster dose were available only from study 500. OPA responses post-dose 2 and post-booster were provided only for the Prevenar 13 group in a subset of 100 subjects from study 500. In addition, studies 501 and 3007 provided comparative data on post-dose 2 and post-dose 3 immune responses.

The results from the 4 studies showed that the Prevenar 13 is immunogenic in the 2-dose primary eliciting an acceptable response to 10 of the 13 serotypes. **The exceptions were serotypes 6B, 23F and 3**. The proportion of infants with a 2-dose infant series achieving an antibody level of ≥ 0.35 μg/ml ranged from **27.9%** to 58.4% for 6B, from **55.8%** to 68.6% and for 23F from **73.8%** to 92.8% for serotype 3. For the other common serotypes, the proportion of responders ranged from 85.6% (9V) to 100% (19F) and for the additional serotypes it ranged from 79.2% (6A) to 98.5% (7F and 19A). In general higher antibody concentrations were achieved after 2 doses of Prevenar 13 given at 3 and 5 months of age, compared with 2 and 4 months of age. Following the administration of a third infant dose, in studies 501 and 3007, there was a substantial increase in GMCs for all serotypes,except for serotype 3, with a more pronounced rise in antibody concentrations for serotypes 6B and 23F.

Post-booster ELISA GMCs in the 2+1 schedule were comparable to the antibody levels achieved 1 month after the fourth (booster) dose in a 3+1 schedule. In study 500, post-booster immunogenicity of Prevenar 13 and Prevenar was compared. The 95% CI for the difference in the proportion of responders at ≥0.35µg/ml between Prevenar 13 and Prevenar exceeded -0.10 for each of the 13 pneumococcal serotypes. The post-booster responder proportions for 6B and 23F were both 100% and the GMCs were also high, 10.0 µg/ml and 3.40 µg/ml, respectively. The lowest proportion of responders as well as the lowest GMC was observed for serotype 3.
The proportion of Prevenar 13 recipients with an OPA titer ≥1:8 after the 2-dose series in study 500 was 90% or higher for all serotypes. The responder rate at OPA titer ≥1:8 after the booster dose was 97.9% or higher for all serotypes. The post-dose 2 OPA GMTs were lowest for the additional serotypes, and in particular, for serotypes 1, 3, 5 and 19A. For these 4 types, OPA GMTs were lower than those observed for the least immunogenic Prevenar serotype 6B. After the booster dose, the GMTs increased for all serotypes, but still the lowest GMTs among the 13 serotypes were seen for serotypes 1 and 3 along with 19F, the serotype with the lowest vaccine efficacy for Prevenar.

➢ ***Persistence of antibodies until booster dose***

Prior to booster vaccination, at least 30% (23F) of Prevenar 13-primed and 53.8% (23F) of Prevenar-primed subjects had persisting IgG antibody concentrations ≥0.35 µg/ml to the 7 common serotypes. For serotype 6B an increase in proportion of responders was observed in the pre-booster period. Overall, the highest percentage of subjects with pre-booster antibody concentrations ≥0.35µg/ml was noted for serotypes 14 (≥93%) and 19F (≥80%) in both vaccine groups. In the pivotal trials the non-inferiority criterion at the ≥0.35 µg/ml level was missed by **4 serotypes (4, 9V, 18C, 23F)** in study 006 and by **3 serotypes (4, 18C and 23F)** in 004. A decline in antibody GMCs was observed for both vaccines between the post-primary and pre-booster time points for all serotypes, except 6B. In general, pre-booster GMCs were somewhat higher in the Prevenar group
For the 6 additional serotypes, the persistence of antibody concentrations ≥0.35 µg/ml was lowest for **serotype 3** in all studies, with the responder rates ranging from 14.3% to 34.2%. The corresponding percentages for the other serotypes varied from 66% to 91% for 6A and ≥89% for 19A. A decline in antibody GMCs was observed for all the 6 serotypes between the post-primary and pre-booster time points. Across studies the lowest GMCs were observed for serotype 3 and the highest for 19A.

Data on the UK 2+1 schedule in study 007 were also provided during the procedure and gave some important results. Direct comparison of post-dose 2 responses immune responses between Prevenar 13 and Prevenar showed that the responder rates at 0.35µg/ml and GMCs were somewhat lower in the Prevenar 13 group for the common serotypes, and in particular as regards serotype 6B (10% difference of response rate), whereas after the booster dose no differences in responder rates between vaccine groups were observed and IgG GMCs were in the same order of magnitude, including for serotype 6B. The post-dose 2 responder rates to the additional 6 serotypes ranged from 79% (6A) to 97% and GMCs ranged from 0.63 (serotype 3) to 2.14 µg/ml (7F). At the time of the booster dose particularly low IgG antibody persistence was noted for serotype 3 (12.6% remained at ≥0.35ug/ml). After the booster dose serotype 3 had the lowest response (88%; GMC: 1.0 µg/ml), whereas for the other types responder rates (90-100%) and GMCs were moderate to high. As regards functional OPA response, the post-dose 2 and post-booster responses showed that responder rates at OPA titre ≥1:8 and GMTs were comparable between Prevenar 13 and Prevenar groups for the 7 common serotypes, including 6B. For the 6 additional serotypes, the proportions of positive OPA responder post-dose 2 ranged from 89% (serotype 1) to 100% (7F). In terms of GMTs, low titres were noted for serotypes 1, 3, 5 and 19A. Pre-booster OPA data showed relatively good persistence of OPA response for the 6 additional serotypes with >70% remaining at titre >1:8 (except 19A, 33%). One month after the booster dose, the responder rates were high for all additional serotypes and OPA GMTs increased but were still relatively low for serotypes 1, 3 and 5.

➢ ***Booster vaccination***

Booster dose data were provided from 6 studies. Altogether 3240 subjects received a toddler dose, of whom 1626 subjects received Prevenar 13 and 1614 received Prevenar. The results indicated that Prevenar 13 induces a robust booster response and ELISA GMCs were higher than post-primary responses for all serotypes, except serotype 3. Increases of ELISA responses (at least 4.0-fold increase) were observed after a booster dose of Prevenar 13 compared to pre-booster levels. These

data indicate a priming effect of the 2 and 3 vaccine doses on the immune system and the boostability of the immune response by the Prevenar 13 vaccine against 12 of the 13 vaccine serotypes (exception serotype 3). In general post-booster ELISA responses were somewhat lower than those for Prevenar. Prevenar induced slightly greater fold increases of GMCs from pre- to post-boost than Prevenar 13, but the non-inferiority criterion was met by all the 7 common serotypes. No significant differences in booster response were noticeable by schedule, 2-dose or 3-dose primary series worked similarly well, also for the low immunogenic serotypes 6B and 23F in the infant series. Nor were there any substantial differences noted in serotype-specific ELISA response rates and GMCs after the booster dose between the P80-containing Prevenar 13 formulation and Prevenar 13 without P80 in study 009. The percentages of subjects with opsonic antibody levels at GMT $\geq$ 1:8 after the booster dose were similar for both vaccines. At least 97% of subjects in the Prevenar 13 group and 95% in the Prevenar group attained OPA titres $\geq$1:8 against the common serotypes. With respect to the 6 additional serotypes, at least 98% achieved this threshold. However, as regards OPA GMTs, the 2-fold non-inferiority criterion was missed by two of the common types (14 and 23F) in study 006 and by three serotypes (9V, 18C and 23F) in study 004, although the studies were not powered for this comparison. As regards the additional serotypes, strong post-booster OPA responses were induced by Prevenar 13 against two serotypes (7F and 6A), whereas weaker responses were seen for serotypes 1, 3 and 5.

➢ ***Catch-up immunisation schedules***

Catch-up vaccination with Prevenar 13 in children 7-11 months, 12-23 months and 24 months to 5 years of age was assessed in study 3002. The different catch-up schedules were documented in an appreciable number of children (n=355; 90-153/group). The study was open and functional antibody response was not measured. The 3 catch-up vaccination schedules evaluated were 2 doses at 7 to <12 months with a booster dose at 12 to 16 months, 2 doses at 12 to <24 months, and 1 dose at 24 to <72 months. These are the schedules currently recommended for Prevenar in the 3 age groups. The results showed that the proportion of subjects achieving IgG antibody level $\geq$0.35 µg/ml was high (93% to 100%) for all serotypes and for all 3 age groups, with the exception of serotype 14 in the oldest group (88%). Of the 7 common serotypes, 23 F was the least immunogenic serotype with slightly lower GMCs and also proportion of responders in the two older age groups. Across age groups, the lowest GMCs were observed for serotype 3. Of the other 5 additional serotypes, the strongest responses were seen to serotypes 7F and 19A. The individual serotype GMCs were similar for the 3 age groups, but were always numerically lower (except for 19A) in the oldest age group receiving a single dose. In general, the GMCs were comparable to those achieved after a 3-dose infant series. The results are satisfactory and the dose recommendations given in the SPC are acceptable.

➢ ***Co-administered vaccines***

In all completed clinical trials (except 3002), DTPa-combination vaccines were co-administered with the Prevenar 13 vaccine. Different MenC conjugate vaccines were co-administered in studies 007, 501 and 3007. In the booster dose phase of study 004, the first dose of MMRV vaccine was co-administered. In study 011 in India a whole-cell pertussis combination vaccine was evaluated. This program took into account all the potential co-administrations currently used in the EU, except that immunogenicity was not measured after administration of rotavirus vaccines (and hepatitis A vaccine). Compared with Prevenar, non-inferiority of antibody response to each of the vaccine antigens was demonstrated with Prevenar 13. The only exceptions were related to the antibody response to diphtheria and polio type 2 antigens in Pentavac, although the antibody response to the same antigens in other vaccine formulations was not altered.

➢ ***Switching of vaccines***

Study 008

Study 008 (n=613) was designed as a 3-group study with 2 groups receiving the same vaccine during the primary series. The investigational group was to receive Prevenar 13 for all doses (13v/13v), the active-control group was to receive Prevenar for all doses (7v/7v), and the remaining group was to receive Prevenar for the primary series and Prevenar 13 for the booster dose (7v/13v). In the Applicant´s responses to CHMP D120 LoQ the toddler results were provided. The post-booster

responder rates at 0.35µg/ml and IgG GMCs were generally comparable between the 3 vaccine groups for all 7 common serotypes, although always somewhat higher in the 7v/7v group. For the 6 additional serotypes significantly lower IgG and OPA responses were seen for serotypes 1, 5 and 6A in the 7v/13v group compared with the group that received Prevenar 13 for all doses. For serotype 3 the immune responses were similarly low in both vaccine groups, whereas comparable responses were observed for 7F and 19A.

Overview of the different switching scenarios

Three Dose Infant Series

In countries in which a 3-dose infant series is used, there are 3 transition scenarios that need to be considered at the time of the introduction of Prevenar 13.

Table 1-7: Three Dose Infant Series

Infant Series - Vaccine Doses			**Toddler Dose (12-24 months)**	
7v	**7v**	**7v**	**13v**	**13v**
7v	**7v**	**13v**	**13v**	**--**
7v	**13v**	**13v**	**13v**	**--**

- **7v 7v 7v / 13v 13v**

Based on experience from the 004 (US) and 006 (Germany) non-inferiority trials, as well as the comparisons of Prevenar 13 and Prevenar in the 3005 lot consistency trial, this regimen will provide protective immunity against the 7 common serotypes that is non-inferior to a 4-dose Prevenar regimen. For the additional 6 serotypes, the Polish 3002 study shows that 2 doses at 12-24 months are sufficient. Safety data from study 3011 indicate that there is no evidence of an increase in either the frequency or the severity of local reactions or systemic events associated with Prevenar 13 given as a 5th or 6th dose after immunization with Prevenar.

- **7v 7v 13v / 13v**

Based on experience from the 004 and 006 non-inferiority trials, and the comparisons of Prevenar 13 and Prevenar in the 3005 lot consistency trial, this regimen will provide protective immunity against the 7 common serotypes that is non-inferior to a 4-dose Prevenar regimen. There are no data on the response to the 6 new serotypes after one dose of Prevenar 13 given before the age of 6 months. Therefore, protection against the 6 additional serotypes between 6 and 12 months of age is not known. However, a subsequent dose of Prevenar 13 at 12 months should elicit an appropriate immune response given the data from the Polish 3002 study showing that an adequate immune response is induced after a second dose of Prevenar 13 in the second year of life.

- **7v 13v 13v / 13v**

Based on experience from the 004 and 006 non-inferiority trials, and the comparisons of Prevenar 13 and Prevenar in the 3005 lot consistency trial, this regimen should provide protection against the 7 common serotypes that is non-inferior to a four dose Prevenar regimen. Based on the "2+1" studies in the UK (007) and Italy (500), the response after the booster dose elicits an immune response that is comparable to the response after a 4-dose regimen. Therefore, no further Prevenar 13 dosing would be required.

Two dose infant series

For countries in which a 2-dose infant series is used, there are 2 transition scenarios that need to be considered at the time of the introduction of Prevenar 13.

Table 1-8: Two Dose Infant Series

Infant Series - Vaccine Doses		Toddler Dose (12 – 24 months)	
7v	**7v**	**13v**	**13v**
7v	**13v**	**13v**	**--**

➢ **7v 7v/13v 13v**
Based on experience from the 004 and 006 non-inferiority trials, and the comparisons of Prevenar 13 and Prevenar in the 3005 lot consistency trial, this regimen should provide protective immunity against the 7 common serotypes that is non-inferior to a 4-dose Prevenar regimen. For the additional 6 serotypes, the Polish 3002 study shows that two doses at 12-24 months are sufficient.

➢ **7v 13v/13v**
The data from the 2+1 studies in both the UK (007) and Italy (500) show that this regimen will elicit an acceptable immune response against the 7 common serotypes.
There are no data on the response to the 6 new serotypes after one dose of Prevenar 13 given before the age of 6 months. Therefore, protection against the 6 additional serotypes between 4 or 5 months and 12 months of age is not known. However, a subsequent dose of Prevenar 13 at 12 months should elicit an appropriate immune response given the data from the Polish 3002 study showing that an adequate immune response is induced after a second dose of Prevenar 13 in the second year of life

- Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

- Clinical studies in special populations

Not applicable

Discussion on clinical efficacy

During the procedure, the use of P80-containing Prevenar 13 formulation and its impact on the immune response was discussed. The Applicant provided new data on a direct comparison of immune responses between Prevenar 13 in the final formulation (+P80) and Prevenar in study 3005 (lot consistency study). The results demonstrated that the IgG immune responses elicited by Prevenar 13+P80 were comparable and non-inferior to those elicited by Prevenar against each of the common serotypes. New data on the functional immune responses to serotypes 6B and 23F in study 009, that did not fulfil the primary non-inferiority criterion (for IgG responses), showed that the OPA responses were comparable in recipients that received Prevenar 13+P80 and Prevenar 13-P80. Considering the good correlation between IgG GMC and OPA GMT, there is no reason to believe that OPA responses elicited by the Prevenar 13+P80 and Prevenar vaccine would show a result that is divergent from the one observed for the anti-polysaccharide response. Moreover, the *in vitro* data presented do not suggest that P80 affect antigenicity of Prevenar 13.

The results from studies 004 and 006 for the 7 common serotypes demonstrated that the immune response induced by Prevenar 13 can be considered non-inferior to that induced by Prevenar, despite that a few serotypes (6B in 006 and 6B and 9V in 004) missed the primary criterion. The WHO guideline stipulates that non-inferiority to antibody response for each of the serotypes in the registered vaccine is desirable, but not an absolute requirement. The margin of failure was small for these serotypes and they met all the secondary non-inferiority criteria and the pre-defined additional criteria. In addition, the post-booster responses for 6B and 9V were the strongest among the 7 serotypes and the OPA responses were good. Concerning the 6 additional serotypes, the low post-primary functional immune responses observed for serotypes **1, 3, 5 and 19A** are difficult to interpret due to the lack of a standardised OPA assay and common reference serum as well as the lack of data on vaccine efficacy and identified serotype-specific protective thresholds. However, these data may suggest that the low

post-primary functional immune responses observed for 4 of the 6 additional serotypes, in particular for serotypes 1, 3 and 5, could translate to reduced vaccine efficacy of the Prevenar 13 vaccine against pneumococcal disease due to these serotypes. Until post-marketing data have confirmed the vaccine's effectiveness, **information about the low functional immune response observed for serotypes 1, 3 and 5 has been included in the SPC.**

During the procedure, it was questioned whether the Prevenar 13 vaccine induces hyporesponsiveness or tolerance to serotype 3 impacting negatively on the child´s capacity to respond to a natural serotype 3 infection. The Applicant performed a thorough re-evaluation of the immune response to serotype 3, including a review of the 008 clinical study results, a review of the IgG and OPA antibody responses across the Prevenar 13 program, a review of the characteristics of hypo-responsiveness elicited by plain polysaccharide vaccines, a review of the pneumococcal PS vaccine effectiveness against serotype 3 disease and a discussion of the efficacy and immunogenicity of the investigational 11-valent pneumococcal conjugate vaccine. The results of the review do not suggest that the Prevenar 13 vaccine induces a hyporesponsive state to serotype 3. The Company has committed to conduct a **follow-up of study 008** with repeat vaccination at the approximate age of 36-42 months to measure serotype 3 responses (IgG and OPA) prior and after a booster dose of Prevenar 13. The clinical consequences of the atypical immunogenicity profile of serotype 3 as regards poor boostability are unknown, a **statement has been included in section 4.4 of the SPC**.

The 2-dose primary schedule in infants resulted in lower immune responses than the 3-dose primary series, in particular with regard to serotypes 6B and 23F, which could result in suboptimal protection against IPD and AOM during the pre-booster period. After the booster dose GMC levels are in the range of those after a 3-dose primary series.
In general, persistence of post-primary antibody response to the majority of serotypes was higher in the Prevenar group than in the Prevenar 13 group. Data on pre-booster OPA titres provided for study 007 (2+1 schedule) during the assessment period indicate that the Prevenar 13 will likely be as effective as Prevenar against the 7 common serotypes, whereas the efficacy against the additional serotypes is difficult to predict considering the low functional immune responses observed one month after dose 2. **The Applicant has planned to monitor long-term persistence of immunogenicity after the booster dose. Also, surveillance programs will evaluate the effectiveness both of a 2+1 and 3+1 schedule against IPD, pneumonia, and AOM-related outcomes**.

During the assessment period a summary surveillance report from the Heath Protection Agency in the UK was released, evaluating the impact of the 7-valent pneumococcal conjugate vaccination program in England and Wales. As a number of vaccine failures due to serotype 6B were seen with Prevenar 7 in this study, the concern that Prevenar 13 may not offer adequate protection in a number of recipients for 6B was raised. The applicant has committed to provide a compilation of data on clinical effectiveness (and immunogenicity) of Prevenar 7 from all EU and non-EU countries using the vaccine in national childhood vaccination programme (FUM).

Regarding co-administered vaccines, data suggest that concomitant administration of Prevenar 13 does not affect the immunogenicity of routinely recommended paediatric vaccines. Some findings in the studies have been further addressed such as the unexpected reduced diphtheria response and the lower anti-MenC SBA GMTs (Meningitec) observed for Prevenar 13 *cf.* Prevenar, despite the higher content of CRM_{197} carrier protein in Prevenar 13. Further documentation has been submitted to support the adherence to the claimed vaccination schedules in which the co-administered vaccine antigens were given with Prevenar 13. The data on timing of vaccination for the 3 doses and for the 2 doses in the most stringent vaccination schedules in the relevant studies were deemed satisfactory. A careful re-evaluation of all relevant data in the phase III clinical trial programme for Prevenar 13 and in the post-marketing surveillance period for Prevenar did not give any support for general statements regarding reduced response to pertussis antigens and IPV to be included in the SPC for Prevenar 13.

With respect to switching of vaccines after the primary series, **a 2-dose regimen of Prevenar 13 to Prevenar primed children seems more appropriate, in line with what is recommended for unvaccinated children 12-24 months of age. This is reflected in the SPC.**

With respect to switch from Prevenar to the Prevenar 13 in the midst of the primary series, the transition plan was not considered acceptable as there is a lack of immunogenicity data to support two of the proposed mixed dosing regimens (7v/7v/13v/13v and 7v/13v/13v). The 2 doses of Prevenar 13 in these schedules will most probably result in insufficient protective immunity against the 6 additional serotypes. **In line with the 3-dose catch-up schedule recommended for unvaccinated children at 7 to <12 months of age, a third dose during the second year of life seems indicated, until additional data are available. The data is reflected in the SPC**.

Also, an open-label trial in Alaskan native children to assess the impact of Prevenar 13 (in terms of effectiveness and nasopharyngeal carriage) in a population with high rates of invasive disease has been ongoing throughout the application process. This study addresses the efficacy of use of Prevenar 13 in those patients who have received 0-3 prior doses of Prevenar during the transition period. Additionally, the immunogenicity of Prevenar 13 as a single booster dose in those children who have received Prevenar as their primary series will be addressed in another open label trial enrolling children from the after of > 1 to < 10 years of age.

During the procedure, a specific concern was raised about the absence of firm commitments with national surveillance agencies to investigate specific endpoints, such as investigation of incidence of serotypes with decreased immunogenicity (1, 3, 5, 19A), vaccine effectiveness, and changing epidemiology of the pneumococcus after introduction of the vaccine. Therefore, the company has provided a detailed description of the collaboration with the national surveillance institutions to perform the effectiveness studies in 5 EU countries. The applicant also commits to follow not only replacement with non-vaccine pneumococcal serotypes but also replacement with other bacteria, like staphylococci.

The applicant submitted sufficient immunogenicity data in infants <2 months (6 weeks -<8 weeks) of age (n= >600 + 354 6-week old infants vaccinated with Prevenar 13 in study 011 in India) to support an indication in children older than 6 weeks. This is also supported by comparable post-primary and post-booster ELISA IgG responses in subjects vaccinated <2 months of age and the overall vaccinated group. A separate safety analysis in this age group was not performed. For unsolicited AEs there were no safety signals in sufficient numbers of Prevenar 13 children to allow analysis by age of enrollment. For solicited AEs no safety signal has been seen with Prevenar 13 compared to Prevenar recipients and thus, no unequivocal signal will be apparent in any analysis in children <2 months of age.

Clinical safety

Most of the clinical trials of Prevenar 13 have included Prevenar, thereby permitting a direct safety comparison between the two vaccines. Given the similarity of Prevenar 13 to Prevenar, the clinical development of Prevenar 13 confirms the safety profile that has been established for Prevenar. The safety profile of Prevenar is well defined on the basis of the vaccine´s pre-licensure clinical evaluation and post-licensure experience, with approximately 195 million doses having been distributed worldwide since year 2000.

- Patient exposure

The safety of Prevenar 13 was evaluated based on data from 12 infant studies evaluating the safety and immunogenicity of Prevenar 13 administered with other paediatric vaccines. In the 12 studies a total of **4429** subjects received at least 1 dose of Prevenar 13. All infant studies included healthy infants aged between 6 weeks and 3 months at time of the first dose of Prevenar 13.
In addition, **354** older infants and young children from 7 months to < 6 years were vaccinated with Prevenar 13 co-administered with other paediatric vaccines.

- Adverse events

The safety of Prevenar 13 was evaluated on the basis of prompted AEs, including local reactions and systemic events, as well as of spontaneously reported AEs.

Prompted Adverse events

Local Reaction

Results of the pooled data analyses demonstrate that, after all doses in both the infant series and the toddler dose, the incidence and intensity of local reactions at the study vaccine injection site for the Prevenar 13 group were similar to those reported for Prevenar (Table 2-1). Although the analyses showed some statistically significant differences between the 2 vaccine groups (*moderate induration* and *moderate erythema* higher for Prevenar 13 after dose 1; *significant tenderness* higher for Prevenar after dose 2), these were relatively small.

In the catch-up study 3002, in which children in 3 different age groups all received Prevenar 13, the incidence of *tenderness* after dose 1 increased across groups by age, being reported for approximately 15% of subjects in group 1 (7 to <12 months of age); 33% of subjects in group 2 (12 to <24 months of age), and 42% in group 3 (24 to <72 months of age). However, within group 1, the incidence remained essentially constant (~15%) after all 3 doses (with the third dose administered between 12 and 16 months of age).

Table 2-1: Subjects Reporting Local Reactions: Infant and Toddler Doses (All 12 Infant Studies)

	Dose 1[a]			Dose 2 [a]			Dose 3[a]			Toddler[b]		
	13vPn n(%)	7vPn	p-value[c]	13vPn	7vPn	p-value[c]	13vPn	7vPn	p-value[c]	13vPn	7vPn	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	342 (32.6)	219 (33.5)	0.569
Mild[e]	710 (19.8)	403 (20.0)	0.364	787 (25.6)	447 (26.5)	0.973	713 (27.6)	344 (27.9)	0.908	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	0	0		0	0	
Erythema												
N	3623	2049		3155	1762		2684	1292		1099	601	
Any	954 (26.3)	569 (27.8)	0.249	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)	0.249	1114 (35.3)	619 (35.1)	0.578	1027 (38.3)	478 (37.0)	0.338	479 (43.6)	302 (43.7)	0.267
Severe[e]	0	0		2(0.1)	0	0.543[f]	1(0.0)	0	>0.999	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 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.

Systemic events

Systemic events evaluated in all 12 infant studies include *fever, use of antipyretic medications*, *decreased appetite, irritability, increased sleep*, and *decreased sleep*. All events were reported at similar incidences in both vaccination groups (Table 2-2). The results of the meta-analysis of prompted data on systemic events other than *fever* show no statistically significant differences in the frequency between recipients of Prevenar 13 and recipients of Prevenar, with the exception of *decreased sleep* that was reported after the 1st dose of Prevenar 13 and Prevenar, respectively.

Information regarding *hives* (*urticaria*) was collected systematically only in Study 004 and Study 3005.

Table 2-2: Subjects Reporting Systemic Events, Fever and Antipyretic Medications: Infant and Toddler Doses (All 12 Infant Studies)

	Dose 1[a]			Dose 2[a]			Dose 3			Toddler[b]		
	13vPn n(%)	7vPn	p-value[c]	13vPn	7vPn	p-value[c]	13vPn	7vPn	p-value[c]	13vPn	7vPn	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 (41.09	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)	948 (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		2580	1253		1103	721	
	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 (43.2)	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	7171 (27.8)	406 (32.4)	0.359	474 (43.0)	359 (49.8)	0.472
≥38°C but ≤ 39°C	863 (25.0)	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°	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 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.

Decreased Appetite, Irritability, Increased Sleep, and Decreased Sleep

The pooled data analyses show that *decreased appetite*, *irritability*, *increased sleep*, and *decreased sleep* was reported at similar frequencies for the Prevenar 13 and Prevenar groups (Table 2-2). The ranges for the incidence of each event across studies are summarized in Table 2-3.

Table 2-3: Ranges for Incidence of Systemic Events by Study (All 12 Infant Studies)

		Infant series		Toddler dose[a]	
		Prevenar 13	Prevenar	Prevenar 13	Prevenar
Decreased appetite	Low	14.7%	21.1%	22.4%	21.8%
	High	58.8%	55.8%	53.4%	57.4%
Irritability	Low	37.4%	39.4%	38.8%	47.5%
	High	86.1%	85.1%	88.1%	85.2%
Increased sleep	Low	20.2%	22.7%	19.0%	35.2%
	High	71.9%	72.5%	58.6%	55.0%
Decreased sleep	Low	18.5%	17.7%	13.1%	14.9%
	High	55.1%	57.0%	43.3%	45.4%

Follow-up time = 4 days after each dose for all studies except study 003
(stage 1 = 15 days, stage 2 = 8 days).
a. Toddler dose data are available for 6 studies: 003, 004, 006, 009, 500, and 501.

Fever

"*Any fever*" (≥ 38°C) were recorded for between 24.4% and 38.4% of subjects in each vaccine group after each dose in the infant series. For both vaccines, febrile reactions were more common following the toddler dose, with *mild fever* noted in 41.1% and 48.2% of Prevenar 13 and Prevenar recipients, respectively, and moderate *fever* in 6.6% and 8.3%, respectively. In comparative studies *mild fever* was reported at similar frequencies in the vaccine groups. During the infant series, the incidence of *moderate fever* in each study was ≤ 8.8% for Prevenar 13 and ≤ 7.0% in the Prevenar group after all doses, but after the toddler dose the incidence was similar for the two groups. In comparative studies the incidence of *moderate fever* was similar between the groups. The incidence of *severe fever* (>40.0ºC) did not exceed 2.1% (2 subjects) for any vaccine group after any dose in any study. In the catch-up study, in each age group, after any dose, *mild fever* was reported for <8.1% of subjects and *moderate fever* were reported for < 2.3% subjects. No *severe fever* was reported during the study. Statistically significant increase in *severe fever* at dose 1 was seen in the Prevenar group (Table 2-2).

Possible explanations for the wide range of fever across studies were given. Among these was indicated that temperature readings were performed according to the method used in the clinical practice in respective countries. The variation in the use of antipyretics between studies provides another explanation for the range of fevers between studies. Different trends in the use of paracetamol based formulations compared with the non-steroidal anti-inflammatory preparations may also have an impact on temperature ranges between studies. Variation in the use of prophylactic antipyretic medication may reflect cultural /social variations in the approach to expected side effects of vaccination and may confound evaluation of fever response to the investigational and concomitant vaccines. Studies conducted in different countries showed an inconsistent relationship of usage of prophylactic antipyretics to fever rates. The variation in the use of antipyretics to treat fever is potentially a more objective measurement of parental response to actual high temperature measurements. The use of antipyretic prophylaxis and antipyretic treatment differs between geographical areas, which are also discussed in the present response report as well as the impact of cultural factors rather than by vaccine reactions.

Use of Antipyretic Medications

Data from the meta-analysis indicate that, for each dose, the proportion of infants and children receiving an *antipyretic medication*, given either to *treat* or to *prevent* symptoms, were not different between the 2 vaccine groups (Table 2-2).

After each dose in the infant series, the incidence of use of *antipyretic medications* to *treat* symptoms was between 45.9% and 55.3% for each vaccine group. After the toddler dose, ~43.0% of subjects in the Prevenar 13 group and 50.4% of subjects in the Prevenar group received *antipyretic medications* for the *treatment* of symptoms. In the individual studies, during the infant series, the use of *antipyretic medication* to *treat* symptoms was reported for 8.9% to 77.1% of subjects in the Prevenar 13 group and for 19.1% to 76.5% in thePrevenar. After the toddler dose the incidence ranged from 15.5% to 77.3% for Prevenar 13 and from 27.7% to 74.5% for Prevenar.

The use of *antipyretic medications* to *prevent* symptoms was reported for between 46.0% and 51.1% of subjects in each vaccine group after each dose in the infant series and for 36.1% of subjects in the Prevenar 13 group and 46.5% of subjects in the Prevenar group after the toddler dose. During the infant series, *antipyretic medications* were used to *prevent* symptoms in 8.3% to 85.1% of subjects in the Prevenar 13 and in 9.5% to 86.0% in the Prevenar groups, respectively. After the toddler dose the incidence was between 15.2% and 82.2% in the Prevenar 13 group and between 18.6% and 83.2% for Prevenar.group. In comparative studies the incidence was generally similar between the 2 groups.

In the catch-up study, *antipyretic medications* were used to *treat* symptoms in no more than 13.3% of subjects in any group after any dose, and such medications were used to *prevent* symptoms in no more than 14.3% of subjects in any group after any dose.

Specific adverse events

Special attention was made to reports on the incidence of some specific adverse events including *rash* and *urticaria – hives* although only collected in Study 004 and 3005 conducted in the US comparing non-inferiority of Prevenar 13 to Prevenar vaccine in healthy infants with routine paediatric vaccination.

Rash
The overall incidence of *rash* was determined by data reviewed for MedDRA preferred terms: *rash, rash papular, rash erythematous, rash macular, rash maculopapular, rash generalized, rash morbilliform, rash pruritic, rash rubelliform*, and *rash vesicular.* The incidence of any type of *rash* during the infant series was similar (2.7%vs 2.8%) in the Prevenar 13 and Prevenar groups; and after the toddler dose 0.5% and 1.6%, respectively. No *rash* of any type was serious, and only 2 subjects in the Prevenar group discontinued study vaccine because of *rash*.

Hives/Urticaria
During the infant series, *urticaria* was reported in approximately 0.4% of subjects in the Prevenar 13 group and 0.5% in the Prevenar group. The incidence after the toddler dose was approximately 0.1% in both groups. Only 2 of the reported AEs of *urticaria* were considered by the investigator to be related to study vaccine. Both occurrences were during the infant series in the Prevenar 13 group (~0.045%).

Table 2-4 shows the incidence of reports on *hives* within 7 days in the infant series after each dose and after the toddler dose. Three (3) of the reports in the Prevenar 13 group were determined to be inconsistent with *hives,* while the rest were neither confirmed nor determined .In the Prevenar group, 2 were determined to be inconsistent with *hives* and after the toddler dose.

Table 2-4: Subjects Reporting Hives Within 7 Days - Study 004

Dose	Vaccine Group as administered						p-value[c]
	Prevenar 13			Prevenar			
	N[a]	n[b]	%	N[a]	n[b]	%	
Dose 1	178	3	1.7	188	2	1.1	0.678
Dose 2	118	3	2.5	120	0	0.0	0.120
Dose 3	89	4[d]	4.5	79	0[d]	0.0	0.123
Toddler dose	62	3	4.8	47	3	6.4	>0.99

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Fisher exact test, 2-sided.
d. One (1) report of hives was recorded in error on the e-diary of subject 004-027-002402 in the Prevenar 13 group. The case of hives was actually in subject 004-027-002403 in the Prevenar group.

During the infant series there were 27 reports of suspected *hives* in the Prevenar 13 group (Table 2-5), of which 15 were confirmed as consistent with *hives* by investigator assessment. In the Prevenar group there were 3 reports of suspected *hives*, with 2 confirmed by the investigator.

Table 2-5: Subjects Reporting Hives Within 7 Days - Study 3005

Dose	Vaccine Group as administered						p-value[c]
	Prevenar 13[d]			Prevenar			
	N[a]	n[b]	%	N[a]	n[b]	%	
Dose 1	996	7	0.7	164	0	0.0	0.602
Dose 2	741	10	1.3	127	1	0.8	>0.99
Dose 3	686	10	1.5	112	2	1.8	0.680

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Fisher exact test, 2-sided, of Prevenar 13 (combined across lots) versus Prevenar.
d. Data are pooled across the three Prevenar 13 lots.

Spontaneously Reported Adverse Events

All Adverse Events

During the infant series, "any event" was reported at similar frequencies in the Prevenar 13 (64.8%) and Prevenar (63.4%) groups. Most reported types of events were grouped in the following SOCs: *infections and infestations* in 51.3% inPrevenar 13 and in 49.9% in Prevenar groups, respectively; *gastrointestinal disorders* in 15.7% vs 14.6%,; *skin and subcutaneous tissue disorders* in 15.2% vs 14.3%; *respiratory, thoracic and mediastinal disorders* in 13.8% vs 11.5%; and *general disorders and administration site conditions* in 9.7% vs 10.4%, of the Prevenar 13 and Prevenar groups, respectively. The rate of events reported following the toddler dose was lower in both groups: 33.0% inPrevenar 13 recipients and 35.5% in Prevenar recipients. The most frequently reported types of events were the same as those in the infant series.

Numerically significant differences in frequency were found for 52 AEs, classified according to SOC and preferred term, between study vaccine groups: the frequency of 16 of these events was higher among Prevenar 13 recipients and the frequency for 36 of the events was higher among Prevenar recipients. Except for *nasopharyngitis* during the period between the infant series and the toddler dose, the differences between vaccine groups for the events occurring with higher frequency in the Prevenar 13 group were in all cases $\leq$ 0.5%.

Adverse Events Considered Related to Study Vaccine

During the infant series, AEs considered related to study vaccine by the investigator were reported in 3.9% and 4.3% of subjects vaccinated with Prevenar 13 and Prevenar, respectively. After the toddler dose, the rate was 1.6% vs 2.8%, respectively. Related AEs that were most frequently reported were grouped into the following SOCs: *general disorders and administration site conditions*, *gastro-intestinal disorders* (mostly *diarrhea* and *vomiting*) and *psychiatric disorders* (largely *crying* and *restlessness*).

- Serious adverse event/deaths/other significant events

Deaths

During the study period, *death* occurred in 4 infants. All 4 cases were attributable to SIDS. Three (3) cases occurred among Prevenar 13 recipients (3 days after dose 2, 14 days after dose 1, and 76 days after dose 3) and one (1**)** in the Prevenar group (13 days after dose 1).

Table 2-6: Listing of Adverse Events Resulting in Death (All 12 Infant Studies)

Study	Subject	AE MedDra Term	AE Verbatim Term	Vaccine Administered	Last Dose	Days since last dose	Related to Study Vaccine[a]
60963005	000107	**SIDS**	Infant death cause unknown	Prevenar	Dose 1	13	Yes [b]
60963005	000320	**SIDS**	Sudden unexplained infant death	Prevenar 13	Dose 1	14	No
60963005	007651	**SIDS**	Asphyxia due to SIDS	Prevenar 13	Dose 2	3	No
6096501	000452	**SIDS**	Sudden unexpected death in infancy	Prevenar 13	Dose 3	76	No

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 causality, determining that the death was not related to study vaccine

Experience with Prevenar also suggests that no causal relationship exists between administration of the vaccine and SIDS. To determine the observed number of infant deaths in Prevenar 13 studies the Company evaluated data from all Prevenar 13 studies conducted in the US (**1908** subjects received Prevenar 13 and **701** subjects received Prevenar). The results showed that the standardized mortality ratios (SMRs) were less than 1 and not statistically significant. The observed number of deaths in this clinical program is consistent with the expected incidence of SIDS in the general infant population. The incidence of SIDS is low in Europe although available data are old and from no later than 2001.However, it could be anticipated that the incidence decline in Europe would be similar to that recorded in the US. A true comparison would be difficult due to various circumstances such as misclassification, incomplete case reporting and various case definitions as well as under –or

overestimation. It seems, though, that the global incidence may be considered comparable and the available data would be generally representative

Serious adverse events

The incidence of SAEs reported during each period in the studies was 4.5% or less for each vaccine group. The most frequently reported types of SAEs (MedDRA SOCs) are summarized in Table 2-7.

Table 2-7: 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)

SOC Preferred Term	Infant series		Between Infant Series and Toddler Dose[a]		Toddler dose[a]		6-Month Follow-up[b]	
	Prevenar 13 N=4423	Prevenar N=2451	Prevenar 13 N=1863	Prevenar N=1357	Prevenar 13 N=1701	Prevenar N=1210	Prevenar 13 N=950	Prevenar N=455
Any event	168(3.8)	92(3.8)	83(4.5)	45(3.3)	18(1.1)	19(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(0.19	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(0.39	2(0.1)	3(0.2)	1(0.1)	0(0.0)	0(0.0)

Infant series = from dose 1 through post infant series blood draw.
Between infant series and toddler dose = from the post infant series blood draw through the toddler dose.
Toddler dose = from the toddler dose through the post toddler dose blood draw.
6-month follow-up = from post toddler dose blood draw to 6-month follow-up contact.
a. Post infant 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 00

The table below indicates the listing of SAEs considered related to the study vaccine of the total of all 12 infant studies.

Table 2-8: Listing of Serious Adverse Events Considered Related to Study vaccine by the Investigator (All 12 Infant Studies)

Study	Subject	AE MedDRA PT	AE Verbatim Term	Vaccine administered	Last dose	Days since last dose	Duration (days)	Severity[a]	Related[b]
6096004	000160	Nephroblastoma	Bil. Wilm´s tumor	Prevenar	Dose 3	117	C	LT	Yes
6096004	002269	Febrile convulsion	Febrile seizure	Prevenar 13	Dose 2	4	1	Mi	Yes
6096004	002269	Pyrexia	Fever	Prevenar 13	Dose 2	4	5	MO	Yes
6096006	000244	Febrile convulsion	Febrile convulsion	Prevenar	Toddler dose	1	3	MO	Yes
6096009	000420	Bronchitis	Bronchitis	Prevenar 13	Dose 3	2	6	MO	Yes
60963000	000812	Crying	Unconsolable crying	Prevenar 13	Dose 1	1	1	MI	Yes
60963005	000107	SIDS[c]	Infant death cause unknown[c]	Prevenar	Dose 1	13	1	LT	Yes
60963005	002857	Allergy to vaccine	Vaccine allergic reaction	Prevenar 13	Dose 2	1	8	MI	Yes
60963005	004255	Bronchiolitis	Bronchiolitis	Prevenar 13	Dose 3	1	13	SE	Yes
60963005	004275	Pyrexia	Fever	Prevenar 13	Dose 2	8	3	SE	Yes
6096500	001824	Infantile spasms	Infantile	Prevenar	Dose 2	38	C	SE	Yes

			spasms						
6096501	000205	Pyrexia	High fever	Prevenar	Dose 3	2	6	MO	Yes
6096501	001430	Febrile convulsions	Febrile seizures	Prevenar	Dose 3	2	2	SE	Yes

Abbreviation: C = continuing.
a. Mild (MI), moderate (MO), severe (SE), or life-threatening (LT).
b. Based on investigator assessment.
c. The investigator initially determined that this event was related to the test article, since there was no other explanation. However, autopsy results revealed that the cause of death was sudden infant death syndrome (SIDS) and the investigator has since changed his assessment of causality, determining that the death was not related to test article

Serious AEs that the investigations considered related to study vaccine were reported for 13 subjects (7 in the Prevenar 13 and 6 in the Prevenar vaccine group) (Table 2-8). In the catch-up study, SAEs were reported for 9 subjects. None of these SAEs were considered related to study vaccine. AEs related to study vaccine included *injection site reactions, diarrhea*, and *rhinitis.* The incidence of SAEs for each of the study periods was 4.5% or less for each vaccine group. By far, the most frequently reported SAEs were *infections and infestations.*

Adverse events of clinical interest

Some AEs of potential clinical interest were individually evaluated. *Anemia* and *immune system disorders*, were evaluated more closely because of more striking numerical differences between the groups, and additional events (*wheezing diagnoses, apnoea*), were reviewed because of an association with Prevenar or vaccines in general.

Anaemia
During the infant series, *anaemia* (PT) was reported at a higher incidence in the Prevenar 13 group than in the Prevenar group (1 subject, 0.04%). All cases of *anaemia*, including the MedDRA preferred terms *anaemia, iron deficiency anaemia,* and *microcytic anaemia*, were reviewed. These events were reported in a total of 39 subjects: 30 subjects vaccinated with Prevenar 13 and 9 subjects vaccinated with Prevenar. Only 1 case was considered by the investigator to be related to study vaccine *(anaemia* in a subject vaccinated with Prevenar 13).

Table 2-9: Percent (%) of Subjects with Adverse Events: Dose 1, Dose 2, Dose 3 and Toddler Dose (All 12 Infant Studies) with reference to anaemia.

SOC/PT	Dose 1		Dose 2		Dose 3		Toddler dose	
	Prevenar 13 N=4423	Prevenar N=2451	Prevenar 13 N=4213	Prevenar N=2329	Prevenar 13 N=3484	Prevenar N=1850	Prevenar 13 N=1701	Prevenar N=1210
Any event	17683(37.6)	881(35.9)	1854(44.0)	993(42.6)	1348(36.5)	687(37.1)	561(33.0)	430(35,8)
Blood and lymphatic system disorders	9(0.2)	2(0.1)	10(0.2)	2(0.1)	13(0.4)	5(0.3)	6(0.4)	4(0.3)
Anaemia	6(0.1)	0(0.0)	6(0.1)	2(0.1)	6(0.2)	1(0.1)	4(0.2)	3(0.2)
Iron deficiency anaemia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4(0.1)	1(0.1)	2(0.1)	1(0.1)
Leukocytosis	2(0.0)	1(0.0)	1(0.0	0(0.0)	1(0.0)	0(0.0)	0(0.0)	0(0.0)
Lymphadenopathy	1(0.0)	0(0.0)	1(0.0)	1(0.0)	1(0.0)	2(0.1)	0(0.0)	0(0.0)
Lymphadenitis	0(0.0)	0(0.0)	1(0.0)	1(0.0)	1(0.0)	0(0.0)	0(0.0)	0(0.0)
Microcytic anaemia	0(0.0)	1(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Neutropenia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.0)	0(0.0)	0(0.0)
Thrombocytaemia	0(0.0)	0(0.0)	0(0.0)	1(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Thrombocytopenia	0(0.0)	0(0.0)	1(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Immune System Diagnoses
After dose 2 in the infant series, the incidence of *immune system disorders* was higher in the Prevenar 13 group (12 subjects, 0.3%) than in the Prevenar group (0 subjects, 0.0%) Only 1 event was considered by the investigator to be related to study vaccine*: allergy to vaccine,* which occurred in temporal association with Prevenar 13 vaccination. The AEs that accounted for most of the difference in incidence between vaccine groups were milk allergy and food allergy. There was no evidence of

temporal association with the vaccine for these events, and none were considered to be related to vaccination.

Wheezing

A post-marketing observational surveillance study of infants vaccinated with Prevenar has shown an increased risk of hospitalization for various conditions collected under the term "*wheezing diagnoses"* when compared with a historical control group. This increase was seen after the primary series in children vaccinated with DTaP, but not DTP-HbOC or over the duration of the study. Other analyses in the study, as well as the long-term follow-up of the large-scale, multicenter, controlled pivotal efficacy study, did not confirm this finding**.**

The overall incidence of diagnoses related to *wheezing* and *asthma* was 2.9% in the Prevenar 13 group and lower for both vaccine groups in the other study periods. When the terms "*bronchiolitis"* and "*bronchitis*" are added to the above mentioned events, the overall incidence during the infant series increases to 13.9% in the Prevenar 13 group and 13.2% in the Prevenar group. Adding in the 2 terms related to RSV infections, the overall incidence was 15.1% for Prevenar 13 and 14.0% for Prevenar during the infant series. The incidence of the defined "*wheezing diagnoses*" was consistently similar between the Prevenar 13 and Prevenar groups.

Table 2-10: Number (%) of subjects with selected respiratory terms: Infants series, Between Infant series and Toddler dose, Toddler dose(all 12 Infant Studies)

SOC/PT	Infant Series		Between Infant Series and Toddler Dose		Toddler Dose	
	Prevenar 13 N=4423	Prevenar N=2451	Prevenar 13 N=1863	Prevenar N=1357	Prevenar 13 N=1701	Prevenar N=1210
Any event	128(2.9)	60(2.4)	11(0.6)	14(0.1)	10(0.6)	11(0.9)
Respiratory, thoracic and mediastinal disorders	128(2.9)	60(2.4)	11(0.6)	14(0.1)	10(0.6)	11(0.9)
Wheezing(asthma, status asthmaticus, wheezing, bronchial hyper reactivity, bronchospasm and reactive airway disease)	128(2.9)	60(2.4)	11(0.6)	14(0.1)	10(0.6)	11(0.9)
Selected terms	614(13.9)	323(13.2)	58(3.1)	30(2.2)	56(3.3)	56(4.8)
Wheezing/Bronchiolitis/Bronchitis	614(13.9)	323(13.2)	58(3.1)	30(2.2)	56(3.3)	56(4.8)

Apnoea

All cases of *apnoea* (MedDRA PTs of *apnoea, sleep apnoea syndrome*, and *apnoeic attack*). These events were reported for 3 subjects (0.07%) vaccinated with Prevenar 13 and for 3 subjects (0.12%) in the Prevenar group. The events were *serious* in 3 subjects in the Prevenar 13 group and in 1 subject in the Prevenar group. None of the events were considered related to study vaccine, and none were associated with prematurity.

Seizures

*Seizures (*MedDRA PTs of *febrile convulsions, convulsions, partial seizures*, and *epilepsy*) were reported at similar frequencies in the Prevenar 13 and Prevenar groups, with no statistically significant differences in incidence between the 2 groups in any study period.

Table 2-11: Number (%) of Subjects with Seizures (Combined terms): Infant Series, Between Infant Series and Toddler Dose, Toddler Dose and 6-Month Follow-Up telephone Contact (All 12 Infant Studies)

SOC PT	Infant series		Between Infant Series and Toddler Dose[a,b]		Toddler Dose[b]		6-Month Follow-up[c]	
	Prevenar 13 N=4423	Prevenar N=2451	Prevenar 13 N=1863	Prevenar N=1367	Prevenar 13 N=1791	Prevenar N=1210	Prevenar 13 N=950	Prevenar N=455
Seizures[d]	5 (0.1)	1(0.0)	7(0.4)	3(0.2)	2(0.1)	2(0.2)	3(0.3)	1(0.2)

Infant series = from dose 1 through postinfant series blood draw.
Between infant series and toddler dose = from the post infant series blood draw through the toddler dose.
Toddler dose = from the toddler dose through the post toddler dose blood draw.
Mixed model used to calculate difference between vaccine groups in percentages of subjects reporting an event(random effect for protocol).
*. Denotes significant difference in incidence between Prevenar 13 and Prevenar at the 0.05 (2-sided) level.
a. Adverse events were collected differently for the period between the infant series and the toddler dose thanthey were for the infant and toddler doses. At the toddler dose visit, parents/guardians were to report any newchronic medical condition and any serious adverse events that had occurred since the previous visit.
b. Post infant series data are available for 6 studies: 003, 004, 006, 009, 500, and 501.
c. 6-Month follow-up data are available for 3 studies: 003, 004, and 009.
d. "Seizures" includes MedDRA preferred terms of partial seizures, convulsion, febrile convulsion, and epilepsy.

Lymphadenopathy
"*Lymphadenopathy localized to the region of the injection site*" was identified as an ADR associated with Prevenar, based on post-marketing experience. Adverse events corresponding to the MedDRA PTs of *lymphadenopathy* and *lymphadenitis* were reported in a few subjects in both the Prevenar 13 and Prevenar groups during the infant studies of Prevenar 13.

Hypersensitivity Reaction
"*Hypersensitivity reaction including face oedema, dyspnoea, bronchospasm*" was identified as an ADR for Prevenar based on post-marketing reports. The Prevenar 13 safety data were reviewed for the specific MedDRA PTs of *hypersensitivity*, *face oedema, dyspnoea,* and *bronchospasm.* There have been no reports of *face oedema* in trials of Prevenar 13, and all cases of *hypersensitivity, dyspnoea*, and *bronchospasm were* determined to be related as there was no temporal association with the vaccine.

Flushing
In addition is should be noted that the Swedish MPA forwarded a summary of safety reactions reported for Prevenar to the MAH during the period of 2007-01-01 to 2008-08-01 requesting information about: Flush reactions occurring within minutes after injection with Prevenar and which disappear within minutes 10-15 minutes have been reported. Sometimes it is limited to the injected thigh, sometimes it spreads to the other thigh or the whole legs and sometimes the whole body turns red". In the assessment of FUM 120 for Prevenar was concluded:

No cases of *flushing* were presented specifically and were not discussed or commented on. However, *"Facial flushing* "was reported from 3 cases enrolled in one of the 14 studies of the Prevenar 13 vaccine according to the search conducted on the Wyeth safety surveillance database. From the safety data base of Prevenar and Prevenar 13 a total of 1746 case reports were identified describing at least one of the search terms: *Injection site erythema erythema, generalised erythema, rash erythematous*, *flushing* and *hot flush*. According to the case definitions described by the MPA, 244 reports were selected for further analysis. The preferred terms *Flushing* and *hot flush* were recorded in 17 and 2 of the 244 reports respectively. *Facial flushing* was reported from 3 cases enrolled in one of the 14 studies of the Prevenar 13 vaccine currently in development.

- Laboratory findings

No specific laboratory findings.

- Safety in special populations

High risk paediatric populations have so far not been studied in the present development program.

- Safety related to drug-drug interactions and other interactions

Effect of prophylactic medication on reactogenicity
The systematic evaluation of the effect of prophylactic medication (paracetamol) on the reduction of febrile reactions following the concomitant administration of Prevenar and Infanrix hexa has been concluded in a study conducted by the company. The results show that prophylaxis can significantly reduce fever following the infant doses but has less effect following the booster dose. Another study showed that prophylactic use of acetaminophen significantly reduces the fever in infants 2-6 months of age post vaccination but there were no significant reduction in infants > 6 months. A similar study of prophylactic use of ibuprophen showed no significant effect on fever >38°C. The use of different concomitant vaccines would be expected to have an impact on temperature ranges between studies.

Additional analyses of clinical data on antipyretic use and immunogenicity
During the procedure, data on antipyretic use on Day 1 and both IgG and OPA immune responses were presented for infants and toddlers. The analysis that was provided pooled the data across all 13

clinical trials in the Prevenar 13 dossier. Pooled analyses across trials simplify the results for 13 serotypes across 13 trials, but also limit the ability to assess trial-level effects.
The data indicate that any reduction in antibody response following vaccination with Prevenar 13 is negligible and not medically relevant and does not follow any consistent pattern. These data are particularly reassuring as they represent common medical practice on the use of antipyretics following vaccination in the different countries where the studies were conducted.

- Discontinuation due to adverse events

Withdrawals and Vaccination Discontinuations
Overall, an AE resulted in the withdrawal from the study for 36 infants, of whom 21 (0.47%) were in the Prevenar 13 group and 15 (0.61%) in the Prevenar group). In both groups, the AE occurred during the infant series (n=22) or during the period between the infant series and the toddler dose (n=14). The most frequent AEs resulting in withdrawal from the study included *nervous system disorders* (8 subjects in each group) and *infections* (5 subjects in the Prevenar 13 group and 3 subjects in the Prevenar group).

Study 011 on hold in India
113 subjects were withdrawn because of a clinical hold by the DCGI (Drugs Controller General of India) 10-Oct-2007 were all from cohort 1 in Study 011, conducted in India. Four reports of serious adverse events (SAEs) that was unexpected and conducted outside of India were received and all of them had occurred in subjects who had received Prevenar (Prevenar, licensed in India) and considered possibly related to study vaccine. Although the hold in India was lifted and Study 011 was continuing at all sites by December 2007, this delay in vaccinations resulted in the discontinuation of many subjects from the study. An additional cohort 2 was enrolled including 354 subjects.

- Post marketing experience

Not applicable.

Discussion on clinical safety

The integrated safety database includes data for 6929 subjects randomly assigned to treatment in the 12 infant studies: 4458 were assigned to Prevenar 13 and 2471 to Prevenar. One study 3002 included 354 children older than 6 months and up to 5 years.

The results of the meta-analysis of safety data from all studies demonstrate that Prevenar 13 has a similar local reactogenicity profile as Prevenar. Numerically significant differences were small and no consistent pattern in differences was seen across doses. A trend towards increased rate of *tenderness* with age at first dose was seen throughout all 3 age group. There was no age or dose related differences in erythema or indurations. However, there was a tendency toward increased *tenderness* with age overall and with subsequent dose administration. Older subjects generally exhibited increased rate of local reactions compared with the infants.

Fever $\geq$ of 38ºC were recorded for between 24.4% and 38.4% of subjects in each vaccine group after each dose in the infant series. Numerically significant difference between the vaccine groups in the incidence of fever was noted after dose 1. In the older subjects febrile reactions were less common than in infants. The proportion of infants and children receiving an antipyretic medication, given either to treat or to prevent symptoms, were not different between the 2 vaccine groups.
Regarding the effect of antipyretic use on the immunogenicity of vaccine, the current database is limited as critical information such as the purpose of the antipyretic treatment (preventive or curative), the name of the antipyretic, the dose and exact time of administration in relation to vaccination have not been recorded. Therefore, the company has committed (FUMs) to collaborate with other

companies to investigate the possible "class effect" of antipyretic use on the immunogenicity of vaccine.

Adverse events of special interest included wheezing diagnoses, apnea, convulsions/seizures, and anaphylaxis/hypersensitivity which were addressed in the pharmacovigilance plan with pre-specified endpoints in the post authorisation safety study and as pre-specified topics for review in PSURs. Apnea, convulsions/seizures, and anaphylaxis/hypersensitivity have also been included in section 4.8 of the SPC.

No new or important safety signals were identified in any of the Prevenar 13 clinical studies. Based on the study results the reactogenicity profile of Prevenar 13 could be considered to be similar to that of Prevenar, with no clinically significant difference in the frequency or severity of AEs reported among infants in the clinical studies. In addition to the AEs that have been noted for Prevenar 13 in the Prevenar 13 clinical program, section 4.8 (Undesirable Effects) of the SPC also includes ADRs that were reported during the Prevenar clinical development program as well as during Prevenar post-marketing experience.

The safety and immunogenicity of Prevenar 13 in HIV positive children and sickle cell children is to be addressed in several post-marketing studies.

With respect to switching of vaccines, a new safety concern, one of "missing information", has been added to the RMP: transition plan. Planned pharmacovigilance activities for this concern are monitoring for vaccine failure occurring during the 2-3 month transition through collaboration with the national surveillance systems and PSUR analysis. Planned risk minimisation activities for this concern include a Dear Health Care Professional Letter to describe how transition should be conducted for children who started with Prevenar and clear visual differentiating the two vaccines.

The impact of Prevenar 13 on nasopharyngeal carriage is being investigated through both observational surveillance after vaccine introduction in France and a clinical trial, comparing isolates obtained from children receiving Prevenar with those obtained from children receiving Prevenar 13, a study which is currently ongoing in Israel. These activities have been assessed satisfactory.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

Table 3.1. Summary of EU Risk Management Plan (version 3.2).

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
A. Important identified risks:		
No important identified risks requiring further follow-up have been identified.	Post-approval observational safety study and routine pharmacovigilance to monitor the safety profile of Prevenar 13 vaccine	None
B. Important potential risks:		
Unanticipated safety signals not seen in clinical trials of Prevenar 13 vaccine	Post-approval observational safety study 4002 in at least 43,000 children vaccinated with Prevenar 13 to monitor the safety profile of Prevenar 13. The study is designed to evaluate rates of all medically attended events in the hospital and emergency department settings and pre-specified events in hospital, emergency department, and outpatient clinic settings. Anaphylaxis, hypersensitivity, seizures, convulsions, wheezing, and apnea events will be included as pre-specified endpoints in the study (see Annex 3 in Section 8.3 for study protocol of the RMP).	None
Vaccine failure in children who are fully immunized according to local recommendations	Post-approval adverse event reports of vaccine failure. Follow-up questionnaire of vaccine failure reports to ascertain whether serotype information was collected	SPC warning that as with any vaccine, Prevenar 13 may not protect all individuals.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
C. AEs which were not associated with Prevenar 13 in clinical trials or with Prevenar in post-authorisation observational safety studies, but are included in the Prevenar SPC:		

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
- Wheezing diagnoses - Apnea - Convulsions/seizures - Anaphylaxis/hypersensitivity	Wheezing diagnoses, apnea, convulsions, seizures, anaphylaxis and hypersensitivity will be pre-specified endpoints in the post-authorisation observational safety study (4002) and will be tracked as pre-specified topics in PSURs.	None
D. Important missing information:		
Effectiveness of Prevenar 13 consistent with the high effectiveness of Prevenar	Population-based surveillance of the incidence rates of IPD in 5 European countries for 5 years using national surveillance systems (in France, Germany, the Netherlands, Norway and the UK), pneumonia rates in the UK and Netherlands, and AOM rates in the UK for 5 years	None
Potential changes in the epidemiology of non-vaccine *S pneumoniae* serotypes associated with reductions in vaccine serotypes	The 5 European population-based surveillance systems will be used to monitor potential changes in non-Prevenar 13 serotypes for 5 years	None
Long-term vaccine effectiveness	European, Canadian and US surveillance systems will be used to monitor long-term effectiveness	None
Safety and immunogenicity in high risk pediatric populations: HIV-infected children Premature infants <37 weeks of gestational age Children with sickle cell disease previously immunized with 23-valent PS vaccine	Clinical trials of safety and immunogenicity in HIV-positive children, premature infants, and children with sickle cell disease previously immunized with 23-valent PS vaccine	SPC warning that children with impaired immune responsiveness may have reduced antibody responses

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
Impact of Prevenar 13 on nasopharyngeal carriage, including monitoring replacement with non-pneumococcal bacteria in the nasopharyngeal flora of children.	Ongoing surveillance of nasopharyngeal carriage of *S. pneumoniae* in France through the ACTIV program and in a clinical trial in Israel (Study 3006). Monitoring of replacement with non-pneumococcal bacteria in the nasopharyngeal flora of children in France through the ACTIV program.	None
Safety of more than 4 doses of CRM-based pneumococcal conjugate vaccine when Prevenar 13 is administered for protection against the 6 additional serotypes in children previously vaccinated with a primary series of Prevenar	Two studies (Study 3011 in the US and Study 3010 in Alaska) will assess the safety of more than 4 doses of Prevenar 13 for catch-up program considerations	None
Immunogenicity of 1 booster dose of Prevenar 13 against the 6 additional serotypes after a primary series of Prevenar	Study 3011 catch-up study to confirm the Study 008 results that 1 toddler booster dose of Prevenar 13 provides adequate immunogenicity against the additional 6 serotypes among children who have received a primary series of 3 doses of Prevenar	SPC Section 4.2 states that protective immunity to the 6 new serotypes requires age-appropriate dosing as described in the posology section

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
D. Important missing information (Cont'd):		
Transition Plan	Vaccine failures occurring during the 2-3 month transition period will be evaluated by the UK, French, German, Dutch and Norwegian national surveillance programs. Vaccine failure reported to the Company via routine pharmacovigilance activities will be reviewed. PSUR analysis will identify all reports of vaccination failure occurring in patients who are transitioning from Prevenar to Prevenar 13.	The MAH will inform health care professionals about a) the differentiating characteristics of Prevenar 13 and Prevenar vaccines, i.e. differences in packaging, the product label and different colour of syringe and tip cap and b) how to transition to Prevenar 13 for children who started a vaccination schedule with Prevenar. In order to ensure that potential adverse event reports can be unambiguously linked to the type of vaccine administered, the MAH will ensure that the two vaccines have different batch numbers, different color of the plunger and tip cap of the syringe, and different carton packaging and label.

Transition Plan

Following marketing authorization approval of Prevenar 13 Infant vaccine, the switch-over from Prevenar to Prevenar 13 vaccine will occur according to a structured transition plan summarized in Table 3.2.

Table 3.2. Transition Plan

GOALS	
Ensure the uninterrupted supply of Prevenar or Prevenar 13	• Supplies of Prevenar 13 vaccine will be available at launch
Clear visual differentiation of vaccines	• Different carton packaging • Different product label on syringe • Different colour of the plunger and tip cap of syringe
Inform health care professionals about the transition	• The MAH will agree with national competent authorities on a communication to health care professionals about the differentiating characteristics of Prevenar 13 and Prevenar vaccines, and how to transition to Prevenar 13 for children who started a vaccination schedule with Prevenar.

GOALS	
Ensure potential and adverse event reports can be unambiguously linked to the type of vaccine administered	• Batch number • Different colour of the plunger and tip cap of the syringe • Different carton packaging and label

The CHMP, having considered the data submitted in the application, is of the opinion that additional risk minimisation activities are required beyond those included in the product information:

> The MAH should inform health care professionals about the differentiating characteristics of Prevenar 13 and Prevenar vaccines, i.e. differences in packaging, the product label and different colour of syringe and tip cap and how to transition to Prevenar 13 for children who started a vaccination schedule with Prevenar.
>
> In order to ensure that potential adverse event reports can be unambiguously linked to the type of vaccine administered, the MAH shall ensure that the two vaccines have different batch numbers, different colour of the plunger and tip cap of the syringe, and different carton packaging and label.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The manufacture of the Pneumococcal polysaccharides, the monovalent bulk conjugates and the final sterile liquid suspension are appropriately controlled. Adequate release and shelf life specifications have been set. Commitments are made by the applicant to update some missing information, which does not impact on the risk/benefit assessment of this vaccine.

Non-clinical pharmacology and toxicology

The non-clinical program was in accordance with CHMP guidelines. The immunogenicity of the vaccine was demonstrated in animal models. No important safety concerns were identified.

Efficacy

The 13-valent pneumococcal conjugate vaccine (Prevenar 13) was demonstrated to induce an immune response to all 13 serotypes in all 3-dose primary vaccination schedules (6-10-14 weeks, 2-3-4 months and 2-4-6 months). The vaccine induced a functional immune response as measured by opsonophagocytic (OPA) assay. The majority of subjects who received a 3-dose primary series achieved an antibody concentration $\geq$0.35µg/ml (90.5-99.5%) and an OPA titre $\geq$1:8 (84-100%), except for certain serotypes. For 12 of the 13 serotypes (except serotype 3), a good priming effect of the 3-dose and 2-dose schedules was shown with an anamnestic response following a booster dose. These data indicate the presence of an immune memory. The immune response to routine paediatric vaccines co-administered with Prevenar 13 was assessed and no clinically relevant immune interferences were observed.

The Prevenar 13 vaccine was demonstrated to be slightly less immunogenic than Prevenar overall and, in particular, with regard to certain serotypes (6B and 9V). The clinical relevance of this finding is not known, but will probably not affect vaccine efficacy against the 7 common serotypes. Also, the clinical trial results demonstrated that functional immune response elicited by Prevenar 13 was low for 3 of the 6 additional serotypes. Although the meaning of a low OPA GMT value for an individual serotype is not known, that may suggest reduced efficacy against invasive disease caused by these serotypes.

Safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

A user consultation test has been performed and was considered to be acceptable.

Risk-benefit assessment

Benefits

The introduction of Prevenar in the childhood immunisation program in the US in the year 2000 have resulted in a dramatic decline in rates of IPD due to the 7 vaccine serotypes in the target group, as well as in unvaccinated older subjects (herd protection). Significant reductions of pneumococcal AOM and pneumonia in children have also been demonstrated. Prevenar has 80 to 90% serotype coverage in the US, but somewhat lower in Europe (60-80%) and in other continents (40-80%). The Prevenar 13 vaccine with the additional serotypes 1, 3, 5, 6A, 7F and 19A is expected to provide an increased coverage of approximately 90% of serotypes responsible for IPD in children aged <5 years in most regions of the world, and more than 73-100% of isolates in Europe. The 13-valent vaccine includes serotypes responsible for a substantial burden of pneumococcal disease in Europe, such as serotypes 6A and 19A, as well as serotypes 1 and 3 associated with complicated pneumonia and pleural empyemas and serotype 7F associated with a higher risk of more severe invasive disease.

Uncertain benefits include the efficacy of the Prevenar 13 vaccine against serotypes 1, 3, and 5 in pneumonia and otitis media. The results demonstrated that functional immune response elicited by Prevenar 13 was lower for 3 of the 6 additional serotypes compared with all the other vaccine serotypes. The OPA GMTs for the concerned additional serotypes in Prevenar 13 lay in the same range as those for 19F and 6A in Prevenar. For protection against non-invasive disease higher antibody titres are required and it is questioned whether the OPA titres observed for serotypes 1, 3 and 5 would be sufficient to protect against pneumonia and otitis media due to these serotype. The poor boostability observed for serotype 3 is of unknown clinical relevance, but may result in reduced vaccine efficacy against pneumococcal disease due to this serotype.

Risks

The safety profile of Prevenar 13 is comparable to the licensed 7-valent pneumococcal conjugate vaccine (Prevenar) and no new or significant risks have been identified. The Prevenar 13 vaccine is commonly associated with range of local and systemic reactions. These adverse events are not often of severe intensity and the safety profile would not preclude the use of Prevenar 13 for primary vaccination, booster vaccination or catch-up vaccination.

Data showing that after introduction of earlier vaccines, e.g. 7-valent pneumococcal conjugate vaccine and Hib vaccine, diseases caused by vaccine-related serotypes decreased dramatically and an increase of infections caused by other serotypes (e.g. pneumococcal serotype 19A) was noticed. Serotype replacement is considered as an important potential risk which must be included in the risk management plan. Data showing that after introduction of Prevenar, diseases caused by vaccine

serotypes decreased dramatically and an increase of infections caused by other serotypes in particular 19A was noticed. Risk minimisation measures are in place. Monitoring of replacement with non-pneumoccal bacteria, like staphylococci, have also been included in the risk management plan.

The Prevenar 13 may induce suboptimal vaccine efficacy to certain serotypes with a risk of breakthrough infections and only short term persistence of efficacy.

The 2-dose primary schedule in infants resulted in lower immune responses than the 3-dose primary series, in particular with regard to serotypes 6B and 23F, which could result in suboptimal protection against IPD and AOM during the pre-booster period.

It has to be noted that there are no data demonstrated for use in the populations at high risk for infection with the pneumococcus. Any use in these populations may not provide satisfactory protection and could result in break-through infections.

Balance

The overall benefit/risk of Prevenar 13 is considered favourable.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- Pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

- Additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Prevenar 13 for the "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" was favourable and therefore recommended the granting of the marketing authorisation.