



European Medicines Agency
Evaluation of Medicines for Human Use

ASSESSMENT REPORT

FOR

Synflorix

Common Name: **Pneumococcal polysaccharide conjugate vaccine (adsorbed)**

Procedure No. EMEA/H/C/000973

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

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LIST OF ABBREVIATIONS

11Pn-PD	Undecavalent (11-valent) pneumococcal protein D conjugate (vaccine). Serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.
11Pn-PD&Di	Undecavalent (11-valent) pneumococcal protein D and diphtheria toxoid conjugate (vaccine). Serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.
11Pn-PD-DiT	Undecavalent (11-valent) pneumococcal protein D, diphtheria toxoid and tetanus toxoid conjugate (vaccine). Serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F & 23F.
23vPS	23-valent pneumococcal vaccine Pneumovax 23
AOM	Acute otitis media
ATP	According to protocol
CDAP	(1-cyano-4-dimethylamino-pyridinium tetrafluoroborate)
CDC	Centers for Disease Control and Prevention, Atlanta, USA
CFU	Colony forming unit
CI	Confidence interval
C-PS	Cellular polysaccharide
DT or Di	Diphtheria toxoid
DTPa	Diphtheria, tetanus and pertussis (acellular) vaccine
ELISA	Enzyme linked immunosorbent assay
ESMS	Electrospray Mass Spectroscopy
GMC/T	Geometric Mean Concentration/Titre
GSK	GlaxoSmithKline
HAV	Hepatitis A virus (vaccine) (<i>Havrix</i>)
HBV	Hepatitis B virus (vaccine)
Hib	<i>Haemophilus influenzae</i> type b
HPSEC	Size exclusion HPLC
HRV	Human Rotavirus Vaccine
IEF	Isoelectric focusing
IPD	Invasive pneumococcal disease
IPV	Inactivated poliomyelitis (vaccine)
LAL	<i>Limulus</i> amoebocyte lysate
MALLS	multiple angle laser light scattering
MenC	<i>Neisseria meningitidis</i> polysaccharide C
MenC-TT	Meningococcal C-tetanus toxoid conjugate vaccine
Meningitec	Wyeth's meningococcal group C oligosaccharide-CRM ₁₉₇ conjugate vaccine
MMRV	Measles, mumps, rubella and varicella vaccine (<i>Priorix tetra</i>)
MSD	Molecular size distribution
NeisVacC	Baxter's meningococcal grp C polysaccharide-tetanus toxoid conjugate vaccine
NTHi	Non-typeable <i>Haemophilus influenzae</i>
OD	Optical density
OPA	Opsonophagocytic assay
OPV	Oral poliomyelitis (vaccine)
PD	Protein D
Pneumovax 23	Sanofi-Aventis' 23-valent pneumococcal polysaccharide vaccine
POET	Pneumococcal Otitis Efficacy Trial
Prevenar	Wyeth's 7-valent pneumococcal saccharide CRM ₁₉₇ conjugate vaccine. Serotypes: 4, 6B, 9V, 14, 18C, 19F and 23F.
Priorix tetra	GSK Biologicals' measles, mumps, rubella and varicella vaccine
PS	Polysaccharide
RCDC	Reverse cumulative distribution curve
Rotarix	GSK Biologicals' live attenuated human rotavirus vaccine
SAE	Serious adverse event
SD	Standard deviation
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
SOP	Standard operating procedure
TT	Tetanus toxoid
WHO	World Health Organisation

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant GlaxoSmithKline Biologicals S.A. submitted on 30 December 2007 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Synflorix, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 June 2006.

The legal basis for this application refers to:
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 tests or studies.

Scientific Advice:

The applicant received Scientific Advice from the CHMP on 25 July 2003 and 29 July 2005. The Scientific Advice pertained to quality and clinical aspects of the dossier.

Licensing status:

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 EMA on 30 December 2007.
- The procedure started on 30 January 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 April 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 20 April 2008.
- The Biologics Working Party during its meeting of 19-21 May 2008 adopted a BWP Report to be transmitted to the CHMP for endorsement.
- During the meeting on 27-30 May 2008 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 30 May 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 August 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 October 2008.
- The Biologics Working Party during its meeting of 13-15 October 2008 adopted a BWP Report to be transmitted to the CHMP for endorsement.
- During the CHMP meeting on 20-23 October 2008, 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 18 December 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 January 2009.
- The Biologics Working Party during its meeting of 12-14 January 2009 adopted a BWP Report to be transmitted to the CHMP for endorsement.

- During the meeting on 19-22 January 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 Synflorix on 22 January 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 16 January 2009.
- The CHMP opinions were forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decisions on 30 March 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Streptococcus pneumoniae is the leading cause of invasive pneumococcal disease (IPD) (including septicemia, meningitis, and bacteraemic pneumonia) and non invasive pneumococcal diseases (such as acute otitis media (AOM), non-bacteraemic pneumonia, sinusitis, and bronchitis) in young children. WHO estimates that about 16 million people, including up to 1 million children under 5 years old, die every year of pneumococcal disease. The highest incidence of IPD is found at the extremes of age - in young children <2 years of age and in elderly adults. The highest morbidity and mortality rates have been reported in developing countries, but the disease burden is considerable also in industrialised countries. Extrapolation of data on hospitalizations due to IPD from England and Wales (prior to introduction of Prevenar) to the EU paediatric population <5 years of age indicate that there would be 6500 IPD cases and 61,000 pneumonia cases annually. Acute otitis media is most prevalent in early childhood and it has been estimated that each year in the EU 2.1 million AOM cases occur in children <5 years of age. Bacteria are isolated in ~70% of 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, 6B, 9V, 14, 19A, 19F, and 23F) among the resistant organisms is shared.

Pneumococcal capsular polysaccharide vaccines have been licensed since 1977. The 23-valent unconjugated vaccines (23vPS) are designed to provide coverage of ~90% of the most frequently reported isolates. These vaccines do not, however, induce immune memory and children below 2 years of age do not respond to polysaccharides. By using conjugate technology the polysaccharide antigens can induce a T-cell response, enabling its use in young children. Prevenar, containing 7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) individually conjugated to CRM₁₉₇ protein was the first pneumococcal conjugate vaccine being licensed in the EU (2001) for use in children from 2 months of age for the prevention of IPD. Efficacy was 97.4% in preventing vaccine-serotype IPD and 57% against vaccine-serotype pneumococcal AOM. Synflorix is a second generation vaccine being developed and contains other carrier proteins (protein D, DT and TT) and three more pneumococcal serotypes (1, 5 and 7F) in addition to the seven shared with Prevenar. The three additional serotypes are among the major IPD-causing serotypes worldwide and represent in Europe a combined average of 13% of all IPD in children <5 years of age. Protein D was selected as a carrier protein, due to its potential to provide protection against *H. influenzae* infections.

There are at least 91 distinct pneumococcal serotypes, but only 10 to 15 cause the vast majority of IPD worldwide. The global epidemiology of pneumococcal serotypes and their role in disease differ between continents. However, worldwide a limited set of 7 serotypes (= 1, 5, 6A, 6B, 14, 19F and 23F) account for 66-76% of IPD among children <5 years of age across regions. The most common serogroups responsible for paediatric IPD in the industrialised countries are in descending order: 14, 6, 19, 18, 23, 9, 1, 7, 4, and 5, whereas other serogroups predominate in the developing countries. The epidemiology in Europe differs from that in the US, mainly by the serotypes 1, 5 and 6A being more common. Prevenar serotypes account for more than 50% of IPD isolates worldwide and covers in Western Europe at least two-thirds of all isolates. Synflorix is estimated to cover at least two-thirds of all invasive isolates in children aged <5 years in virtually all countries studied and more than 80% of isolates in Western Europe.

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 from an average of 17,240 cases per year in the pre-vaccination era to 4,454 cases in 2003. A significant decline in IPD caused by penicillin-resistant strains has also been reported. In addition, substantial decreases in IPD in other, non-

immunized age groups have been documented, and the number of cases prevented through this 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 serotypes not contained in the vaccine. 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 awaited.

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). These criteria (published in WHO technical Report Series (TRS) 927, annex 2), with additional emphasis on the assessment of the functionality of the anti-pneumococcal antibodies measured by the OPA assay, were confirmed in a WHO sponsored follow-up meeting (World Health Organization (WHO) 2008. *WHO/Health Canada Consultation on Serological Criteria for Evaluation and Licensing of New Pneumococcal Vaccines*, 7-8 July 2008, Ottawa, Canada)¹.

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 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.

¹ Meeting report published on the WHO website:

<http://www.who.int/biologicals/publications/meetings/areas/vaccines/pneumococcal/en/index.html>

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.

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 seven serotypes 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 Global Alliance for Vaccines and Immunization (GAVI), given their important contribution to the burden of disease in developing countries. Therefore, new pneumococcal conjugate vaccines including more pneumococcal serotypes would offer additional benefit and expand the pneumococcal disease coverage in infants and young children.

2.2 Quality aspects

Introduction

Synflorix is composed of the capsular polysaccharides purified from 10 serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F each conjugated to a carrier protein, either protein D (PD), tetanus toxoid (TT or T) or diphtheria toxoid (DT).

Protein D is used as carrier protein for 8 out of the 10 serotypes (serotypes 1, 4, 5, 6B, 7F, 9V, 14 and 23F). All polysaccharides conjugated to PD are formulated at a dosage of 1 µg of polysaccharide per dose (serotypes 1, 5, 6B, 7F, 9V, 14, 23F), with the exception of serotype 4 at 3 µg. Serotype 19F conjugated to DT and serotype 18C conjugated to TT are formulated at 3 µg of polysaccharide.

Synflorix is a preservative-free liquid suspension, adjuvanted with aluminium phosphate, and presented as a mono-dose (in glass syringes or glass vials) or two-dose (in glass vials) ready for intramuscular injection. The volume per nominal dose is 0.5ml.

Active Substance

The 10 active ingredients included in Synflorix consist of the *Streptococcus pneumoniae* polysaccharide serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F each conjugated to a carrier protein (either PD, TT or DT).

The purified polysaccharides, tetanus toxoid, diphtheria toxoid and protein D are considered as intermediates.

- Manufacture

The production process of conjugates implies the following main steps:

1. Fermentation of *S. pneumoniae* bacterial strains, followed by inactivation and purification of the **polysaccharides** (PS),
2. Fermentation of *E. coli* for the production of the **recombinant protein D** (PD), followed by PD purification,
3. Fermentation of *Clostridium tetani* for the production of **tetanus toxin** (TT), followed by TT detoxification and purification,
4. Fermentation of *Corynebacterium diphtheriae* for the production of **diphtheria toxoid** (DT), followed by DT detoxification and purification,
5. Production of **conjugates**: coupling of each of the *S. pneumoniae* serotype polysaccharides to either PD, DT or TT utilizing CDAP (1-cyano-4-dimethylamino-pyridinium tetrafluoroborate) as chemical reagent.
6. Purification and sterile filtration of the conjugates.

Process control and/or validation:

The company has established a system of process control during the manufacturing of the active substances using “in-process tests” with assigned specifications and “monitoring tests” used to monitor the process consistency and performance.

Validation of the intermediates and active substance production process was performed by the demonstration of process consistency through compliance with the pre-established quality control (QC) standards and by the identification and validation of the manufacturing process critical parameters.

Consistency was demonstrated for the identified unit-steps of the different intermediates and drug substance production processes. Critical process parameters have been satisfactorily identified and batch data provided.

Production and control of starting materials/intermediates

S. pneumoniae Polysaccharides

Seed lot system: the bacteria used for the preparation of the polysaccharides are strains of *S. pneumoniae* isolated from patients with otitis media. Master and working seeds from these strains were derived and have been grown and stored in the absence of any material of animal origin. Satisfactory quality control testing are in place and satisfactory stability data and storage conditions have been described for these seed lots.

Master and working seeds are tested for purity (by growing the seeds on rich media supplemented with optochin), and identity (by optochin test, gram staining and Quellung reaction).

Fermentation and purification: the production of the polysaccharides of the different serotypes is very similar and differs just in a few aspects of the purification process, depending on the nature of the PS: acid or neutral PS.

The content of a working seed vial is used to inoculate the fermentor; the fermentation occurs under controlled temperature, air-flow rate conditions and stirring, and it is stopped according to optical density (OD) measurement.

At the end of the fermentation, inactivation of bacteria is achieved using phenol added to the fermentation broth.

The pneumococcal polysaccharides are purified by precipitation with appropriate reagents, ultrafiltration and column chromatography. After purification, the polysaccharides are precipitated with alcohol followed by filtration in order to recover the polysaccharide as a pellet which is vacuum dried.

The PS bulks are stored as desiccated powders at -20°C or -70°C depending on the serotype.

The description of the fermentation and purification process of the pneumococcal polysaccharides and the corresponding in-process and release testing is adequate. Critical process parameters have been satisfactorily documented.

Characterisation: Characterisation analyses of polysaccharide bulks documenting identity, structure, size, integrity and content of functional groups (O-acetyl groups, hexosamines, methylpentoses and

uronic acids) were performed. With regard to functional groups, traditional chemical assays and H-NMR were utilized and results compared. H-NMR is used as the routine release test for identity and quantification of functional groups as of the second commercial campaign of polysaccharide bulks. Satisfactory characterization of batches produced at commercial scale were presented.

Impurities: the characterisation of the impurities of the polysaccharides has been satisfactorily described and includes series of bacterial-strain related and process-related impurities. The data presented demonstrate the efficiency and the consistency of the purification process in eliminating process-related impurities.

Specification: the company releases the polysaccharides based upon water content, alcohol content, identity, molecular size distribution, residual protein and nucleic acid content, phosphorous content, nitrogen content, O-acetyl content, hexosamines content, methylpentoses content, uronic acid content, CPS content and endotoxin.

The specifications applied to most of the tests are those recommended by the applicable guidelines (Ph. Eur. 966 guideline 'Pneumococcal Polysaccharide Vaccine'; WHO guideline 'Recommendations for production and control of *S. pneumoniae* conjugate vaccines' (WHO Technical Report Series 927, 2005); Ph. Eur. Monograph 2150 'Pneumococcal polysaccharide conjugate vaccine' (adsorbed)). Analytical methods have been adequately described and validated.

With regard to the H-NMR specifications for functional group contents, the Ph. Eur. specifications based on the traditional chemical assays were adapted using a correlation factor taking into account the intrinsic differences between both methods.

Batch analysis: Batch analysis data are demonstrative of a consistent production process and are compatible with the specifications for the pneumococcal polysaccharides.

Stability: The stability of purified *S. pneumoniae* polysaccharides (PS) is assessed by long-term, real-time stability studies (up to 84 months) on three batches per polysaccharide serotype. Batches are stored at -20°C or -70°C depending on the serotype.

Prior to conjugation, the size of the polysaccharides is mechanically reduced for most of the serotypes. The microfluidised PS bulks are stored at +2-8°C.

Protein D

Protein D (PD) is a 40kDa cell-surface protein originally derived from non-typeable *H. influenzae* and produced from the recombinant *E. coli* strain B1084 (derived from strain AR58). This specific strain is modified to express the outer surface protein of *Haemophilus influenzae*, protein D.

Seed lot system: the genetic construct of the recombinant strain has been acceptably described as is the control of the seed lot system. Tests and specifications applied on the Master Seed (MS) and the current Working Seed (WS) include *E. coli* identification, plasmid retention, microbial purity and antigen identity.

Fermentation and purification: the purified protein D bulk manufacturing process is divided into 2 stages: fermentation and purification. Fermentation covers the *E. coli* preculture in liquid medium and culture in a fermentor including the induction phase for the expression of the protein D. After fermentation, the biomass is homogenised using a high-pressure homogeniser.

The protein D is purified by a series of chromatographic steps and diafiltration, and finally sterile filtered using a 0.22µm filter.

Protein D purified bulk is stored frozen at -45°C.

The description of the fermentation and purification process of the protein D and the corresponding in-process and release testing is adequate. Critical process parameters have been satisfactorily documented.

Characterisation: in addition to the tests conducted in routine for lot release, the following structural properties were analysed: molecular weight by MALLS and Electrospray Mass Spectroscopy (ESMS),

electrophoresis profiles by SDS-PAGE, Western Blot and isoelectric focusing (IEF), primary structure by amino acid analysis, peptide mapping and N-terminal sequence analysis, secondary structure by circular dichroism spectroscopy.

This extensive characterization data package demonstrate the quality, the consistency and the good stability profile of protein D bulk when stored at -45°C.

Impurities: the data presented demonstrate the efficiency and the consistency of the purification process in eliminating process-related impurities.

Specification: Routine release of protein D includes tests such as identity, purity, sterility, protein content and endotoxin content. The specifications proposed for the release of protein D purified bulk have been established based on batch analysis data obtained from the lots produced to date. They are in line with the testing proposed for the control of carrier proteins in the relevant guidelines (WHO guideline 'Recommendations for production and control of *S. pneumoniae* conjugate vaccines (TRS 927, 2005), and Ph. Eur. guideline 2150 'Adsorbed pneumococcal conjugate vaccine').

Analytical methods have been adequately described and validated.

Stability: The stability of protein D at -45°C has been assessed by long-term, real-time stability studies.

Purified tetanus toxoid (TT)

Seed lot system: The strain of *C. tetani* that is used to manufacture purified tetanus toxoid is the Harvard strain No 49205 Y-IV-4. The seed lot system was established using meat-free culture media.

The testing programs performed on the master seed and the working seed are identical and include tests for microbiological purity, colony morphology, haemolysis and purity by microscopic examination.

Fermentation and purification: the manufacturing process of the purified tetanus toxoid consists of three main stages: fermentation, detoxification and purification.

The production of purified tetanus toxoid is performed following the WHO and general GMP requirements. Purified tetanus toxoid, complies with WHO (TRS 800), Ph. Eur. (Monograph 0452) requirements and GSK Bio specification.

The description of the fermentation and purification process of the TT and the corresponding in-process and release testing are adequate.

Characterisation: In addition to the routine QC testing, characterisation was conducted on the purified TT bulks including SDS gel electrophoresis, isoelectric focusing and other physicochemical tests. Consistent results in SDS-PAGE band pattern and other characteristics were obtained for the different parameters assessed.

Impurities: Manufacturing impurities are satisfactorily assessed through the QC release testing program.

Specification: The tests and specifications for release of the TT bulks are complying with WHO (TRS n° 800) and Ph. Eur. requirements on bulk Tetanus Toxoid (Ph. Eur. 0452).

Analytical methods have been adequately described and validated.

Satisfactory batch analysis data demonstrative of a consistent manufacturing process and compatible with present specifications are provided.

Stability: the stability of purified tetanus toxoid at 2-8°C has been assessed by long-term, real-time stability studies. Test methods and specifications applied are the same as those applicable for QC release of the toxoid.

Purified diphtheria toxoid (DT)

Seed lot system: the strain of *Corynebacterium diphtheriae* that is used to manufacture purified diphtheria toxoid was obtained from SmithKline Beecham (Belgium) in 1999. The seed lot system was established using meat-free culture media.

The testing programs performed on the master seeds and the working seeds are identical and include: microbiological purity on blood and TSA agar, colony morphology, haemolysis and microscopic examination (Gram-staining).

Fermentation and purification: the manufacturing process of the purified diphtheria toxoid consists of 3 main stages: fermentation, detoxification and purification.

The production of purified diphtheria toxoid is performed following the WHO and general GMP requirements. Purified diphtheria toxoid, complies with WHO (TRS 800), Ph. Eur. (Monograph 0443) requirements and GSK Bio specification.

The description of the fermentation and purification process of the DT and the corresponding in-process and release testing are adequate.

Characterisation: In addition to the routine QC testing, characterisation was conducted on the purified DT bulks including SDS gel electrophoresis, isoelectric focusing and other physicochemical tests. Consistent results in SDS-PAGE band pattern and other characteristics were obtained for the different parameters assessed.

Impurities: Manufacturing impurities are satisfactorily assessed through the QC release testing program.

Specification: The tests and specifications for release of the DT bulks are complying with WHO (TRS n° 800) and Ph. Eur. requirements on bulk Diphtheria Toxoid (Ph. Eur. 0443). Analytical methods have been adequately described and validated.

Satisfactory batch analysis data demonstrative of a consistent manufacturing process and compatible with present specifications are provided.

Stability: the stability of purified diphtheria toxoid at 2-8°C has been assessed in long-term, real-time stability studies. Test methods and specifications applied are the same as those applicable for QC release of the toxoid.

Pneumococcal polysaccharide conjugates

Manufacture of the bulk conjugates

The conjugation process consists of the following steps:

1. Mechanical reduction of the size and viscosity of the polysaccharides by microfluidisation for most of the serotypes
2. Conjugation of each of the *S. pneumoniae* serotypes polysaccharides to its respective carrier protein is done utilizing CDAP as chemical reagent under controlled pH
3. Conjugates purification by size exclusion chromatography
4. Sterile filtration in aseptic condition

The conjugate bulks are stored at 2-8°C and each adsorbed separately on aluminium phosphate prior to formulation into the final vaccine.

The description of the production process for the polysaccharide conjugation and the corresponding in-process controls and release tests are adequate. Critical process parameters have been satisfactorily documented.

Characterisation

The purified *S. pneumoniae* conjugate bulks are characterised for their molecular properties by routine QC methods. These routine QC tests include structural analyses such as: molecular size distribution, total protein content, total polysaccharide content, and use of said contents for determination of PS/carrier ratio, free PS content and free carrier content. Additional characterisation by biochemical and physicochemical methods were performed, and the overall characterization package provided for the conjugates is adequate.

Impurities

The purity of each conjugate lot is assessed through the QC release testing program and the purification process was also shown to efficiently and consistently eliminate the conjugation reagents.

- **Specification**

The release specifications for the active substance (*S. pneumoniae* conjugate bulks) include: identity, sterility, molecular size distribution, protein content, PS content, PS/carrier ratio, free PS content, free carrier content and endotoxin content.

Analytical methods have been adequately described and validated.

Batch analysis

Batch analysis data for consistency batches used in 10PN-PD-DiT phase III clinical trials and for commercial batches are demonstrative of a consistent production process and for all serotype conjugates, the results of all tests complied with the pre-set specifications.

Container closure system

The closure system is of pharmaceutical grade. The compatibility between the conjugate bulks and primary container/closure materials is demonstrated through stability studies.

- **Stability**

For each serotype, three conjugate batches were stored at 2-8°C and tested according to the stability plan. Critical parameters investigated were: molecular size distribution free polysaccharide content, mean molecular weight by MALLS and free carrier protein content.

Finished Product

Synflorix vaccine is a suspension for injection. The vaccine is formulated on the basis of polysaccharide content and the amount of protein is dependent on the polysaccharide-to-protein ratio (different between serotypes). The pneumococcal conjugates are adsorbed onto aluminium phosphate adjuvant. The formulation is preservative free and the volume per nominal dose is 0.5ml.

All polysaccharides conjugated to PD are formulated at a dosage of 1µg of polysaccharide per dose (serotypes 1, 5, 6B, 7F, 9V, 14, 23F), with the exception of serotype 4 at 3µg. Serotype 19F conjugated to DT and serotype 18C conjugated to TT are formulated at 3µg of polysaccharide.

The composition of Synflorix is as follows:

1 dose (0.5 ml) contains:

Pneumococcal polysaccharide serotype 1 ^{1,2}	1 microgram
Pneumococcal polysaccharide serotype 4 ^{1,2}	3 micrograms
Pneumococcal polysaccharide serotype 5 ^{1,2}	1 microgram

Pneumococcal polysaccharide serotype 6B ^{1,2}	1 microgram
Pneumococcal polysaccharide serotype 7F ^{1,2}	1 microgram
Pneumococcal polysaccharide serotype 9V ^{1,2}	1 microgram
Pneumococcal polysaccharide serotype 14 ^{1,2}	1 microgram
Pneumococcal polysaccharide serotype 18C ^{1,3}	3 micrograms
Pneumococcal polysaccharide serotype 19F ^{1,4}	3 micrograms
Pneumococcal polysaccharide serotype 23F ^{1,2}	1 microgram

¹ adsorbed on aluminium phosphate	0.5 milligram Al ³⁺
² conjugated to protein D (derived from non-typeable <i>Haemophilus influenzae</i>) carrier protein	9-16 micrograms
³ conjugated to tetanus toxoid carrier protein	5-10 micrograms
⁴ conjugated to diphtheria toxoid carrier protein	3-6 micrograms

Synflorix vaccine is presented in neutral glass vials of 3 ml (monodose and 2-dose presentations) stopped with grey butyl rubber stoppers or in pre-filled glass syringes of 1.25 ml (monodose presentation) closed with grey butyl rubber stoppers. The compatibility of the vaccine with the container-closure components is demonstrated through stability studies. The container-closure system is identical to that used for other commercial vaccines manufactured by GSK Biologicals.

- Pharmaceutical Development

Formulation development

The compatibility of the 10 active ingredients with each other was demonstrated in clinical trials, by the satisfactory immune response induced against vaccine antigens. The compatibility between the active ingredients and the excipients is supported by the satisfactory real-time stability data generated at the recommended storage temperature.

Pre-clinical and clinical data are provided demonstrating the need for the vaccine to be adjuvanted. There is no clinically relevant concern for the safety and reactogenicity profile of the adjuvanted vaccine.

The vaccine is preservative free. Normally multidose presentations should be preserved but if the time allowed for use after breaching is short and well justified, a non-preserved multidose presentation can be accepted. In this case a maximum storage of 6 hours under refrigerated conditions has been proposed, and it is acceptable.

- Adventitious Agents

No materials of animal origin are used in the production of the Master or Working seed of *E. coli* strain B1084, or in the routine production process of protein D.

With regard to the *S. pneumoniae* seeds, all seeds have been produced on culture media without any material of animal origin.

Tetanus toxoid and diphtheria toxoid are produced according to a meat-free/preservative-free production process.

The only animal derived materials used are derived from bovine milk, from which casein hydrolysate, casein peptone and tryptone N1 are derived. The milk is sourced from healthy animals in the same conditions as milk collected for human consumption and therefore complies with the TSE Note for Guidance EMEA/410/01 Rev 2. No viral issues are present. Non-animal material is tested to acceptable specifications. The material is acceptably sterilized prior to use.

- Manufacture of the Product

The manufacture of Synflorix consists of the following unit steps:

- 1) Preparation of the AlPO_4 adsorbed conjugate monobulks,
- 2) Mixing the AlPO_4 adsorbed conjugate monobulks with sodium chloride, water for injections and adjustment of the Al^{3+} concentration,
- 3) Filling into 3-ml glass vials or 1.25 ml glass syringes and closure with rubber stopper,
- 4) Labelling and packaging.

The adsorbed monobulks are stored at 2-8°C.

Synflorix final bulk can be stored at 2-8 °C in the formulation tank before filling,

Synflorix final container results from the aseptic filling of the final bulk under constant agitation into siliconised sterile 1.25ml syringes (type I glass) or into 3 ml colourless washed, siliconised, depyrogenated, sterilised glass vials (type I) by an automatic filling/stoppering machine. After filling, the syringes or the vials are automatically closed with grey butyl rubber stoppers. Vials are then capped with flip-off caps.

Process control and validation

Consistency of production has been validated through quality control testing performed on the adsorbed conjugate monobulks and Synflorix lots. The compliance of adsorbed conjugate monobulks of the different serotypes and Synflorix lots with the quality control specifications retrospectively shows the consistency of the products or product intermediates thereby validating and confirming the robustness of each production step as well as the overall production process of Synflorix.

Validation of Synflorix production process is performed through the demonstration of process consistency and the identification and validation of the manufacturing process critical parameters. Critical process parameters have been satisfactorily documented.

Validation of the vaccine aseptic filling system is run in compliance with EU guidelines and is performed through three media fill studies simulating a filling operation in syringes or in vials to validate the assurance of sterility for the filling room under evaluation or to demonstrate the capability of entire aseptic process to produce sterile vaccines in their final containers.

In conclusion, validation of the manufacturing was satisfactory.

- Product Specification

The following QC tests are performed on the adsorbed conjugate monobulks to ensure their quality: sterility, identity, free polysaccharide content, completeness of adsorption (% unbound conjugate) and aluminium content.

In addition to the quality control tests listed above, additional tests are conducted to further characterise the adsorbed conjugate monobulks for their content and other physico-chemical properties.

The final bulk vaccine is tested for sterility.

Release tests for the final containers are the following: description, identity of serotype, sterility, pH, endotoxin content, volume, aluminium content and polysaccharide content for each serotype.

The test for abnormal toxicity is not included in the routine release tests. This omission is justified as the test was performed during product development and on the clinical lots.

Release limits, where proposed, have been established using information from the testing of development batches and batches used in clinical studies, as well as in accordance with the variability

of the methods as assessed by their validation. The relevant guidelines (WHO TRS 927 and Ph. Eur. 2150) have also been taken into account.

Analytical methods have been adequately described and validated.

During early stages of product development, the company used ELISA assays for the determination of the identity and the antigen content in the final container. At a later stage, for clinical phase III material and commercial material, serotype-specific rate nephelometry was developed.

The specifications set for PS content of each serotype determined by the rate nephelometry assay are in accordance with the Eur. Ph. for most of the serotypes.

The applicant has committed to further improve the method and to update the specifications in order to adhere to the Ph. Eur for all serotypes.

Control of Excipients

The ingredients other than the active substance incorporated in Synflorix vaccine are: aluminium phosphate, sodium chloride and water for injection.

Quality Control of aluminium phosphate is performed according to GSK in-house procedures.

The sodium chloride and water for injections is controlled in accordance with the Ph Eur. The applicant's monograph on aluminium phosphate is the same as for other products authorised through the centralised procedure and acceptable.

Impurities

No impurities are generated by the formulation or the filling process.

Batch Analysis

Routine quality results on 4 phase-III final bulks are given as well as routine quality results on four 1-dose phase-III final container lots, three 2-dose vials lots and four prefilled syringes lots. These batch results include lots used in the pivotal lot-to-lot consistency, non-inferiority clinical trial 10PN-PD-DIT-001. The lots induced consistent immune response for each serotype.

• Stability of the Product

Adsorbed conjugate monobulks:

For each serotype, three lots of the phase-III adsorbed monobulks were stored at 2-8°C and tested at regular time intervals for up to 36 months. The lots were also tested following accelerated (7days 37°C) conditions.

The data presented support the proposed shelf-life of 36 months for adsorbed conjugates of serotypes 1-PD, 4-PD, 5-PD, 6B-PD, 7F-PD, 9V-PD, 14-PD, 18C-TT, 23F-PD and the proposed shelf-life of 18 months for 19F-DT adsorbed conjugate.

Formulated bulk:

The Synflorix final bulk can be stored at 2 to 8 °C until filling for maximum 1 month.

Final container (vial and syringe):

On the basis of a long-term, real-time stability study on three consistency lots of each presentation (vials and syringes) of finished product, a shelf life of 36 months at +2°C to +8°C is accepted.

The most important parameters that have been monitored throughout stability follow-up of the Synflorix phase III lots are: conjugate content by ELISA, PS content by rate nephelometry, and completeness of adsorption.

Other tests and methods applied in stability follow-up of Synflorix vaccine final bulk and final container include those applied for release testing of the Phase-III lots and additionally, following parameters have also been assessed at different time-points: pH, *in-vivo* potency on mice, and container closure integrity.

Stability of the vaccine up to 36 months at 2-8°C has been demonstrated.

Stability of Synflorix vaccine in final containers (vials and syringes) has also been evaluated following accelerated (25°C and 37°C) stability programs. Overall, the data provided demonstrate good stability of Synflorix after exposure for up to 1 month at 25°C, and after exposure for 7 days at 37°C.

Discussion on chemical, pharmaceutical and biological aspects

Synflorix is composed of the capsular polysaccharides purified from 10 serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F each conjugated to a carrier protein, either protein D (PD), tetanus toxoid (TT or T) or diphtheria toxoid (DT).

Protein D derived from non-typeable *H. influenzae* is used as carrier protein for 8 out of the 10 serotypes (serotypes 1, 4, 5, 6B, 7F, 9V, 14 and 23F). Tetanus toxoid and diphtheria toxoid are used as carrier protein for serotypes 18C and 19F, respectively. The applicant has responded satisfactorily to all of the major objections and questions identified during assessment of the MAA.

Since the claim for protection against AOM caused by non-typeable *H. influenzae* at this stage is not supported by clinical data there is no need for an assay of the protein D content in the specification at the level of the drug product. The applicant has provided clarification regarding the analytical differences seen between manufacturing batches. These differences are either due to methodological reasons or, when actual differences are seen, can be considered to be without significance for the overall activity of the product as they do not affect the results of predictive tests.

With regard to the rate nephelometry assay for quantification of each serotype in the final vaccine, the applicant has committed to further improve the method and to update the specifications in order to adhere to the Ph. Eur for all serotypes.

The proposed shelf life of 36 months at 2-8°C for the drug product (vials and syringes) is acceptable in view of the fact that the applicant has provided full time data for both presentations to support this claim.

The applicant has also committed to follow the stability of microfluidised polysaccharides for the next three lots of each serotype and the stability of TT and the derivatised TT and to report deviating results if found.

In conclusion, information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of the tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.3. Non-clinical aspects

Pharmacology

- Primary pharmacodynamics

Immunogenicity studies were conducted in mice, guinea pigs and rabbits. These studies may not be predictive of human response, and therefore are considered as supportive data only.

The first generation 11Pn-PD vaccine and Synflorix were compared in BALB/c mice and guinea pigs immunogenicity studies in co-administration with Infanrix Hexa (DTPa-HBV-IPV/Hib). The vaccine induced polysaccharide-specific serum IgG to all serotypes in both animal species. In mice, the immune response to the serotypes 18C and 19F was stronger when conjugated to TT and DT than when conjugated to PD, in line with clinical results. For the other conjugates, the immune responses were equal or somewhat stronger. In the guinea pig, a lower immune response was seen for serotypes 5, 6B and 23F with the 10-valent formulation. It was stated that the guinea pig model is not predictive for those serotypes, as shown by comparison of previous preclinical experiments with results from clinical trials. The predictivity of the animal models for human immunogenicity is not clear and the

assessment of comparability for the immune response between the two formulations must be based on clinical data.

The rabbit was the animal species used for the toxicological studies. An 11Pn-PD-DiT vaccine formulation mixed with lyophilised MenC-TT vaccine was shown to be immunogenic in female New-Zealand white rabbits by performing anti-pneumococcal polysaccharide (serotypes 1, 3, 5, 6B, 7F, 19F and 23F) serological analysis in a preliminary study. Based on this, the immune response induced by an 11-valent phase-II vaccine formulation 11Pn-PD-DiT (3 on TT) formulation was investigated in a pivotal repeat-dose toxicity study in the rabbit. Serological analysis restricted to the determination of anti-PS6B showed the presence of circulating antibody titres against PS6B. These data support the use of rabbits for toxicity studies.

To support a protection against *Haemophilus influenzae* AOM for Synflorix, GSK conducted a head-to-head comparison of the passive protective capacity of human paediatric sera obtained after immunisation with Synflorix in Study-003 (10PN-PD-DIT-003) and 11Pn-PD in POET versus 'placebo'. This was performed in the juvenile otitis media chinchilla model. The passively transferred sera provided ~34% protection against otitis media, and there were no significant differences between the 2 vaccines. The chinchilla model has been developed as a model for colonization of the nasopharynx with non-typeable *H. influenzae* and development of otitis media. A series of experiment has shown the model to be reproducible and capable of showing protection by antibodies. With sera derived from the POET study the protection in the chinchilla AOM model was comparable to the protection observed clinically. While the model indeed is of importance for non-clinical proof of concept during vaccine development, its utility for predicting clinical outcome and as a potential surrogate for efficacy is not clear. This would require a larger amount of data showing correlation between clinical efficacy and efficacy in the chinchilla model for several different vaccine candidates. While the data support a similar protection with the two vaccine formulations (11Pn-PD and Synflorix) they cannot replace clinical evidence.

- Secondary pharmacodynamics

These studies are not required for vaccines.

- Safety pharmacology programme

A GLP study was performed to assess the potential effects of the 11Pn-PD-DiT vaccine on cardiovascular and respiratory parameters in anaesthetised SPF male Wistar rats. An 11-valent *S. pneumoniae* conjugate 11Pn-PD-DiT vaccine was administered intramuscularly (IM) at a dose of 0.2 ml/animal in a group of 4 animals following a thirty minute stabilisation period. A vehicle control group (0.9% w/v saline) was run in parallel using another 4 animals.

Cardiovascular (blood pressure, heart rate and ECG (lead II)) and respiratory (respiration rate, tidal volume and minute volume) parameters were recorded continuously for a period of two hours post dose.

In one vaccine-treated animal, there was a transient (30 min) decrease in systolic, diastolic and mean blood pressure with concurrent ST depression in the electrocardiogram. A decrease in respiration rate was also recorded 40 minutes post-dose. The latter never returned to pre-dose values but indicated signs of recovery.

Overall, the observed effects were considered to be incidental and not treatment-related as these effects were not noted in the other 3 vaccine-treated animals.

- Pharmacodynamic drug interactions

These studies are not required for vaccines.

Pharmacokinetics

Pharmacokinetic testing is not required for vaccines.

Toxicology

No toxicology studies have been performed with the final vaccine formulation. This is acceptable since all components of the final vaccine were tested in one or more of the repeat-dose toxicity studies performed with similar 11-valent formulated vaccines containing higher amounts of antigen, carrier proteins or residues. There is no concern that the final formulation would demonstrate toxicity not observed in the performed studies.

- Single dose toxicity

Single dose toxicity and local tolerance of the 11Pn-PD-DiT vaccine after a single 0.5 ml intramuscular injection was studied in New Zealand White rabbits. An important finding was a local inflammatory response, comparable to that observed in studies with vaccine containing aluminium-based adjuvants.

- Repeat dose toxicity (with toxicokinetics)

In a repeat-dose toxicity study, rabbits were given five 0.5 ml doses, two weeks apart. The tested vaccines were the 11Pn-PD-DiT vaccine, the 11Pn-PD vaccine used in the clinical POET trial, and Infanrix Hexa (DTPa-HBV-IPV/Hib_{ads}). A necrotizing mixed inflammatory cell reaction was observed on day 3 after the fifth inoculation with all three vaccine formulation. On day 30 after the fifth inoculation, the incidence of this inflammatory reaction had decreased. A second repeat-dose toxicity study with the four injections of the 11Pn-PD formulation in rabbits demonstrated the same type of local inflammatory reaction. This reaction was reversible with no necrosis observed on day 84/85 after the last inoculation.

- Genotoxicity

No studies on genotoxicity have been performed. Such studies are not required for vaccines.

- Carcinogenicity

No studies on carcinogenicity have been performed. Such studies are not required for vaccines.

- Reproduction Toxicity

No studies on reproductive and developmental toxicity have been performed. This vaccine is not intended for women of child-bearing potential and therefore such studies are not required.

- Local tolerance

Local tolerance was assessed as part of the single dose and repeat dose toxicity studies presented above. Changes associated with local inflammatory reactions were found to be reversible over time.

- Other toxicity studies

Impurities

Specific toxicology studies were reported demonstrating that the residual amounts of process-specific impurities are of no toxicological concern.

Ecotoxicity/environmental risk assessment

The vaccine is composed of polysaccharides conjugated to carrier proteins. No toxicity to the environment is expected for these components. The excipient aluminium phosphate (0.5 mg/dose) was submitted to a Phase I environmental risk assessment, resulting in a Predicted Environment Concentration of $2.5 \cdot 10^{-5}$ µg/l. The PEC value is below the threshold level of 10^{-2} µg/l.

2.4 Clinical aspects

Introduction

No clinical study has evaluated the efficacy of Synflorix against IPD. Immunogenicity, safety and clinical consistency of Synflorix have been evaluated in the target population. The only efficacy study, the Pneumococcal Otitis Efficacy Trial (POET) was performed with an 11-valent vaccine formulation (11Pn-PD). As recommended by WHO, the claim for efficacy of Synflorix against IPD is based on immunological comparisons with the licensed 7-valent pneumococcal CRM₁₉₇ conjugate vaccine (Prevenar) or the related 11Pn-PD vaccine.

Non-inferiority of the immune response compared with 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; to assess persistence of the immune response in the second year of life; and to evaluate the presence of immune memory through administration of a plain polysaccharide vaccine to Synflorix-primed subjects. Additionally, co-administration of Synflorix with commonly administered commercially available paediatric vaccines was evaluated, as well as the impact of prophylactic anti-pyretic medication, and booster inter-changeability (i.e., booster vaccination of Synflorix in Prevenar-primed subjects).

A total of **14 studies** (10PN-PD-DIT-001, -002, -003, -004, -005, -007, -008, -010, -011, -012, -013, -014, -017 and -022) conducted with Synflorix and **2 studies** [Undeca-Pn-010 (POET) and its extension study Undeca-Pn-037] conducted with the 11Pn-PD formulation provide data to support the submission. The study design and main objectives of studies are described in the tables 1-4 below as well as in the section describing the individual study.

Table 1: Study design and main objectives of studies conducted with Synflorix evaluating PRIMARY vaccination groups (Total vaccinated cohort for safety)

Study number	Design Main study objectives	Age Vaccine schedule	Study vaccine + Co-administered vaccines	Number of subjects	
				Per group	Total
10PN-PD-DIT-001 (Finland, France, Poland) Phase III	Double-blind (for non-inferiority), randomized, controlled	Healthy infants	Synflorix (3 lots) + Infanrix hexa*	1235	1650
	<u>Primary objectives:</u> Lot-to-lot consistency Immunological non-inferiority of Synflorix versus Prevenar for at least 7 of the pneumococcal serotypes	6 to 12 weeks	Prevenar + Infanrix hexa* (DTPa-HBV-IPV/Hib)	415	
	<u>Key secondary objectives:</u> - Non-inferiority versus Prevenar in terms of post-immunization febrile reactions with rectal temperature > 39°C - Reactogenicity of Synflorix when co-administered with DTPa-combined vaccines - Immunogenicity of DTPa-combined vaccines when co-administered with Synflorix	2-3-4 months	* except for dose 2 in France (co-ad with Infanrix IPV/Hib)		
10PN-PD-DIT-002 * (Denmark, Norway,	Open, randomized <u>Primary objective:</u> Assessment of the post-dose 2 immune response elicited by Synflorix co-administered	Healthy infants 8-16 weeks 2-4-11	Synflorix at 2-4-11 months + Infanrix hexa or Infanrix IPV/Hib at 2-4-11 months Synflorix at 2-3-4-11	175	351

Slovenia, Sweden) Phase IIIa	with DTPa-combined vaccines <u>Key secondary objectives:</u> Assessment of post-dose 3 primary immune response to Synflorix Assessment of persistence of pneumococcal antibodies prior to the booster dose at 11 months of age Assessment of immune response elicited by a booster dose at 11 months of age following 2 or 3 dose primary vaccination Safety and reactogenicity of Synflorix	months 2-3-4-11 months	months + Infanrix hexa or Infanrix IPV/Hib at 2-4-11 months	176	
10PN-PD-DIT-003 (Germany) Phase IIIa	Single-blind, randomized, controlled <u>Primary objective:</u> Assessment of the immunogenicity of Synflorix <u>Key secondary objectives:</u> Safety and reactogenicity of Synflorix Immunogenicity of Infanrix hexa when co-administered with Synflorix	Healthy infants 8 to 16 weeks 2-3-4 months	Synflorix + Infanrix hexa Prevenar + Infanrix hexa	70 64	134
10PN-PD-DIT-005 (Chile) Phase II	Observer-blind, randomized, controlled <u>Primary objective:</u> Reactogenicity of Synflorix when co-administered with Infanrix hexa in terms of occurrence of grade 3 adverse events (solicited and unsolicited) <u>Key secondary objectives:</u> Safety, reactogenicity and immunogenicity of Synflorix when co-administered with Infanrix hexa Immune response to PD following primary course of Synflorix when co-administered with Infanrix hexa	Healthy infants 6 to 12 weeks 2-4-6 months	Synflorix + Infanrix hexa Havrix + Infanrix hexa	119 121	240
10PN-PD-DIT-010 (Czech Republic) Phase IIIb	Open, randomized, controlled <u>Primary objective:</u> Determination of the percentage reduction in febrile reactions (rectal temperature $\geq 38.0^{\circ}\text{C}$) when prophylactic antipyretic treatment is administered compared to no prophylactic antipyretic treatment after primary vaccination with Synflorix <u>Key secondary objectives:</u> Safety and reactogenicity of Synflorix Immunogenicity of Synflorix when co-administered with Infanrix hexa vaccine Immunogenicity of the Rotarix vaccine co-administered at 3-4 months of age with Synflorix Comparison of the immune response induced by Synflorix to the historical immunogenicity data obtained with the 11Pn-PD vaccine formulation in study Undeca-Pn-010 (POET), 1 month after primary vaccination	Healthy infants 9 to 16 weeks 3-4-5 months	Synflorix + Infanrix hexa + Rotarix with prophylactic antipyretic medication Synflorix + Infanrix hexa + Rotarix without prophylactic antipyretic medication	226 233	459
10PN-PD-DIT-011 ** (Germany, Poland, Spain) Phase IIIb	Open, randomized, controlled <u>Primary objective:</u> Non-inferiority of Synflorix versus Prevenar, both co-administered with DTPa-combined and Hib-MenC vaccines, in terms of post-immunization febrile reactions with rectal temperature $>39.0^{\circ}\text{C}$ <u>Key secondary objectives:</u> Immunogenicity, safety and reactogenicity of Synflorix Immunogenicity post dose 2 of Hib-MenC conjugate when co-administered with Synflorix or Prevenar and DTPa-HBV-IPV Immunogenicity post dose 3 of Hib-MenC and DTPa-HBV-IPV vaccines when co-	Healthy infants 6 to 16 weeks 2-4-6 months* *Meningitec and NeisVac-C: were administered at 2 and 4 months	Synflorix + Infanrix hexa + Meningitec Synflorix + Infanrix hexa + NeisVac-C Synflorix + DTPa- HBV-IPV + Hib-MenC Prevenar + DTPa- HBV-IPV + Hib-MenC	385 387 386 390	1548

	administered with Synflorix or Prevenar				
10PN-PD-DIT-012 (Philippines, Poland) Phase IIIb	Observer blind, randomized, controlled <u>Primary objective:</u> Non-inferiority versus Prevenar in terms of post-immunization febrile reactions with rectal temperature > 39°C <u>Key secondary objectives</u> Immunogenicity post dose 3 of Synflorix when co-administered with DTPw-HBV/Hib and OPV or IPV vaccines. Immunogenicity post dose 3 DTPw-HBV/Hib and OPV or IPV vaccines when co-administered with Synflorix Safety and reactogenicity of Synflorix when co-administered with DTPw-HBV/Hib and OPV or IPV vaccines.	Healthy infants 6 to 12 weeks 6-10-14 weeks 2-4-6 months	Synflorix + DTPw-HBV/Hib + OPV Prevenar + DTPw-HBV/Hib + OPV Synflorix + DTPw-HBV/Hib + IPV Prevenar + DTPw-HBV/Hib + IPV	300 100 303 103	806
10PN-PD-DIT-013*** (Finland) Phase IIIb	Open, controlled <u>Primary objective:</u> Immunogenicity of Synflorix when given as a catch-up immunization in children older than 7 months <u>Key secondary objectives:</u> Safety and reactogenicity of Synflorix when given as a catch-up immunization Immunogenicity, safety and reactogenicity of 3-dose primary course of Infanrix IPV/Hib co-administered with Synflorix	Infants and toddlers < 6 months 3, 4, 5 months	3 primary doses and 1 dose in second year of life of Synflorix+ Infanrix IPV/Hib	150	150
TOTAL number of subjects in primary total vaccinated cohort					5338
TOTAL number of subjects in total vaccinated cohort primed with Synflorix					4145

* Study 10PN-PD-DIT-002 evaluated both primary and booster vaccination: numbers of subjects are the numbers evaluated for the primary vaccination phase

** For Study 10PN-PD-DIT-011 24 subjects enrolled in study centre 28251 were excluded from the Total vaccinated cohort due to GCP compliance issues and consequence of an audit

*** Study 10PN-PD-DIT-013 evaluated primary, booster and catch-up vaccination: numbers of subjects is the number evaluated in the primary vaccination phase below 6 months of age

Table 2: Study design and main objectives of studies conducted with Synflorix evaluating BOOSTER vaccination groups (Total vaccinated cohort for safety)

Study number	Design Main study objectives	Age Vaccine schedule	Study vaccine + Co-administered vaccines	Number of subjects	
				Per group	Total
10PN-PD-DIT-002* (Denmark, Norway, Slovenia, Sweden) Phase IIIa	Open, randomized <u>Primary objective:</u> Assessment of the post-dose 2 immune response elicited by Synflorix co-administered with DTPa-combined vaccines <u>Key secondary objectives:</u> Assessment of post-dose 3 primary immune response to Synflorix Assessment of persistence of pneumococcal antibodies prior to the booster dose at 11 months of age Assessment of immune response elicited by a booster dose at 11 months of age following 2 or 3 dose primary vaccination Safety and reactogenicity of Synflorix	Healthy infants (2-4)11 months (2-3-4)11 months	2-dose primed: Synflorix + Infanrix hexa or Infanrix IPV/Hib 3-dose primed: Synflorix + Infanrix hexa or Infanrix IPV/Hib	174 171	345
10PN-PD-DIT-004** (Germany) (NB: 11-valent vaccine- Only included in the safety assessment)	Open <u>Primary objective:</u> Immunological memory following priming with either 3µg 18C-TT 11Pn-PD-DiT, 11Pn-PD or Prevenar through administration of a single dose of unconjugated 23-valent pneumococcal polysaccharide vaccine Immune response after a booster dose of Synflorix following primary vaccination with	Toddlers 11-18 months	11Pn-PD, 11Pn-PD-DiT or Prevenar primed: Pneumovax + Infanrix hexa 11Pn-PD-DiT primed: Synflorix + Infanrix hexa	150 397	547

Phase II	one of 8 different 11Pn-PD-DiT vaccine formulations <u>Key secondary objectives:</u> Safety and reactogenicity of Synflorix vaccine co-administered with Infanrix hexa as a booster dose Persistence of antibodies induced by the different pneumococcal conjugate vaccines 7-14 months after priming				
10PN-PD-DIT-007 (BST-001) (Finland, France, Poland) Phase IIIa	Single-blind, partially randomized, controlled <u>Primary objective:</u> Non-inferiority of a booster dose of Synflorix versus Prevenar, when co-administered with Infanrix hexa, in terms of post-immunization febrile reactions with rectal temperature >39.0°C <u>Key secondary objectives:</u> Safety, reactogenicity and immunogenicity of a booster dose of Synflorix when co-administered with Infanrix hexa vaccine Immunogenicity of a booster dose of Synflorix following 3-dose primary vaccination with Prevenar (interchangeability) Persistence of pneumococcal antibodies 8 to 14 months after completion of the 3-dose primary vaccination course	Toddlers 12-18months	Synflorix primed: Synflorix + Infanrix hexa Prevenar primed: Prevenar + Infanrix hexa Prevenar primed: Synflorix + Infanrix hexa	737 92 283	1112
10PN-PD-DIT-008*** (BST-003) (Germany) Phase IIIa	Open, controlled <u>Primary objective:</u> Immunological memory, following 3-dose primary vaccination with either Synflorix or Prevenar, through administration of a single dose of unconjugated 23-valent pneumococcal polysaccharide vaccine <u>Key secondary objective:</u> Persistence of pneumococcal antibodies induced by Synflorix or Prevenar 7 to 10 months after completion of the 3-dose primary course	Toddlers 11-14 months	Synflorix primed : Pneumovax + Infanrix hexa Prevenar primed : Pneumovax + Infanrix hexa	60 53	113
10PN-PD-DIT-013**** (Finland) Phase IIIb	Open, controlled <u>Primary objective:</u> Immunogenicity of Synflorix when given as a catch-up immunization in children older than 7 months <u>Key secondary objectives:</u> Safety and reactogenicity of Synflorix when given as a catch-up immunization Immunogenicity, safety and reactogenicity of 3-dose primary course of Infanrix IPV/Hib co-administered with Synflorix	Infants and toddlers 12 to 15 months	Synflorix+ Infanrix IPV/Hib (3 dose primed) Synflorix+ Infanrix IPV/Hib (2 dose catch-up)	145 145	145 145
10PN-PD-DIT-014 (Czech Republic) Phase IIIb	Open, randomized, controlled <u>Primary objective:</u> Determination of the percentage reduction in febrile reactions (rectal temperature $\geq 38.0^{\circ}\text{C}$) when prophylactic antipyretic treatment is administered compared to no prophylactic antipyretic treatment after booster vaccination with Synflorix <u>Key secondary objectives:</u> Safety, reactogenicity and immunogenicity of booster dose of Synflorix co-administered with Infanrix hexa. Persistence of antibodies 7-10 months after completion of the three-dose primary vaccination course Persistence of antibodies 12-15 months after the booster dose	Toddlers 12-15 months	Synflorix + Infanrix hexa + prophylactic antipyretic medication Synflorix + Infanrix hexa without prophylactic antipyretic medication (received prophylactic antipyretic medication during primary vaccination) Synflorix + Infanrix hexa without prophylactic antipyretic medication	178 27 209	414
10PN-PD-	Open, randomized, controlled	Toddlers	Synflorix + Infanrix	359	1437

DIT-017 (Germany, Poland, Spain) Phase IIIb	<u>Primary objective:</u> Non-inferiority of Synflorix versus Prevenar, both co-administered with DTPa-combined and Hib-MenC vaccines, in terms of post-booster febrile reactions with rectal temperature >39.0°C <u>Key secondary objectives:</u> Safety, reactogenicity and immunogenicity of booster dose of Synflorix co-administered with DTPa-combined and MenC or Hib-MenC vaccines. Persistence of antibodies 5-12 months after completion of the three-dose primary vaccination course Hib-MenC vaccines. Immunogenicity of a booster dose of Hib MenC conjugate vaccine when co-administered with Synflorix or Prevenar and DTPa- combined vaccines.	11 to 18 months	hexa or DTPa-IPV/Hib*+ Meningitec Synflorix + Infanrix hexa or DTPa-IPV/Hib* + NeisVac-C Synflorix + DTPa-HBV-IPV or DTPa-IPV*+ Hib-MenC Prevenar + DTPa-HBV-IPV or DTPa-IPV* + Hib-MenC * for Spain	363 358 357	
10PN-PD-DIT-022 † (BST-001) (Finland) Phase IIIa	Open, randomized, controlled <u>Primary objective:</u> Incidence of post-immunization rectal temperature >39.0°C following a booster dose of Synflorix when co-administered with a first dose of MMRV vaccine <u>Key secondary objectives:</u> Safety, reactogenicity and immunogenicity of a booster dose of Synflorix co-administered with MMRV vaccine Persistence of antibodies 8 - 10 months after completion of the 3-dose primary course Safety, reactogenicity and immunogenicity of MMRV when co-administered with Synflorix	Toddlers 12-14 months, 14-16 months	Synflorix primed : visit 1: Synflorix + MMRV ; visit 2 : MMRV + Infanrix hexa Synflorix primed : visit 1: MMRV + Infanrix hexa; visit 2: Synflorix + MMRV Synflorix primed : Synflorix + Infanrix hexa	110 100 114	324
TOTAL number of subjects in Booster Total vaccinated cohort					4582
TOTAL number of subjects in Booster total vaccinated cohort receiving Synflorix					3870

* Study 10PN-PD-DIT-002 evaluated both primary and booster vaccination: numbers of subjects are the numbers evaluated for the booster vaccination phase

** Study 10PN-PD-DIT-004 evaluated a booster dose of Synflorix after primary course of 8 different 11-valent vaccine formulations

*** Study 10PN-PD-DIT-008 evaluated immune memory with a dose of Pneumovax after primary vaccination with Synflorix

**** Study 10PN-PD-DIT-013 evaluated primary, booster and catch-up vaccination: numbers of subjects are the number evaluated in the booster phase below 6 months of age and 7-11 months of age groups.

† Study 10PN-PD-DIT-022 included two groups that received two doses of vaccines and one group that received one dose of vaccine: numbers of subjects are the numbers for the dose that included Synflorix.

Table 3: Study design and main objectives of studies conducted with Synflorix evaluating CATCH-UP vaccination groups (Total vaccinated cohort for safety)

Study number	Design Main study objectives	Age Vaccine schedule	Study vaccine + Co-administered vaccines	Number of subjects	
				Per group	Total
10PN-PD-DIT-013 (Finland) Phase IIIb	Open, controlled <u>Primary objective:</u> Immunogenicity of Synflorix when given as a catch-up immunization in children older than 7 months <u>Key secondary objective:</u> Safety and reactogenicity of Synflorix when given as a catch-up immunization Immunogenicity, safety and reactogenicity of 3-dose primary course of Infanrix IPV/Hib co-administered with Synflorix	Infants and toddlers 7-11 months 12-23 months ≥ 24 months catch-up schedules	7-11 months: 2 doses Synflorix (interval of 4 weeks) + 1 dose in second year of life 12-23 months: 2 doses Synflorix (interval of 8 weeks) ≥ 24 months: 1 dose Synflorix	150 150 150	450
TOTAL number of subjects in Catch-up Total vaccinated cohort / ATP cohort for immunogenicity					450

Table 4: Study design and main objectives of studies conducted with previous 11-valent vaccine formulations SUPPORTIVE for the claimed indication and Synflorix formulation and number of subjects vaccinated

Study number	Design Main study objectives	Age Vaccine schedule	Study vaccine + Co-administered vaccines	Number of subjects	
				Per group	Total
Undeca-Pn-010 POET (Czech & Slovak Republics) Phase III	Double blind, randomized, controlled <u>Primary objective:</u> Efficacy of the 11Pn-PD vaccine in preventing acute otitis media (AOM) caused by vaccine pneumococcal serotypes in fully vaccinated children less than 2 years of age <u>Key secondary objectives:</u> Efficacy of the 11Pn-PD vaccine in preventing AOM caused by NTHi in fully vaccinated children less than 2 years of age Impact of the 11Pn-PD vaccine on nasopharyngeal carriage of <i>S. pneumoniae</i> and <i>H. influenzae</i> Immunogenicity, safety and reactogenicity of the 11Pn-PD vaccine	Infants 3-4-5 and 12-15 months	11Pn-PD + DTPa-HBV-IPV/Hib HAV + DTPa-HBV-IPV/Hib	2489 2479	4968
Undeca-Pn-037 (Czech Republic) Phase III	Open <u>Primary objective:</u> Immune memory induced by the full four dose vaccination schedule of the 11Pn-PD vaccine through administration of a single dose of unconjugated 23-valent pneumococcal polysaccharide vaccine <u>Secondary objective:</u> Persistence of antibodies induced by the full four dose vaccination schedule of the 11Pn-PD vaccine	Toddlers 3-4 years	11Pn-PD vaccinated: Pneumo 23 HAV vaccinated: Pneumo 23	51 49	100

Safety data from **27 clinical trials** conducted with different 11-valent vaccine formulations were submitted to support the safety profile of the candidate vaccine.

Ongoing clinical studies

Trials are ongoing including a Phase III study (COMPAS study) in Latin America evaluating, as co-primary objectives, the protective efficacy of Synflorix against pneumonia and AOM.

GCP

According to the Applicant, each clinical trial was performed in compliance with the Good Clinical Practice guidelines in operation at the time of initiation of each study, and the Declaration of Helsinki and its amendments were respected.

Pharmacokinetics

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

Pharmacodynamics

In relation to vaccines, pharmacodynamic studies are essentially compromised of 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 an in-house 22F-inhibition ELISA for measurement of total anti-pneumococcal IgG concentrations and an in-house opsonophagocytic (OPA) assay for measurement of functional antibody response.

ELISA

The ELISA assay is a third generation ELISA differing from the WHO reference ELISA by a pre-adsorption step with 22F polysaccharide, by the use of GSK purified polysaccharide for coating and the use of monoclonal anti-human mouse IgG antibody as secondary antibody. All these measures were taken to increase the specificity of the ELISA. This assay was compared to the WHO reference ELISA in three studies. In these bridging experiments an antibody concentration of 0.2 µg/ml in the GSK third generation ELISA was shown to be equivalent to the 0.35 µg/ml WHO reference threshold.

OPA

The functionality of anti-pneumococcal polysaccharide antibodies was evaluated using serotype-specific opsonophagocytic activity (OPA) assays. *S. pneumoniae* opsonophagocytic activity was measured by a killing-assay using a HL60 cell line based on the reference CDC assay. Baby rabbit complement was used as the source of complement. Each of the serotype-specific assays was validated. There are currently no standardised OPA assays available. The titre is the dilution at which 50% of killing occurs, normalised using an adjustment factor. Cut-off used for seropositivity was an opsonic titre of 8.

Total IgG antibodies against the non-lipidated form of protein D of *Haemophilus influenzae* was measured by an ELISA developed and validated by the applicant.

The methods, cut-offs and approach for assessment of the immune response to co-administered vaccine antigens were the same as those employed during the clinical development of the applicant's licensed vaccines.

Immunogenicity endpoints

Vaccine serotype total anti-pneumococcal IgG concentrations were measured in the majority of subjects. Total IgG antibodies against cross-reactive serotypes 6A and 19A were also measured. Functional antibodies were measured by opsonophagocytic (OPA) assay in all subjects with sufficient serum and in some studies in a subset of 25%-50% of the subjects selected through a sub-randomisation process. Overall, OPA was evaluated on serum from a total of 1510 and 693 subjects following primary and booster vaccination with Synflorix, respectively.

In all primary, catch-up and booster vaccination studies, the following immunogenicity endpoints were used to evaluate the Synflorix response:

- Antibody concentrations against serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F and against protein D
- Percentage of subjects having vaccine serotype (+ 6A and 19A) antibody concentrations \geq 0.20 µg/ml
- Opsonophagocytic activity against vaccine serotypes and vaccine related serotypes 6A and 19A
- Seropositivity status, defined as ELISA antibody concentrations \geq 0.05 µg/ml, opsonophagocytic activity \geq 1: 8, anti-PD antibody concentrations \geq 100 EL.U/ml.

Discussion on methods and endpoints

The antibody threshold 0.20 µg/ml obtained with the 22F-ELISA was further justified during the procedure by provision of a new bridging study to the WHO reference ELISA using post-primary sera from children vaccinated with Prevenar and the clarification that the 89-SF reference serum was not absorbed with 22F PS. The impact on the 22F-ELISA assay of the pre-adsorption with 22F polysaccharide, the purified coating polysaccharides and the monoclonal antihuman mouse IgG antibody were addressed.

Preliminary results from a small inter-laboratory OPA study, submitted during the procedure, showed that the agreement between five laboratories, including the GSK assay, was generally good. The exception was serotype 9V for which geometric mean titres (GMTs) were overestimated in the GSK OPA assay. The Company has committed to investigate this overestimation, to optimise the OPA assay and to provide the CHMP with annual reports of the progress of the WHO standardisation of OPA.

The OPA assay that measures functional immune response has an important role in the assessment of new pneumococcal vaccines. The OPA data confirms that the antibody response measured by ELISA is functional. According to the (*WHO/Health Canada Consultation on Serological Criteria for Evaluation and Licensing of New Pneumococcal Vaccines, 7-8 July 2008, Ottawa, Canada*) the OPA is considered less precise than the ELISA in the absence of an internal assay standard. So far no reliable protective threshold titre for the OPA has been established. The interpretation of OPA data with regard to predicting protective efficacy is therefore unclear. The WHO TRS 127 states that ELISA antibody concentrations in the range of 0.20-0.35 µg/ml correlated with OPA titres 1:8, which correlated with protective efficacy for some serotypes. Therefore, the WHO recommends that at least an assessment of subjects reaching this cut-off should be performed which could be used for comparison between vaccines. Accordingly, the applicant presented the results of the clinical studies as the proportion of subjects achieving an OPA titre $\geq 1:8$. In addition, this threshold was employed for exploring serotype-specific correlations between OPA and ELISA.

The correlation coefficients between ELISA and OPA assays for the 7 Prevenar serotypes in the candidate vaccine ranged from 0.79 (for serotype 19F) to 0.95 (for serotype 4) indicating a good correlation between the assays. For serotype 1, a less good correlation (0.69) was shown, whereas it was acceptable for serotype 5 (0.86). The lower correlation coefficient for serotype 1 is not possible to interpret at the current stage, effectiveness data must be awaited. For serotype 14, OPA activity was observed in the absence of ELISA antibodies, especially in non-immunized subjects, whereas OPA seropositivity while ELISA seronegative was observed for other serotypes, in particular for serotype 7F. Discrepancies in the correlation between assays might partly be due to the IgM response measured by the OPA, which, was supported by limited data using an exploratory IgM ELISA.

- Dose response studies

No data on formal dose response studies for Synflorix were submitted. It is mentioned in the study protocols that early preliminary studies showed that a tetravalent pneumococcal protein D conjugate vaccine (serotypes 6B, 14, 19F and 23F) was safe in adults, toddlers and infants. Based on these results seven additional serotypes (1, 3, 5, 7F, 9V and 18C) were incorporated into an 11-valent vaccine (11Pn-PD formulation).

Based on the results of the POET trial (described below), the Company made changes to the 11Pn-PD vaccine to improve its immunogenicity. These changes included the use of protein carriers other than protein D, various dosages of conjugates, and the optimization of the production process, i.e. tetanus toxoid (T) and diphtheria (Di) toxoid were evaluated as protein carrier for some serotypes; dosage per conjugated serotype has been optimised; the production process consisted in the use of sized polysaccharides, instead of the use of native polysaccharides (PS) before conjugation, the use of an increased protein D/polysaccharide ratio and the reduction of the free polysaccharide content. In

addition, serotype 3 was removed from the final vaccine formulation based on the failure to show protective efficacy against AOM caused by serotype 3 (see below). There was also no evidence of induction of immune memory against serotype 3.

The vaccine composition of Synflorix was based on the results of 4 phase II studies (11Pn-PD&Di-001, 11Pn-PD&Di-007, 11PN-PD-DIT-001 and -002) in which different 11Pn-PD&Di and 11Pn-PD-DiT formulations were tested. In total 3000 infants vaccinated according to the 3-dose primary vaccination schedule were evaluated in these trials.

- Main studies

Efficacy of the 11Pn-PD vaccine against AOM was evaluated with the related 11-valent PD-conjugated vaccine (11Pn-PD) in a double-blind, randomized Pneumococcal Otitis Efficacy Trial (POET).

Results from 11 completed clinical trials (9 phase III and 2 phase II), in addition to study 10PN-PD-DIT-001, supported the immunogenicity of Synflorix. These studies evaluated the following issues:

3-dose primary vaccination followed by a booster dose in the second year of life:

2-3-4 months (studies 10PN-PD-DIT-001, -002 and -003);

3-4-5 months (studies 10PN-PD-DIT-010 and -013);

2-4-6 months (studies 10PN-PD-DIT-005, -011 and -012);

6-10-14 weeks (study 10PN-PD-DIT-012)

2-dose primary vaccination followed by a booster dose at 11 months of age:

2-4 (-11) (study 10PN-PD-DIT-002)

Catch-up immunisation schedules (study 10PN-PD-DIT-013)

Booster vaccination (studies 10PN-PD-DIT-002, -007, -013, -014, -017 and -022)

Immune memory (study 10PN-PD-DIT-008)

Co-administered vaccines

Effect of prophylactic use of paracetamol (studies 10PN-PD-DIT-010 and -014)

METHODS (GENERAL)

The individual study design and main objectives of studies are described in the summary tables 1-4 above and under the individual section of the studies below in this report.

All primary vaccination studies were controlled and all were randomised except study 10PN-PD-DIT-013. Most of the studies were conducted either in a single-blind or an open design due to differences in the appearance/presentation of the study vaccines and/or difference in administration schedules between study groups. Study 10PN-PD-DIT-001 (lot-to-lot consistency), -005 and -012 were double- or observer-blind, studies 10PN-PD-DIT-001 (non-inferiority), -003 and -007 were single-blind, whereas 10PN-PD-DIT-002, -008, -010, -011, -013, -014, -017 and -022 were open studies.

The licenced 7-valent pneumococcal conjugate vaccine, Prevenar, was used as control vaccine in six studies; in 10PN-PD-DIT-001 to demonstrate non-inferiority and as control group in primary studies 10PN-PD-DIT-003, -011 and -012 and in booster studies 10PN-PD-DIT-007 and -017. Hepatitis A vaccine (Havrix) was used as a control vaccine in study 10PN-PD-DIT-005. Immune memory was evaluated by use of a single dose of 23-valent pneumococcal polysaccharide (23vPS) vaccine in study 10PN-PD-DIT-008.

The co-administration of Synflorix was evaluated with different paediatric vaccines including monovalent or combination vaccines [including 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 (V) vaccine,

meningococcal serogroup C conjugate vaccine, and rotavirus vaccine (Rotarix). Co-administration with DTPw and OPV were evaluated in study 012.

Primary immunisation in all studies started between 6 and 16 weeks of age with an interval between doses ranging from 4 to 12 weeks. Catch-up vaccination were performed in children aged >6 months up to 5 years. All studies were conducted in healthy infants and toddlers.

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 study 10PN-PD-DIT-012.

Blood samples for the assessment of the immune response were taken prior to vaccination and one month after the last dose in all the primary and catch-up vaccination studies, except in studies 10PN-PD-DIT-002, -011, and -013 (< 6 month and 7-11 month groups) in which pre-vaccination samples were not taken. In booster studies and in studies evaluating antibody persistence and/or immune memory induced by primary vaccination, a blood sample was taken before and 30 days after the booster dose or the plain polysaccharide challenge, except in study 10PN-PD-DIT-022 in which the post-booster sample was taken 42-56 days after the booster dose.

In all studies except study 008, immunogenicity of the co-administered vaccines was evaluated as part of the secondary endpoints. For these antigens there was protocol-defined prioritisation for testing in case of limited volumes.

Studies were conducted in 10 countries in Europe (Czech Republic, Denmark, Finland, France, Germany, Norway, Poland, Slovakia, Spain, and Sweden) and in Chile and in the Philippines. The majority (>90%) of subjects who participated in the clinical studies were White, except for studies 005 (Chile) and 012 (Philippines). Males and females were approximately equally represented in all studies.

A total of 4145 subjects received Synflorix according to 2-dose or a 3-dose primary vaccination, 3870 subjects received a booster dose and 450 subjects >6 months of age received the vaccine according to different catch-up vaccination schedules. Few subjects were withdrawn or discontinued from the studies (<3%).

Pivotal primary immunogenicity study 10PN-PD-DIT-001

The Applicant's claim for invasive pneumococcal disease is based on study 10PN-PD-DIT-001, using the WHO licensure criteria (see introduction).

METHODS AND BACKGROUND

The post-primary antibody threshold of 0.35 µg/ml that is recommended by the WHO for non-inferiority comparison between vaccines was derived from antibody concentrations measured with an ELISA without 22F pre-adsorption. The Applicant performed bridging studies between the GSK 22F-ELISA and WHO non-22F ELISA and identified an equivalent antibody threshold of 0.20 µg/ml being aligned to the reference non-22F threshold of 0.35 µg/ml. Following CHMP Scientific Advice in 2003, all the clinical studies assessing Synflorix were designed and powered based on the 22F-ELISA and the corresponding 0.20 µg/ml threshold for non-inferiority.

Study 10PN-PD-DIT-001 was designed to evaluate non-inferiority of Synflorix compared to Prevenar. The study was randomised, controlled and included a total of 1650 subjects vaccinated (2-3-4 months) with either Synflorix or Prevenar (3:1 ratio). The primary endpoint was to demonstrate that the 10-valent vaccine administered as a 3-dose primary course was non-inferior to Prevenar against at least 7 out of 10 serotypes. The 22F-ELISA antibody threshold used was 0.20 µg/ml. The statistical criteria had been endorsed by the CHMP.

The criterion used for non-inferiority was as follows: for each of the 7 Prevenar serotypes, non-inferiority will be demonstrated if the upper limit of the 2-sided 96.5% CI (adjusted 1-sided alpha=0.0175) of the difference between groups (Prevenar minus Synflorix) in terms of percentage of subjects with antibody concentrations ≥ 0.2 $\mu\text{g/ml}$, is lower than 10%; for each of the 3 non-Prevenar serotypes (1, 5, 7F) non-inferiority will be demonstrated if the upper limit of the 2-sided 96.5% CI of the difference aggregate response for the 7 Prevenar serotypes and the Synflorix group, in terms of percentage of subjects with antibody concentrations ≥ 0.2 $\mu\text{g/ml}$ is lower than 10%.

RESULTS

Primary non-inferiority analysis

Non-inferiority to Prevenar was demonstrated for 8 out of 10 serotypes as the upper limits of the 96.5% CIs for the difference between groups (Prevenar minus Synflorix or aggregate response for the 7 Prevenar serotypes minus Synflorix) in terms of percentage of subjects with pneumococcal antibody concentrations ≥ 0.20 $\mu\text{g/ml}$ were below the pre-defined limit of 10% for serotypes 1, 4, 5, 7F, 9V, 14, 18C and 19F (Tables 5 and 6).

Non-inferiority was not reached for serotypes 6B and 23F for which the observed difference between groups in percentage of subjects with antibody concentration ≥ 0.20 $\mu\text{g/ml}$ was 13.12% and 12.72%, respectively, and thus limits of the 96.5% CIs around these differences were higher than 10%. The upper limit of the 96.5% CI was 18.3% and 16.1%, respectively.

Table 5: Comparative analysis between Prevenar and Synflorix in percentage of subjects with antibody concentrations ≥ 0.20 $\mu\text{g/ml}$, one month post-dose 3 (ATP immunogenicity cohort)

Antibody	Synflorix		Prevenar		Difference in % ≥ 0.2 $\mu\text{g/ml}$ (Prevenar minus Synflorix)		
	N	%	N	%	%	96.5%CI	
Anti-4	1106	97.1	373	100	2.89	1.71	4.16
Anti-6B	1100	65.9	372	79.0	13.12	7.53	18.28
Anti-9V	1103	98.1	374	99.5	1.37	-0.28	2.56
Anti-14	1100	99.5	374	99.5	-0.08	-1.66	0.71
Anti-18C	1102	96.0	374	98.9	2.92	0.88	4.57
Anti-19F	1104	95.4	375	99.2	3.83	1.87	5.50
Anti-23F	1102	81.4	374	94.1	12.72	8.89	16.13

The percentage of vaccinees reaching the threshold for the three additional serotypes (1, 5 and 7F) was respectively 97.3%, 99.0% and 99.5% and was at least as good as the aggregate Prevenar response against the 7 common serotypes (95.8%).

Table 6: Difference between the aggregate response of the 7 Prevenar serotypes and the Synflorix group for serotypes 1, 5 and 7

Antibody	Synflorix		Aggregate Prevenar response		Difference in % ≥ 0.2 $\mu\text{g/ml}$ (Aggregate Prevenar minus Synflorix)		
	N	%	N	%	%	96.5%CI	
Anti-1	1100	97.3	2616	95.8	-1.52	-2.50	-0.52
Anti-5	1104	99.0	2616	95.8	-3.25	-4.02	-2.50
Anti-7F	1107	99.5	2616	95.8	-3.70	-4.42	-3.01

Aggregate Prev response % = percentage of pneumococcal antibody concentrations ≥ 0.2 $\mu\text{g/ml}$ for the combined 7 Prevenar serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) ; 96.5% CI = 96.5% Efron's percentile confidence interval (bootstrap method)

Post-hoc exploratory inferential analyses

ELISA 0.35 $\mu\text{g/ml}$ threshold

A *post-hoc* analysis was performed using the established 0.35 $\mu\text{g/ml}$ threshold, which showed that the non-inferiority criterion was met only for 7 out of 10 serotypes. The upper limit of the 95% CIs exceeded 10% for 6B (21.1%), 19F (11.3%) and 23F (24.8%).

Opsonophagocytic assay (OPA)

A *post-hoc* inferential analysis was performed on the difference between groups in terms of percentage with OPA titres ≥ 8 . Opsonophagocytic activity was evaluated on a subset of 25% of subjects

(Synflorix n=300; Prevenar n=100). The observed difference was <5% for all serotypes common to both vaccines, including serotypes 6B and 23F. The upper limit of the 95%CI around difference was below 10% for all serotypes, except for serotypes 1 (36.1%) and 19F (10.6%) (Figure 1, tables 7 and 8).

Figure 1

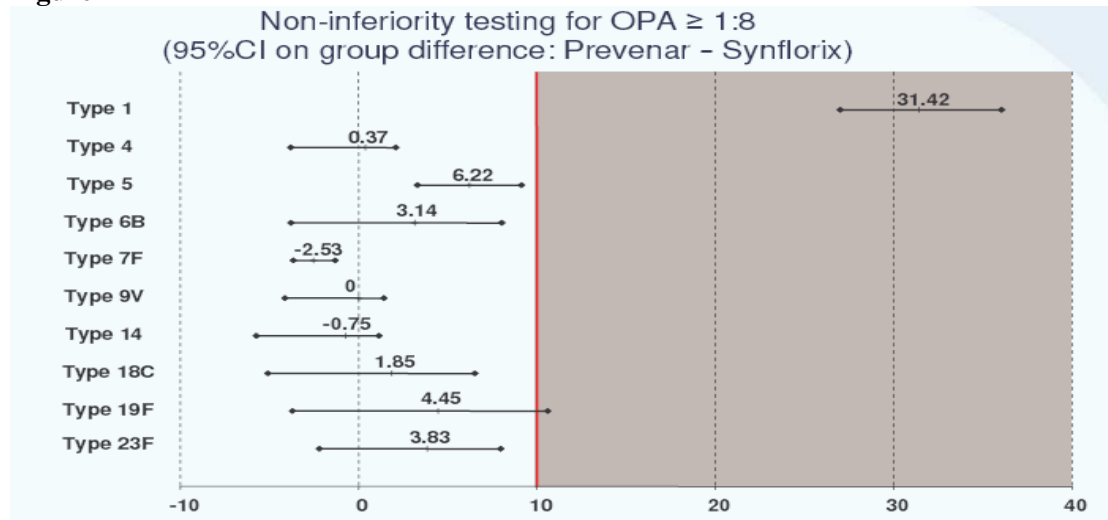


Table 7: Study 10PN-PD-DIT-001: Comparative analysis between Prevenar and Synflorix groups in the percentage of subjects with OPA titre greater than or equal to 8, one month post-dose III (ATP cohort for immunogenicity)

Antibody	Synflorix		Prevenar		Difference in % ≥ 8 (Prevenar <i>minus</i> Synflorix)		
	N	%	N	%	%	95%CI	
Anti-4	267	99.6	88	100	0.37	-3.81	2.09
Anti-6B	262	92.4	89	95.5	3.14	-3.80	8.03
Anti-9V	268	100	89	100	0.00	-4.14	1.41
Anti-14	267	99.6	89	98.9	-0.75	-5.73	1.14
Anti-18C	266	93.6	88	95.5	1.85	-5.09	6.52
Anti-19F	268	87.7	89	92.1	4.45	-3.72	10.61
Anti-23F	261	93.9	87	97.7	3.83	-2.20	7.96

Table 8: Study 10PN-PD-DIT-001: Comparative analysis between the aggregate response for the seven Prevenar serotypes and Synflorix in the percentage of subjects with OPA titre greater than or equal to 8, one month post-dose III (ATP cohort for immunogenicity)

Antibody	Synflorix		Aggregate Prevenar response		Difference in % ≥ 8 (Aggregate Prevenar <i>minus</i> Synflorix)		
	N	%	N	%	%	95%CI	
Anti-1	268	65.7	619	97.1	31.42	27.01	36.05
Anti-5	263	90.9	619	97.1	6.22	3.30	9.13
Anti-7F	264	99.6	619	97.1	-2.53	-3.67	-1.32

Descriptive immunogenicity data

One month post-dose 3, at least 95.4% of subjects in the Synflorix group had antibody concentrations ≥0.20 µg/ml against the vaccine serotypes, except for serotypes 6B (65.9%) and 23F (81.4%). The post primary ELISA GMCs were significantly lower (no overlap of CIs) for all the 7 common serotypes in the Synflorix group compared to those in the Prevenar group.

Pre-booster GMCs (8 to 12 months after the last primary dose) were generally similar for the two vaccines.

As regards OPA, at least 87.7% of Synflorix vaccinees had an OPA titres ≥ 1:8, one month post-dose 3, against all vaccine serotypes, except for serotype 1 (65.7%). The GMTs were lower for 5 serotypes

(4, 6B, 14, 18C, and 23F) and higher for 2 serotypes (9V and 19F) in the Synflorix group compared to those in the Prevenar group.

POET efficacy study

METHODS AND BACKGROUND

The Pneumococcal Otitis efficacy Trial (POET) evaluated the protective efficacy of the related 11-valent vaccine against AOM. This study allows a comparison of the immunogenicity data of Synflorix with the immunogenicity data of the 11Pn-PD vaccine from POET trial in order to provide a basis for AOM efficacy of Synflorix. No immunological correlate of efficacy has been established for pneumococcal mucosal infections and therefore vaccine efficacy estimates for AOM must rely on clinical efficacy data.

The POET trial was conducted in Czech Republic and Slovak Republic and enrolled 4968 infants randomly assigned to receive either 11Pn-PD or hepatitis A vaccine at the ages 3, 4, 5 and 12-15 months of age and followed up until the end of the second year of life. The study was well conducted with a relevant case definition of clinical AOM and confirmation of all cases by an ENT specialist. A sample of middle ear fluid for bacteriological culture was obtained from the majority AOM episodes (96%). There were few study withdrawals and discontinuations (~1%). The primary objective of the study was to demonstrate efficacy against the first occurrence of vaccine-pneumococcal-serotype AOM. The key secondary objective was to assess efficacy against AOM caused by NTHi. This aim is based on the presence of the carrier protein D in the vaccine, a cell-surface protein derived from an NTHi strain, which in preclinical studies has induced protection against NTHi AOM. The ATP efficacy follow-up period started 2 weeks after the third vaccine dose. Efficacy was also evaluated in an ITT population (TVC).

RESULTS

During the per-protocol follow-up 333 clinical AOM episodes (0.08 per person-year) were recorded in the 11Pn-PD group and 499 (0.13 per person-year) in the control group giving a 33.6% (95% CI: 20.8, 44.3) reduction in the overall incidence of AOM.

The primary objective of the study was met. The efficacy against the first confirmed episode of AOM caused by vaccine serotypes was 52.6% (2-sided p-value of 0.016 for the null hypothesis that VE=30%) (Table 9). The lower limit of the 95% CI was equal to 35%. Vaccine efficacy was 57.6% (95% CI: 41.4, 69.3) against any vaccine serotype AOM episode in the ATP cohort and 58.4% (95% CI: 43.5, 69.3) in the TVC cohort. Efficacy against any AOM episode due to any pneumococcal serotype was 51.5 % (95% CI: 36.8, 62.9).

The secondary objective was not met since the efficacy against the first episode of AOM caused by NTHi was 31.1% in the ATP cohort (the 2-sided P-value of 0.074 for the null hypothesis that VE=0% is not below the 5% alpha level) (Table 9). The lower limit of the 95% CI was equal to -3.7%. In the TVC cohort significant efficacy was observed. Efficacy against any AOM episode due to NTHi was 35.3% (95% CI: 1.8, 57.4) in the ATP cohort and 33.3% (0.3, 55.4) in the TVC cohort.

Table 9: Protective efficacy for time to first occurrence of AOM (ATP and Total Cohorts for efficacy)

	11Pn-PD		HAV		Vaccine Efficacy	
	N of 1st episodes	Incidence /1000 py	N of 1st episodes	Incidence / 1000 py	%	95% CI
<u>ATP Cohort for efficacy</u>	N=2455		N=2452			
- Vaccine pn. serotypes	57	14.4	118	30.4	52.6	35.0 to 65.5
- Nontypeable <i>H. influenzae</i>	39	9.8	56	14.2	31.1	-3.7 to 54.2
<u>Total Cohort for efficacy</u>	N=2489		N=2479			
- Vaccine pn. serotypes	64	14.2	132	29.8	52.6	36.1 to 64.9
- Nontypeable <i>H. influenzae</i>	43	9.5	63	14.0	32.7	0.77 to 54.3

Statistically significant serotype-specific efficacy was shown for four serotypes, 6B (VE: 87.6% (58.4, 96.3)), 14 (VE: 95.5% (66.0, 99.4)), 19F (VE: 44.4% (8.3, 66.3)) and 23F (VE: 72.3% (24.8, 89.8)). For other vaccine serotypes, the number of AOM cases was too limited to allow any efficacy conclusion to be drawn.

In contrast, no protection against AOM caused by serotype 3 was shown, despite a sufficient number of episodes. Concerning serotype 3 the OPA responses for this type cannot be directly compared with those of the other vaccine serotypes, since a non-pathogenic atypical SSI 3/1 serotype 3 isolate was used to measure OPA activity, whereas for the other serotypes, clinical isolates were used. A possible explanation for lack of vaccine efficacy against serotype 3 AOM is that either the atypically abundant expression of capsular polysaccharide in planktonic growth or the acapsular forms associated with biofilm growth could make serotype 3 strains less susceptible to anti-polysaccharide antibody mediated defence mechanisms. Whether this also applies to serotype 3 IPD is an open question. Efficacy was also shown against AOM caused by all vaccine-related serotypes combined (mainly 6A), but statistical significance was not reached for any individual serotype.

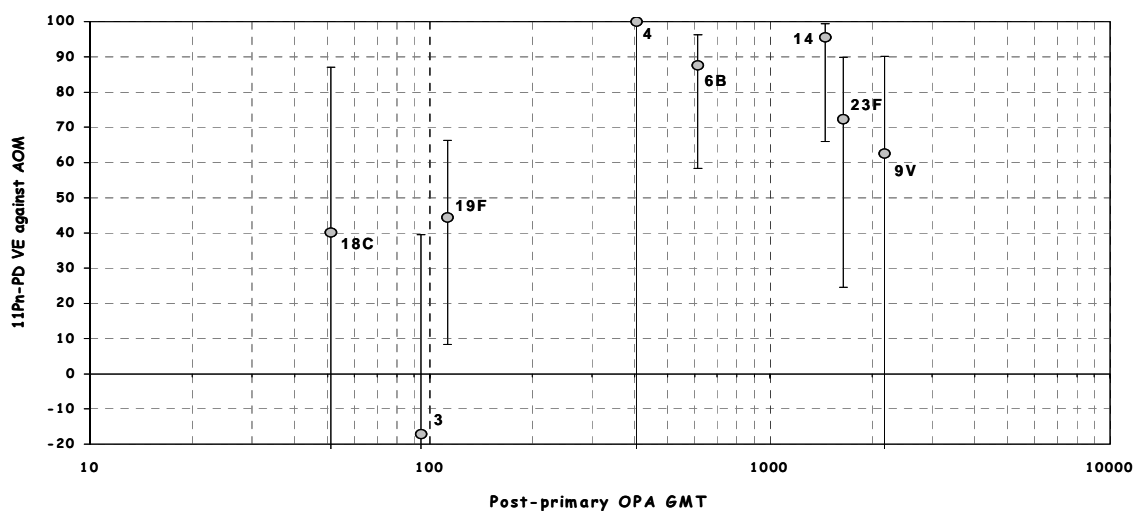
Overall vaccine efficacy (i.e. efficacy against first episode of AOM regardless of aetiology) was 34.5% (95% CI: 22.9, 44.3). Although not statistically significant, a trend for reduction of recurrent AOM (≥ 3 episodes in 6 months or ≥ 4 in 12 months) was observed (55.6% (95% CI: -1.9, 80.7)). The same trend was observed for ventilation tube placement (60.3% (95% CI: -26.7, 87.5)).

During the follow-up period there was no evidence of pneumococcal serotype replacement disease, even though NPH carriage data suggested some increase in non-vaccine types at some time points. There was no significant effect on carriage rates of NTHi although some reductions were noted. At one time point (age: 15-18 months) a significant 40% reduction of the NPH carriage of *H. influenzae* was observed.

Correlation between efficacy and antibody levels

There was no clear correlation between efficacy and serotype specific immune responses in the POET trial as determined by either OPA or ELISA. However, there was a trend towards a relationship between OPA GMTs and efficacy with the more efficacious types having the highest OPA titres (Fig 2). Based on these results, OPA activity against each serotype was used as the primary endpoint for the immunological comparison between Synflorix and the 11Pn-PD vaccine formulation tested in POET.

Figure 2 Relationship between pneumococcal serotype-specific OPA GMTs post-dose III and efficacy against pneumococcal AOM in POET



No correlation between protection against AOM episodes due to NTHi and antibody levels against the carrier protein D could be established, as post-primary anti-PD IgG antibody concentrations in 11Pn-

PD vaccinees that remained NTHi AOM episode-free were similar to those measured in 11Pn-PD vaccinees that developed at least one NTHi AOM episode during the efficacy follow-up period.

In the absence of an appropriate *in vitro* functional assay to measure anti-protein D immunity, the validated *in vivo* juvenile chinchilla otitis media model was used to demonstrate comparable biological functionality of anti-PD immune responses against NTHi following vaccination of human infants with either Synflorix or with 11Pn-PD in POET. The results in the chinchilla model were considered supportive, but cannot substitute for human efficacy data.

Study Undeca-Pn-037-Extension of POET trial

This study was performed to address the concern that the 11Pn-PD vaccine induced immune tolerance or hyporesponsiveness to serotype 3. A total of 100 subjects, who had participated in the POET trial and received 4 doses of the 11Pn-PD or HAV vaccine, were enrolled. The study subjects were vaccinated with one single dose of 23vPS vaccine. The mean age at the time of vaccination was 3.6 years. Antibody levels declined for all serotypes in the two year period between the post booster (fourth dose) and prior to the 23vPS dose. The percentage of subjects still reaching the 0.20 µg/ml threshold varied among serotypes from 20 % (serotype 4) to 93% (serotype 14). Some of the serotypes such as 6B, 14 and 19F had less pronounced antibody decline. As regards OPA, the seropositivity rates (GMT > 1:8) ranged from 13-16% (serotype 1 and 18C) to 92-100% (serotypes 6B, 9V and 14). Ten to 15 days after the 23vPS booster, antibody GMCs against each serotype increased substantially, with increases ranging between 6- and 180-fold compared to pre-23vPS levels, indicating persistence of immune memory. The polysaccharide vaccine elicited immune responses in both the primed (100% >0.20µg/ml) and the unprimed (71.4% >0.20µg/ml) groups for all serotypes, including serotype 3. OPA GMTs increased substantially and were between 4- and 1472-fold higher than pre-booster levels. The highest fold-rise was observed for type 1.

The results indicated that the serotype 3 PD-conjugate did not induce a hypo-responsiveness and that the capacity of children to respond to a natural infection would not be impaired.

Immunological bridging between 11Pn-PD and Synflorix

METHODS

Because the 11Pn-PD formulation was no longer available, a head-to-head comparison with Synflorix vaccine was not possible. Instead a comparison of the immune response induced by the 10-valent vaccine to historical immunogenicity data obtained with the 11Pn-PD vaccine in POET was performed in the study 10PN-PD-DiT-010.

The primary aim of study 10PN-PD-DIT-010 was to assess whether paracetamol, given as prophylactic treatment, significantly reduced the rate of febrile reactions in children receiving at 3, 4, and 5 months of age primary vaccination. Another aim of the study, which was amended to the study protocol in November 2006, was to compare the immunogenicity data of Synflorix with the immunogenicity data of the 11Pn-PD vaccine from POET trial, to provide a basis for AOM efficacy of Synflorix.

Study 10PN-PD-DIT-010 was conducted in the same setting (Czech Republic) and used the same immunisation schedule (3-4-5 months) as that in the POET study.

Primary immunogenicity analysis

The objective of comparison of immunogenicity data from study 10PN-PD-DIT-010 to the historical immunogenicity data obtained in POET would be reached if the upper limits of the 95% CIs for OPA GMTs ratios for the 10 common pneumococcal serotypes would be below 2.5. The use of a 2.5 limit for demonstration of non-inferiority based on OPA GMT ratios was chosen given the higher variability of OPA responses (compared to ELISA).

RESULTS

In the primary immunogenicity analysis comparing the OPA GMT ratios (11Pn-PD/Synflorix) one month post-dose 3 dose, it was shown that the upper limit of the 95% CI around the GMT ratio was below the pre-specified 2.5 limit for 8 out of 10 vaccine pneumococcal serotypes and therefore the objective of the study was not met. The upper limit was >2.5 for serotypes 1 and 5. For three serotypes 4, 18C and 19F, all of which have a higher amount of PS (3 µg) and two that used other carriers than PD (DT and TT), the OPA titres were higher in the Synflorix group. However, considering the unexpected finding in study 10PN-PD-DIT-010 that paracetamol had a negative impact on vaccine-induced immune response and that half of the study subjects were administered prophylactic paracetamol, whereas only 1.5% of the study subjects in POET received paracetamol at the time of vaccine administration, a reanalysis was performed taking into account these facts.

In the comparison made between POET 11Pn-PD subjects and the 10Pn-PD-DIT-010 subjects who were not administered paracetamol at the time of vaccination, the immunological non-inferiority of Synflorix was demonstrated for all serotypes except serotype 1 (Table 10). OPA GMT ratios were lower than 1 for 3 serotypes (UL of the 95% CI <1 for serotypes 4, 18C, 19F), similar to 1 for 4 serotypes (the 95% CI included 1 for serotypes 6B, 7F, 14, 23F), and higher than 1 for 3 serotypes (LL of the 95% CI >1 for serotypes 1, 5, 9V).

Table 10: Post-dose III OPA GMT ratios (11Pn-PD in POET over non-antipyretic Synflorix group from study 10PN-PD-DIT-010) for vaccine serotypes (ATP cohort for immunogenicity)

Anti body	11Pn-PD		10PnNAP		GMT ratio (11Pn-PD /10PnNAP)		
	N	GMT	N	GMT	Value	95% CI	
						LL	UL
OPSONO-1	99	41.7	176	23.7	1.76	1.16	2.66
OPSONO-4	102	399.8	175	744.6	0.54	0.43	0.67
OPSONO-5	103	99.0	171	72.5	1.36	1.01	1.85
OPSONO-6B	106	567.5	162	684.8	0.83	0.56	1.23
OPSONO-7F	102	2619.0	170	2345.3	1.12	0.84	1.48
OPSONO-9V	104	1758.6	169	1230.3	1.43	1.08	1.89
OPSONO-14	105	1262.2	175	1161.6	1.09	0.83	1.42
OPSONO-18C	97	47.4	170	202.2	0.23	0.17	0.32
OPSONO-19F	100	106.5	165	369.5	0.29	0.20	0.41
OPSONO-23F	100	1722.5	170	1497.2	1.15	0.83	1.60

These conclusions were supported by a *post-hoc* analysis of the OPA responses in study 10PN-PD-DIT-001 (performed according to the more compressed 2-3-4 month primary vaccination schedule). This analysis, which used the same non-inferiority criteria as those defined in the 010 protocol, showed that the upper limit of the 95% CIs around the OPA GMT ratio (11Pn-PD in POET/Synflorix in study 10PN-PD-DIT-001) was below 2.5 for all vaccine serotypes.

With respect protein D, lower ELISA GMCs were observed in the Synflorix group. The clinical significance of this reduced anti-PD response is not known. The results of the passive protection experiments in the chinchilla otitis model using sera from children immunised with the 10Pn vaccine support the biological function of the anti-PD antibodies. However, whether sufficient antibody levels will be reached following vaccination of children to afford protection against NTHi AOM is unclear.

When comparing immune responses following booster vaccination with the 11Pn-PD and Synflorix, no substantial differences in the magnitude of the ELISA or OPA responses were observed for any serotype (including for serotype 1) except that OPA GMTs were somewhat lower for serotypes 5 and 9V in the Synflorix group. The booster dose data were considered important supporting the comparability of the two vaccines.

- Other studies

Lot-to-lot consistency (study 10PN-PD-DIT-001)

The clinical consistency of the immunogenicity of three consecutive production lots of Synflorix was also evaluated as a co-primary objective in study 001. Lot-to-lot consistency was demonstrated according to pre-specified criteria: the 95% CIs on the adjusted GMC ratios for each pair of lots were within the pre-defined range of [0.4 to 2.5] for each pneumococcal serotype and for protein D. The criteria used were accepted by the CHMP in a Scientific Advice.

It can be concluded that consistency of post-primary antibody response for each of the 10 serotypes was demonstrated for 3 different lots of Synflorix.

3-dose primary vaccination (Studies 10PN-PD-DIT-001, -002, -003, -005, -010, -011, -012 and -013)

Eight primary vaccination studies evaluated immunogenicity of Synflorix in the various 3-dose schedules used in the EU, i.e. 2-3-4 months (studies 001, 002 and 003), 3-4-5 months (studies 010 and 013) and 2-4-6 months (studies 005, 011 and -012). All studies were conducted in Europe, except for study 005 (Chile). In addition, in study 012, half of the subjects were enrolled in Philippines and vaccinated at 6, 10 and 14 weeks of age. Four studies included Prevenar in the control arm. Synflorix was always co-administered with other paediatric vaccines. The study results from the 226 subjects who were part of the antipyretic group in study 10PN-PD-DiT-010 are described in section 'effect of prophylactic antipyretic use' further below.

Synflorix was demonstrated to induce an immune response to all ten serotypes in all vaccination schedules. The GMCs and GMTs varied considerably amongst serotypes for both vaccines and also but less so, by vaccination schedule. Somewhat higher ELISA GMCs were seen with the 2-4-6 month schedule, in the Chilean subjects, as well as in Philippino infants vaccinated according to the EPI schedule. OPA GMTs were less variable across studies. These findings are most likely the results of a population effect (i.e. genetic factors, priming of maternal vaccination with antigens such as tetanus toxoid, pneumococcal nasopharyngeal acquisition) rather than a schedule/age effect. The high baseline levels of maternal pneumococcal antibodies were noteworthy in both study groups of 012 study, but in particular in the Philippino group.

In general, serotype 14 proved to be the most immunogenic type by ELISA and 6B and 23F were the least immunogenic types for both vaccines. Over 93% of subjects who received a 3-dose series with Synflorix and 94.7% of those who received Prevenar reached the ELISA threshold ≥ 0.20 $\mu\text{g/ml}$, except for serotype 6B in both vaccines and 23F in the Synflorix group.

For the three additional serotypes 1, 5 and 7F the proportion of subjects achieving antibody concentrations ≥ 0.20 $\mu\text{g/ml}$ ranged from 93.1% to 100% in Synflorix recipients and from 1.7% to 5.2% in Prevenar recipients. The GMCs were in the same order of magnitude as the 7 common serotypes and varied from 1.00 to 2.82 $\mu\text{g/ml}$ in Synflorix groups, whereas only minimal ELISA reactivity (0.03 to 0.04 $\mu\text{g/ml}$) were observed in Prevenar groups.

As regards the functional immune response, at least 76.3% of subjects (89.8% for Prevenar) across all schedules achieved OPA titres ≥ 8 , except for serotype 1 (43.1%-82.4%). GMTs were usually lower for Synflorix than for Prevenar, with the exception of serotype 19F. Serotype 7F proved to be the most immunogenic by OPA for the 10-valent vaccine and serotype 23F for Prevenar. The least immunogenic types by OPA were the 'additional' serotypes 1 and 5. In addition, post-primary OPA responses to serotype 18C did not reach the same level as for other serotypes but remained within the same range or higher compared to post-primary OPA responses for serotype 19F in Prevenar vaccinees. In all studies 98-100% of subjects receiving Synflorix were seropositive (>100 EL.U/ml) for antibodies to protein D.

Antibody persistence (Studies 10PN-PD-DIT-002, -007, -008, -013, -014, -017 and -022)

Persistence of antibodies 7 to 14 months after 3-dose primary vaccination with Synflorix was assessed in 7 studies including 2931 infants vaccinated with Synflorix and 693 vaccinated with Prevenar. The results of 205 subjects vaccinated with Synflorix and belonging to the antipyretic group in study

10PN-PD-DiT-014 are described in section 'effect of prophylactic antipyretic use' further below. In most of the studies the 2-3-4 or 3-4-5 months schedule was used for primary and in 3 studies Prevenar was included as a control. A decline in antibody concentrations was seen for both vaccines and for all serotypes, except 6B. Similar to what has been reported for Prevenar, the GMCs for serotype 6B increased somewhat during the observation period. As regards serotype 23F, the antibody decline was very modest in the Synflorix group, in contrast to the Prevenar group. Thus, the low responses observed for 6B and 23F following primary vaccination with Synflorix did not translate into reduced antibody persistence compared to Prevenar in the second year of life. However, with respect to the functional immune response for serotypes 6B and 23F, expected declines in OPA GMTs were observed similarly for both vaccines. At the time of booster 50%-99% of subjects primed with Synflorix and 44%-96% of those primed with Prevenar had antibody concentrations ≥ 0.20 $\mu\text{g/ml}$ to the common serotypes. As regards the three additional serotypes, the proportion of subjects maintaining the threshold ≥ 0.20 $\mu\text{g/ml}$ was low for serotype 1 (36%-72%) and 5 (67%-89%), but higher for serotype 7F (90%-98%). For both vaccines, the percentages of subjects with OPA titres ≥ 8 prior to booster vaccination varied considerably amongst serotypes. Low OPA persistence was observed for serotypes 1, 5 and 18C in the Synflorix group with only 15%-29%, 34%-62% and 14%-41%, respectively of subjects still being seropositive. For Prevenar reduced persistence was noted for serotype 19F (16.4%-23.5%).

Comparative persistence data from studies 10PN-PD-DIT-007, -008, and -017 indicate that the percentages of subjects who had still OPA titres above the threshold at the pre-booster time point were in general similar for Synflorix and Prevenar.

Booster vaccination (Studies 10PN-PD-DIT-002, -007, -013, -014, -017 and -022)

Booster vaccination with Synflorix was received by 3870 children between 11 and 18 months of age, of which 2871 received a fourth dose of Synflorix vaccine after 3-dose priming. The results of 205 subjects vaccinated with Synflorix and belonging to the antipyretic group in study 10PN-PD-DiT-014 are described in section 'effect of prophylactic antipyretic use' further below. Prevenar was included in the control arm of studies 10PN-PD-DIT -007 (N=92) and 10PN-PD-DIT-017 (N=357). Both vaccines induced a booster response with the GMC/GMTs being higher than post-primary responses for all serotypes. Increases of ELISA (at least 3.8-fold increase) and OPA (at least 3.9-fold increase) responses were observed after a fourth dose of Synflorix compared to pre-booster levels. These data indicate a priming effect of the 3 vaccine doses on the immune system and the boostability of the immune response by Synflorix against all serotypes. The magnitude of booster responses differed by serotypes and vaccines. Prevenar induced greater fold increases of GMCs pre- to post-boost for the 'low immunogenic' serotypes 6B and 23F, whereas for the other common serotypes, the booster responses were in the same order of magnitude in both groups. As regards, the 'additional serotypes', 1, 5 and 7, the GMC ratios post- to pre-boost varied from 6.3 to 10.9, 4.3 to 8.1 and 4.0 to 6.3, respectively. Overall, the post-booster GMCs were higher in the Prevenar group for all the 7 serotypes in common, except 19F. The lowest GMCs in the Synflorix group were observed for serotypes 6B, 1 and 5. At least 98.8% of subjects attained the 0.20 $\mu\text{g/ml}$ threshold in both vaccine groups, except for serotype 6B (96.4%-99.0% (Synflorix) and 97.7%-99.3% (Prevenar)) and 23F (97.5%-99.3% (Synflorix) and 98.9%-99.3% (Prevenar)). The percentages of subjects with seroprotective OPA titres were similar for both vaccines. At least 96% of subjects attained OPA titres $\geq 1:8$, except for serotypes 1 (83.3%-97.4%), 6B (84.4%-98.4%) and 19F (91.5%-100%) in the Synflorix groups and 19F (92.5%-98.5%) in the Prevenar groups. The lowest GMTs in the Synflorix group were observed for serotypes 1 and 5. The data on immune response against carrier protein D indicated a good priming effect of the 3-dose schedule and an anamnestic response following the booster dose.

The Applicant has committed to follow-up long-term persistence of the immunogenicity and immune memory, which will provide important information.

Booster interchangeability following 3-dose priming (Study 10PN-PD-DIT-007)

Booster dose of Synflorix following 3-dose priming with Prevenar was explored in study 007. A booster response was observed for all serotypes. Although post-booster ELISA antibody GMCs and OPA GMTs were generally lower compared to four consecutive doses of the same vaccine, at least 97.0% and 94.9% of subjects reached the ELISA and OPA threshold, respectively, for the serotypes

common to both vaccines. For the 3 new serotypes (1, 5 and 7) at least 85% of Prevenar-primed subjects reached the 0.20 µg/ml antibody threshold compared to less than 7.5% in Prevenar primed and boosted subjects. After a booster dose of Synflorix, 50% of the subjects primed with Prevenar were seropositive for protein D antibodies, which were significantly lower compared with subjects who received four doses of the 10-valent vaccine.

A statement in the SPC that subjects who receive a first dose of Synflorix is recommended to complete the vaccination course with Synflorix has been added. In addition, a paragraph in section 5.1 describes the data obtained in the booster interchangeability study.

Vaccine-related serotypes 6A and 19A

The immune response against cross-reactive serotypes 6A and 19A following Synflorix vaccination, was assessed by ELISA and OPA in all primary vaccination studies except one, and in five booster studies. Both Synflorix and Prevenar induced an immune response against the vaccine-related serotypes 6A and 19A, which became more apparent after the booster dose. For serotype 6A higher post-booster GMC/GMTs were observed in the Prevenar group, whereas for serotype 19A, Synflorix appeared to induce a somewhat stronger immune response. For serotype 6A the observed post-booster response in the 10Pn group was in the same order of magnitude as that observed for serotype 1.

2-dose primary vaccination and booster response (Study 10PN-PD-DIT-002)

The immune response to 2-dose primary vaccination with Synflorix compared to 3-dose primary vaccination was assessed in study 10PN-PD-DIT-002, including 351 subjects. The vaccine was meant to be administered according to 2-4-11 month compared to a 2-3-4-11 month vaccination schedule, but in reality the doses were given by the 3-5-12 month schedule, which is the nationally recommended schedule in the countries where the study was conducted. Both vaccination schedules elicited ELISA and OPA responses against all serotypes. Lower ELISA GMCs values were noted for all serotypes after the 2-dose series than after the 3-dose series. In particular, low antibody titres were observed for serotypes 6B and 23F and a significantly smaller proportion of infants achieved an antibody concentration ≥ 0.20 µg/ml for these serotypes. As regards the functional immune response, differences between dose groups were more pronounced. Substantially lower OPA GMTs for the majority of serotypes were observed after a two-dose series than after a three-dose series. Particularly low OPA titres were observed for serotypes 1, 5 and 18C. The differences between groups became less marked following the booster dose, both with respect to ELISA and OPA responses, but was still noticeable for serotype 6B (OPA and ELISA) and serotype 5 (OPA).

The 2-dose schedule proved to be less immunogenic in comparison with the 3-dose schedule and cannot be recommended. The clinical consequences of the lower post-primary and post-booster immune responses observed after a two-dose primary schedule are not known. The 3-dose primary schedule is recommended to ensure optimal protection. This is reflected in the SPC sections 4.2 and 5.1. The effectiveness of the 2-dose Synflorix vaccine schedule will be monitored in the planned post-marketing study in Finland.

Catch-up immunisation schedules (Study 10PN-PD-DIT-013)

Catch-up vaccination with Synflorix in children 7-11 months, 12-23 months and ≥ 24 months to 5 years of age was assessed in study 10PN-PD-DIT-013. The different catch-up schedules were documented in an appreciable number of children (N=450 with 150/group) and included a control group of <6 month olds (N=150) receiving the standard 3 primary series (2-3-4 months). It is to be noted that functional antibody response were only analysed in a subset of subjects (50/group). Only interim data were available on the two younger age groups, but booster data were submitted during the assessment period. Data on the age distribution in the older group showed that the majority (two thirds) was between 24 to 35 months of age. The dose recommendations proposed in the SPC for the respective age groups are for the 7-11 months old: 2 doses with an interval of at least one month and a third dose during the second year of life (after clinical confirmation) and for the 12-23 months old, 2 doses with an interval of at least two months. These dose recommendations are in line with those given in the SPC for Prevenar. The overall pattern of the induced immune responses was very similar

in all age groups with respect to the low ELISA responses to serotypes 6B and 23F and low OPA responses to serotypes 1 and 5. The booster response data for the < 6 months of age and 7-11 months of age groups showed no major differences. In addition, the safety profile was comparable between groups. These data supported the proposed vaccination schedule for previously unvaccinated children aged of 7 to 11 months as stated in section 4.2 of the SPC.

With respect to the 12-23 months group, higher GMC/GMTs post-dose 2 were noted for the majority of serotypes compared to those post-dose 3 in the <6 months group. However, for the least immunogenic types 6B and 23F the ELISA GMCs were as low as in the infants. The functional antibody responses were improved for most serotypes with the exception of serotypes 1 and 5; these were similarly low in both age groups. The need for a booster dose after a two doses in children aged 12-23 months has not been established.

In children above two years of age, the proportion of subjects with antibody concentrations ≥ 0.20 $\mu\text{g/ml}$ was lower for serotypes 14 and 23F compared to the < 6Mo group and higher for serotype 19F. The GMCs were lower for serotypes 1, 5, 14 and 23F and were higher for serotypes 4, 18C and 19F compared to those in the <6Mo control group. OPA titres ≥ 8 were measured in at least 90.2% of the subjects for all serotypes, except serotypes 1 (46.3%), 5 (56.4%) and 6B (64.7%). The proportion of subjects with OPA titres ≥ 8 were lower for serotypes 1, 5 and 6B and higher for serotypes 18C and 19F compared to the < 6 month group.

Considering the suboptimal response observed for 4 serotypes (1, 5, 6B and 23F), the 2-dose schedule could be questioned in 12-23 month olds. A booster dose seems as necessary in this age group as in the infant to ascertain that a seroprotective level is reached for all vaccine serotypes. The Applicant has committed to evaluate booster vaccination of children 12-23 months of age. With respect to children aged > 24 months, the results in study 013 suggest that a second dose is needed to optimize protection. The Company had no claim in the SPC for children ≥ 24 months (i.e. one single dose).

► Immune memory (Study 10PN-PD-DIT-008)

Subjects primed in study 10PN-PD-DIT-003 with three doses of either Synflorix or Prevenar received a single dose of 23-valent plain polysaccharide vaccine (23vPS) at 11 to 14 months of age (mean age of 12.1 months) in study 10PN-PD-DIT-008. Historical data were provided for unprimed children. The pre- and post- 23vPS boost results with respect to the ELISA GMCs indicated a good anamnestic response following primary vaccination. The priming effect varied by serotype, but was discernable for all vaccine serotypes. In particular, good booster responses were seen for serotypes 1 and 5. With respect to serotypes 6B and 23F, a 7-fold rise in GMCs was seen from pre- to post-boost in the Synflorix group, whereas this was higher in the Prevenar group (18-fold). Moreover, lower post-boost GMCs were observed for serotypes 4, 6B and 23F in the Synflorix group. The data on ELISA responses suggest the induction of immune memory in subjects primed with Synflorix and Prevenar receiving a challenge dose with the 23vPS. However, these results did not translate into a similar boost of the more important functional immune responses. The OPA GMTs did not exceed the post-primary levels and were for several of the serotypes even lower than one month after the 3-dose primary series. Both vaccines displayed a similar pattern although it varied some by serotype. The reason for the reduced OPA responses might be the immature immune system of the young infant and its inability to respond to plain polysaccharides. However, these infants were fully capable to respond to a booster dose of the conjugate pneumococcal vaccines. Moreover, the older children in the POET trial who had already received a booster dose responded with high OPA responses after a challenge dose of 23vPs.

The results on avidity for 5 serotypes (1, 6B, 14, 19F and 23F) provided additional support of the induction of an immune memory after a primary vaccination course. In contrast, the OPA/ELISAs ratios post-primary and post-booster did not turn out to be reliable markers of the maturation of the antibody response following Synflorix vaccination. The immune memory data on the 23vPS vaccine in the 10PN-PD-DIT studies did not provide any guidance how to use the 10-valent vaccine in high-risk children following primary immunisation. A statement in the SPC section 4.4 reflects this. The Company committed to perform a study (10PN-PD-DIT-061) to address whether hyporesponsiveness occurs following a full-dose of 23vPS. Subjects in study 10PN-PD-DIT-008 will be revaccinated with Synflorix or Prevenar at approximately 4 years of age.

Co-administered vaccines

In all completed clinical trials, DTPa-combination vaccines were co-administered with Synflorix. In study 10PN-PD-DIT-010, rotavirus vaccine (Rotarix, HRV) was co-administered with the first 2 doses of Synflorix primary vaccination course at 3 and 4 months of age. Different MenC or Hib-MenC conjugate vaccines were co-administered in study 10PN-PD-DIT-011. In the booster vaccination study 10PN-PD-DIT-022, the first or second dose of MMRV vaccine was co-administered with the fourth dose of Synflorix at either 12-14 or 14-16 months of age. This program took into account all the potential co-administrations used in the EU. The methods, cut-offs and approach for assessment of the immune response to co-administered vaccine antigens were the same as those employed during the clinical development of GSK's licensed vaccines. At each time-point, seropositivity/seroprotective rates and their 95% CIs were calculated for the vaccine antigens.

The immune response induced by the co-administered paediatric vaccines was in line with previous observations with the respective DTPa-combined, HRV, MMRV, MenC and Hib-MenC licensed vaccines. Inconsistent post primary results were however observed across studies for poliovirus type 2, which is mentioned in the SPC, section 4.5. Immune responses against the tetanus and PRP antigens were enhanced when co-administered with Synflorix. This higher response is likely due to the presence of the TT-carrier in Synflorix. For the HepB vaccine somewhat lower anti-HBs titres and seroprotection rates were observed in the 10Pn group compared to the HAV control group in study 10PN-PD-DIT-005, but data from other studies did not indicate any immune interference between Synflorix and HepB vaccine.

The evaluation of study 10-PN-PD-DiT-012 concerning the co-administered DTPw-HBV/Hib vaccine antigens revealed that the seroprotection/seropositivity vaccine responses were in general lower in the Philippines (EPI schedule) compared with those in Poland (2-4-6 month schedule). E.g. for the HepB vaccine antigen ~90% of Philippino infants post-dose 3 attained seroprotective anti-HBs titres vs. 99-100% of Polish children and the GMCs were also significantly lower. This was observed in both vaccination groups. A reduced immune response to the HepB vaccine has been observed by other research groups in Philippino children and might be due to interference of maternal antibodies. Lower responses to polio virus types 1 and 3 to OPV vaccine were seen in the Prevenar group, but otherwise there were no significant differences between the pneumococcal vaccine groups.

Concerning the anti-pneumococcal response, there were some differences observed between the three Synflorix primed study groups in study 10PN-PD-DIT-011 receiving concomitant MenC vaccines. The lowest antibody responses were observed in the Pn-HibC group, with lower GMCs for all vaccine serotypes and lower OPA GMTs for 8 of 10 serotypes than in the other two Men C groups. However, post-booster data from study 017 did not suggest any clinically relevant immunological interference between HibC (Menitorix) and Synflorix. There was no control group receiving only pneumococcal vaccines included in the study and comparison with other 3-dose primary studies is difficult due to the different vaccination schedules used. For the MMRV vaccine there was no evidence to suggest that co-administration with Synflorix interfered with the anti-pneumococcal antibody response.

The results suggest no clinically significant effect of Synflorix on the immune response to co-administered vaccine antigens, except for poliovirus type 2. A statement of the enhanced Hib response and the inconsistent immune response to poliovirus type 2 has been included in the SPC.

Effect of prophylactic antipyretic use (Study 10PN-PD-DIT-010 and -014)

Study 10PN-PD-DIT-010 was designed to demonstrate reduction in febrile reactions (rectal temperature $\geq 38.0^{\circ}\text{C}$) when prophylactic antipyretic treatment was administered compared to no prophylactic antipyretic treatment. All subjects received 3-dose primary vaccination with Synflorix co-administered with DTPa-HBV-IPV/Hib at 3, 4 and 5 months of age and with Rotarix at 3 and 4 months of age. One group received three doses of paracetamol: one dose at the time of vaccination and two doses at 6-8 hourly intervals subsequently. The immunogenicity of Synflorix and of the co-administered Infanrix hexa was assessed one month after the third dose. Lower post-primary ELISA GMCs were noted for all vaccine pneumococcal serotypes in the group that received antipyretics compared with the non-antipyretic group, whereas the effect on functional antibodies was more limited. Responses against serotypes 6B, 1 and 5 seemed particularly affected. For Infanrix hexa

antigens, reductions in GMCs were observed for DT, TT, PRN and Hib, but seropositivity/seroprotective levels were not affected, except for anti-PRP.

In a *post-hoc* analysis of study 10PN-PD-DIT-001, the impact of the use of paracetamol on pneumococcal antibody concentrations was confirmed, although the observed differences in antibody GMCs reached statistical significance only in the Prevenar group for serotypes 4, 6B, 9V and 18C, suggesting that this effect is not limited to a specific vaccine.

Study 10PN-PD-DIT-014 is the booster study of 10PN-PD-DIT-010 and was submitted during the procedure. This study had a primary safety objective (described below under safety) but also aimed at evaluating the impact of prophylactic paracetamol on the booster response to the 10-valent vaccine and to co-administered vaccine antigens. Lower GMCs and GMTs were observed in the antibody persistence analysis at the pre-booster time point in the group receiving prophylactic paracetamol (10Pn-AP), which could be expected considering the lower post-primary responses seen in this group compared with the non-antipyretic group (10Pn-NAP). The pre-booster ELISA antibody persistence was lowest for serotype 1 with 56% of subjects maintaining the ≥ 0.20 $\mu\text{g/ml}$ antibody threshold in the 10Pn-AP group vs. 71% in the 10Pn-NAP group. The corresponding percentages for serotype 5 were somewhat higher, 75% and 89%, respectively. Overall, for the other vaccine serotypes at least 73% had antibody concentrations ≥ 0.20 $\mu\text{g/ml}$ in the 10Pn-AP group and 85% in the 10Pn-NAP group.

As regards pre-booster OPA persistence of GMTs $> 1:8$, it was poor for serotypes 1, 5 and 18C (15%, 38% and 22%, respectively) in the 10Pn-AP group, but was also low in the 10Pn-NAP group (24%, 58% and 41% respectively). The pre-booster OPA GMTs were very low for all these serotypes. These findings justify the statement in section 4.4 of the SPC that the prophylactic use of paracetamol might reduce the immune response to Synflorix.

The booster immunogenicity data showed that there were no differences observed between subjects with or without prophylactic antipyretic treatment, with respect to the percentage of subjects achieving anti-pneumococcal antibody concentration > 0.20 $\mu\text{g/ml}$ and OPA titre $\geq 1:8$, except for OPA response to serotype 6B. Differences in terms of pneumococcal antibody ELISA GMCs and OPA GMTs after booster vaccination were observed for several vaccine serotypes, but overall post-booster antibody responses were higher than those after the primary series for all serotypes. The fold-increases (post-booster/pre-booster and post-booster/post-primary) were comparable in the antipyretic and non-antipyretic groups, suggesting that the prophylactic administration of paracetamol does not interfere with the boostability of the induced immune response. The preserved boostability also indicates that the quality of the memory response is not impacted by the prophylactic administration of paracetamol. The Applicant committed to submit the final study report for study 014 as soon as available.

The clinical relevance of these findings, which suggest a negative interference of paracetamol on vaccine immunogenicity, is unknown. The significance of the lower post-primary antibody titres/concentrations is unclear, but the post-booster data suggest that the impact on efficacy, if any, should be limited. As prophylactic use of antipyretic drugs is common vaccination practice in some countries a warning in section 4.4 of the SPC has been added. However, based on the results in study 10PN-PD-DIT-012 demonstrating a higher incidence of fever after co-administering Synflorix with DTPw combination vaccine, a statement in SPC section 4.4 has been added, recommending prophylactic antipyretics for these children and also for children with seizure disorders or with a prior history of febrile seizures.

It was clarified that antipyretics other than paracetamol, including ibuprofen, were rarely used in the Synflorix clinical program. The company assumes that ibuprofen, which also exerts peripheral effects, might potentially also impact immune responses. The applicant committed to conduct a study investigating the impact of prophylactic antipyretic treatment with ibuprofen on vaccine immunogenicity.

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

Not applicable

- Clinical studies in special populations

Not applicable

- Discussion on clinical efficacy

The results of the primary non-inferiority analysis to Prevenar using the 0.20 µg/ml threshold based on the new bridging study, demonstrated that the pre-specified criteria were met for all serotypes, except serotypes 6B and 23F. The clinical relevance of the lower ELISA responses for serotypes 6B and 23F can be questioned, since high OPA seropositivity was demonstrated for both serotypes as well as acceptable GMTs. Importantly efficacy was demonstrated against 6B and 23F acute otitis media in the POET trial supporting the functionality of the immune response. Further data were provided that allowed the assumption that protective efficacy against 6B and 23F IPD and AOM will be in the same range as that for Prevenar, at least up to the age of 24 months. Since the WHO guideline states that non-inferiority to antibody response for each of the serotypes of Prevenar is not an absolute requirement, it can be concluded that the primary objective of the WHO licensure criteria was met by Synflorix. The additional WHO licensure criteria, boostability and immune memory, were also fulfilled for Synflorix.

The most critical issue with Synflorix is the low functional immune responses observed for serotypes 1 and 5, as seen with another pneumococcal conjugate vaccine under development. These two serotypes met the non-inferiority criteria by ELISA when using the aggregate response against the 7 Prevenar serotypes. However, the post-primary OPA responses were lower than for the other serotypes. The clinical implications of this finding are not known, but may suggest lower vaccine efficacy against IPD and AOM due to these serotypes. After the booster dose a strong anamnestic response was observed with 92.5% and 96.8% of subjects reaching an OPA titre $\geq 1:8$ for serotypes 1 and 5 respectively, but still GMTs remained relatively low. Additional non-inferiority analysis was performed comparing the OPA responses for the new serotypes 1, 5 and 7F with that of the least immunogenic (by OPA) Prevenar serotype 19F. For the post-primary OPA responses, serotype 1 failed to fulfill the non-inferiority criteria, whereas with respect to analyses of antibody persistence and post-booster responses all three serotypes were shown to be comparable to Prevenar 19F. Although the clinical relevance of these data is not known, they suggest that vaccine efficacy for serotypes 1 (after the booster dose), 5 and 7F would be comparable to that observed for Prevenar 19F in the CDC effectiveness follow-up study (VE: 87% after at least one dose and 100% after 4 doses). The fact that 2 different pneumococcal conjugate vaccines induce lower post-primary OPA responses against serotypes 1 and 5 indicate that these serotypes may have intrinsic characteristics making them more difficult to kill by any pneumococcal vaccine. According to current data, the majority of invasive disease caused by serotypes 1 and 5 in Europe occurs in children above 1 year of age, i.e. after the booster dose and at a time point when the vaccine would be efficacious. Therefore the potential clinical consequences of the lower immune responses on vaccine efficacy against serotypes 1 and 5 would be limited in Europe. However, this situation may not be stable over time since serotype epidemiology is changing. The applicant has committed to conduct post-marketing studies to evaluate the effectiveness of the 10-valent vaccine against serotypes 1, 5 and 7F during at least 5 years, as well as to evaluate the possibility of performing a study in an African setting or in other developing country to collect data on IPD due to the rarest serotype 5. Until these results are available, it is indicated to include a statement in the SPC (sections 4.4 and 5.1) to reflect the unknown impact on vaccine protection against serotypes 1 and 5 disease.

In the POET trial it was demonstrated that the 11Pn-PD vaccine is efficacious against vaccine-serotype pneumococcal AOM. The results did not demonstrate statistically significant vaccine efficacy against first episode of NTHi AOM, although efficacy against any NTHi AOM episode (analysis as secondary objectives) did reach statistical significance. The overall efficacy profile as regards pneumococcal AOM was very similar to that of Prevenar, which in the EU has gained approval in the AOM indication. In addition, with respect to the overall AOM disease burden, a reduction of 33.6% was observed in the POET trial as compared to only 6% for Prevenar in the Finnish OM trial. Also serotype replacement disease was seen in the FinOM trial with a 33% increase of non-vaccine serotype AOM, whereas there was no evidence of such an increase in the POET trial. However, the follow-up on POET is too short to exclude serotype replacement. Considering that efficacy was only followed up until the second year of life, the applicant has committed to perform a longer term follow-

up of AOM efficacy as well as to evaluate serotype replacement, nasopharyngeal carriage and antibiotic resistance in post-marketing studies. The ongoing COMPAS study (10PN-PD-DiT-028) will provide efficacy data on Synflorix, planned to become available 2012.

In the comparison of the immunogenicity (OPA) of the 11Pn-PD vaccine used in POET and Synflorix used in study 10PN-PD-DIT-010 based on the study subjects who were not administered prophylactic paracetamol, the non-inferiority of the 10-valent vaccine was demonstrated for all serotypes, except serotype 1. The post-primary OPA GMTs ratios were lower for 3 serotypes (1, 5 and 9V) and higher for 3 serotypes (4, 18C and 19F) in the Synflorix group versus the 11Pn-PD group. The post-primary ELISA GMC ratios were comparable for all serotypes, with higher post-primary responses for types 18C and 19F and somewhat lower response for type 6B in the Synflorix group. Comparable post-booster responses for the two vaccines were observed for all serotypes. Based on these data, the bridging of anti-pneumococcal responses between 11Pn-PD in POET study and Synflorix in study 010 to support efficacy against AOM was accepted. The low post-primary OPA GMTs for serotypes 1 and 5 might not provide protection against AOM, considering that protection against mucosal infections is more difficult to obtain than protection against IPD, requiring higher antibody titres. It is noted that current data indicate that serotypes 1 and 5 are rare causes of AOM. A statement about the unknown impact on vaccine protection against serotypes 1 and 5 in sections 4.4 and 5.1 in the SPC has been added.

The limitations of the predictive capacity of pre-licensure immunogenicity data strongly indicate the need for post-marketing studies. Only post-licensing efficacy/effectiveness studies can reveal the magnitude of protective efficacy provided by Synflorix. The company has committed to perform a large post-licensure effectiveness study in Finland and a surveillance study in the EU to monitor IPD following country-wide vaccination with the Synflorix. Further studies will evaluate long-term immunogenicity, efficacy and safety. Specific studies designed to evaluate the effectiveness of the candidate vaccine against serotypes 1, 5 and 7F and to evaluate impact of Synflorix on nasopharyngeal carriage will also be performed.

An important deficiency of the submitted documentation is the lack of data on vaccine immunogenicity in certain high-risk children, i.e. those with sickle cell disease, asplenia, nephrotic syndrome, immunosuppression, cochlear implant and cerebrospinal leaks. There are ongoing studies evaluating safety and immunogenicity of Synflorix in pre-term, low birth weight infants and HIV infected subjects.

Clinical safety

In almost all of the studies Synflorix was co-administered with a DTPa-based combination vaccine. Other co-administered vaccines were human rotavirus vaccine (HRV), meningococcal serogroup C conjugate vaccines and MMRV. In each of these studies the safety and reactogenicity profile was a primary and secondary objective. Analysis of solicited local and general adverse events (AEs) and unsolicited adverse events including serious adverse events (SAEs) was performed for each individual study. Evaluation of safety of Synflorix was based on comparison with Prevenar. Analyses were performed from pooled safety data.

- **Patient exposure**

Safety data with Synflorix have been collected within 14 studies evaluating primary, booster and catch-up vaccination, 4145 subjects received 12, 137 doses of Synflorix, 3725 subjects received a booster dose of Synflorix and 450 subjects were vaccinated with 887 catch-up doses of Synflorix. In addition, more than 55, 000 doses of Synflorix are planned to be administered in all clinical trials populations of ongoing and planned primary, booster and catch-up vaccination studies.

Supportive safety data from 27 clinical trials conducted with different 11-valent vaccine formulations in which 8329 received primary or catch-up vaccination and 4603 subjects received a booster dose of a related 11-valent vaccine (28929 doses).

- Adverse events

Solicited adverse events

Local AEs (*pain, redness and swelling at injection site*) and general AEs (*drowsiness, fever, irritability/fussiness and loss of appetite*) were solicited during the 4 day (day 0-3) post-vaccination period in each study. Additional solicited general AEs were received from study 10PN-PD-DIT-010 (*vomiting and diarrhoea*) because of co-administered Rotarix vaccine and study 10PN-PD-DIT-022 included *rash/exanthema, parotid/salivary gland swelling* and any sign of *meningism* including *febrile convulsions* because of co-administered MMRV vaccine. *Large swelling reaction (> 50 mm)* was solicited in subjects as of 11 months of age in booster and catch-up vaccination studies.

Solicited local adverse event

Primary vaccination

The most frequently reported solicited local AE in primary vaccination 10PN-PD-DiT studies with co-administration of DTPa-based combination vaccines was *redness* with an overall incidence per dose of 38.3%. No consistent increase in incidence of solicited local AEs was observed with consecutive doses over the full primary immunization course. The incidences of at least one and of grade 3 solicited local AEs were in the same range with those reported after DTPa-based vaccine administration. *Pain* was the most frequently reported solicited local AE in primary vaccination study with co-administration of DTPw-based combination vaccine with an incidence of 51.8%.

The results from the comparative analysis of solicited local AEs in primary vaccination with co-administration of DTPa-based combination vaccines are summarized in Table 11. *Redness* was the most frequently reported solicited local AE in both groups. The overall incidences per subject of *pain* and of *swelling > 20mm* were slightly higher in the Synflorix groups. Differences between groups in terms of grade 3 *pain* and *swelling > 30 mm* were small and not significant.

Table 11: Comparison of percentage of subjects reporting solicited local adverse events - pain, redness and swelling - within the day 4 (0-3) follow-up period in Prevenar controlled primary vaccination studies 001, 003, 011 with co-administration of DTPa-based combination vaccines (TVC cohort)

			Group						Relative Risk (Synflorix over Prevenar)			
			Synflorix			Prevenar				95% CI		
Symptoms	Study	Type	N	n	%	N	n	%	RR	LL	UL	P-value
Pain	Pooled	All	2442	1340	54.9	865	419	48.4	1.12	1.00	1.25	0.046
		Grade 3	2442	154	6.3	865	39	4.5	1.33	0.93	1.95	0.121
Redness	Pooled	All	2442	1582	64.8	865	566	65.4	0.99	0.90	1.09	0.827
		> 20 mm	2442	259	10.6	865	79	9.1	1.14	0.88	1.48	0.356
		> 30 mm	2442	100	4.1	865	32	3.7	1.07	0.71	1.66	0.811
Swelling	Pooled	All	2442	1313	53.8	865	428	49.5	1.08	0.96	1.21	0.190
		> 20 mm	2442	372	15.2	865	102	11.8	1.26	1.01	1.59	0.040
		> 30 mm	2442	165	6.8	865	49	5.7	1.16	0.84	1.63	0.418

n/% = number/percentage of subjects reporting at least one specified symptom whatever the number of injections

95% CI = 95% confidence interval for Relative risk (RR) (Exact Stratified Conditional to total number of cases, taking into account the study effect),

P-value = 2-sided Exact Stratified Test conditional to number of cases, taking into account the study effect

There were no differences between Synflorix and Prevenar groups in the percentage of subjects reporting local solicited symptoms after primary vaccination with co-administration of DTPw-based vaccine, in study 10PN-PD-DIT-012 with a Prevenar control group except for swelling. The clinical relevance of this difference can be considered limited since difference between groups in terms of swelling >30 mm was small and not clinically meaningful.

Booster vaccination

The descriptive pooling included the Synflorix groups from studies 10PN-PD-DIT-002, -004, -007, -013, -014, -017 and -022 (only Synflorix + Infanrix hexa group). *Redness* was the most frequently reported solicited local AE with an incidence of 56.4%. Comparative safety data between booster dose of Synflorix and Prevenar was based on Prevenar controlled booster vaccination studies 10PN-PD-

DIT-007 and -017. *Redness* and *pain* were the most frequently reported solicited local AEs in both groups with an incidence for *redness* of 56.0% in the Synflorix groups and 52.0% in the Prevenar group (RR=1.03 [0.89, 1.20]). Incidence of *pain* was 56.9% in Synflorix groups and 47.8% in Prevenar group (RR=1.16 [1.00, 1.36]). No statistically significant differences were observed for any of the solicited local AEs or for those of grade 3 intensity.

The incidences of at least one and of grade 3 solicited local AEs reported after administration of Synflorix were within the same range with those reported after DTPa-based vaccine administration. Observed incidences of *injection site reactions* were higher after booster vaccination with Synflorix than after a primary vaccine dose, but remained within the same range as those reported at the DTPa-based booster injection site.

Catch-up vaccination

The results of the descriptive analysis of solicited local AEs in the three catch-up vaccination groups in study 10PN-PD-DIT-013 (7-11 months of age, 12-23 months of age and ≥ 24 months of age) are summarized in table 12.

Table 12: Overall/dose incidence of solicited local AEs – pain, redness, swelling – reported within the 4 day (day 0 – 3) follow-up period in Synflorix catch-up vaccination study groups (Total vaccinated cohort)

Symptoms	STUDY	Type	7-11 months						12-23 months						≥ 24 months						
			N	n	%	LL	UL	95 % CI	N	n	%	LL	UL	95 % CI	N	n	%	LL	UL	95 % CI	
Pain	013	All	295	93	31.5	26.3	37.2	292	177	60.6	54.8	66.3	148	102	68.9	60.8	76.3				
		Grade 3	295	5	1.7	0.6	3.9	292	33	11.3	7.9	15.5	148	24	16.2	10.7	23.2				
Redness (mm)	013	All	295	153	51.9	46.0	57.7	292	109	37.3	31.8	43.2	148	65	43.9	35.8	52.3				
		> 20mm	295	28	9.5	6.4	13.4	292	12	4.1	2.1	7.1	148	14	9.5	5.3	15.4				
		> 30mm	295	13	4.4	2.4	7.4	292	5	1.7	0.6	4.0	148	9	6.1	2.8	11.2				
Swelling (mm)	013	All	295	87	29.5	24.3	35.1	292	77	26.4	21.4	31.8	148	32	21.6	15.3	29.1				
		> 20mm	295	28	9.5	6.4	13.4	292	20	6.8	4.2	10.4	148	10	6.8	3.3	12.1				
		> 30mm	295	16	5.4	3.1	8.7	292	13	4.5	2.4	7.5	148	7	4.7	1.9	9.5				

N= number of documented doses; n/%= number/percentage of doses followed by at least one type of symptom,; Total : n/%= number/percentage of subjects/doses with at least one local symptom whatever the number of injections

7-11 months = Synflorix 2 doses with 4 weeks interval ; 12-23 months = Synflorix 2 doses with 8 weeks interval

≥ 24 months = Synflorix one dose at 24 months - 5 years of age

As previously reported for the licensed Prevenar vaccine, high incidences of *pain* were reported in the 12-23 months and ≥ 24 months of age groups.

Based on the relative risk, no differences in the occurrence of any solicited local AEs was observed with consecutive doses over the full primary immunization course with Synflorix or Prevenar with DTPa-based combination vaccines, with the exception of any *pain* and *swelling* >20 mm which occurred more often in the Synflorix groups in primary vaccination and *pain* in booster vaccination.

There were no differences between the groups in the percentage of subjects reporting solicited local symptoms after primary vaccination with co-administration of DTPw-based vaccines, in studies with a Prevenar control group except for swelling. The clinical relevance of these differences can be considered limited since differences between groups in terms of grade 3 pain and swelling > 30 mm were small.

Solicited general adverse events

Primary vaccination

The results show that the most frequently reported solicited general AE in primary vaccination 10PN-PD-DIT studies with co-administration of DTPa-based combination vaccines was *irritability* with an overall per dose incidence of 56.0%. The overall per dose incidence of any *fever*: rectal temperature ≥38°, >39°C and >40°C were 34.2%, 2.6% and 0.1%, respectively. For *fever*, causally related to vaccination, the incidences were 33.1%, 2.4% and 0.0%, respectively. Higher *fever* incidences was observed for Synflorix doses co-administered with DTPa-HBV-IPV/Hib compared to Synflorix without co-administration. Data from study 10PN-PD-DIT-005 suggest a trend for higher *fever* incidences following DTPa-HBV-IPV/Hib co-administered with Synflorix compared to DTPa-HBV-IPV/Hib co-administered with HAV. *Irritability* was also the most frequently reported solicited local

AE in primary vaccination study with co-administration of DTPw-based combination vaccine with an incidence of 74.0%. The overall per dose incidence of any *fever*: rectal temperature $\geq 38^\circ$, $>39^\circ\text{C}$ and $>40^\circ\text{C}$ were 60.5%, 5.8% and 0.0%, respectively.

The results from the comparative analysis of solicited general AEs in Prevenar-controlled studies with co-administration of DTPa-based combination vaccines show that *irritability* was the most frequently reported solicited general AE in both Synflorix and Prevenar groups with an overall incidence per subject of 80.5% in the Synflorix groups and 78.0% in the Prevenar groups (RR=1.03 [0.94, 1.12]). No statistically significant differences were observed for any of the solicited general AEs or for those of grade 3 intensity.

Booster vaccination

The most frequently reported AE was *irritability* with an incidence of 57.6%. The incidence of any *fever* ($\geq 38^\circ\text{C}$) was 39.7% and of $> 39^\circ\text{C}$ and $> 40^\circ\text{C}$ were 5.2% and 0.5%, respectively. For any *fever* causally related to vaccination the incidence was 36.8%. A moderate increase of the incidences of *loss of appetite* and *fever* was observed after booster vaccination with Synflorix compared to primary vaccination.

The results from the comparative analysis of solicited general AEs in the Prevenar controlled study show that *irritability* was the most frequently reported solicited general AE with an incidence of 55.9% in the Synflorix groups and 47.5% in the Prevenar groups (RR=1.12 [0.96, 1.30]). No statistically significant differences were observed for any of the solicited general AEs or for those of grade 3 intensity.

Catch-up vaccination

The results of the descriptive analysis of solicited general AEs in the three groups receiving Synflorix in catch-up vaccination are summarized in table 13 below.

Table 13: Overall/dose incidence of solicited general AEs – drowsiness, irritability, fever, loss of appetite – reported within the 4 day (day 0 – 3) follow-up period in catch-up vaccination study groups (Total vaccinated cohort)

Symptom	Type	7-11 months					12-23 months					≥ 24 months				
		N	n	%	95 % CI		N	n	%	95 % CI		N	n	%	95 % CI	
Drowsiness	All	295	121	41.0	35.3	46.9	292	111	38.0	32.4	43.9	148	55	37.2	29.4	45.5
	Grade 3	295	1	0.3	0.0	1.9	292	3	1.0	0.2	3.0	148	1	0.7	0.0	3.7
	Related	295	119	40.3	34.7	46.2	292	108	37.0	31.4	42.8	148	55	37.2	29.4	45.5
	Grade 3 & Related	295	1	0.3	0.0	1.9	292	3	1.0	0.2	3.0	148	1	0.7	0.0	3.7
Irritability	All	295	168	56.9	51.1	62.7	292	152	52.1	46.2	57.9	148	62	41.9	33.8	50.3
	Grade 3	295	5	1.7	0.6	3.9	292	7	2.4	1.0	4.9	148	2	1.4	0.2	4.8
	Related	295	167	56.6	50.7	62.3	292	149	51.0	45.1	56.9	148	62	41.9	33.8	50.3
	Grade 3 & Related	295	5	1.7	0.6	3.9	292	6	2.1	0.8	4.4	148	2	1.4	0.2	4.8
Loss of appetite	All	295	77	26.1	21.2	31.5	292	77	26.4	21.4	31.8	148	41	27.7	20.7	35.7
	Grade 3	295	0	0.0	0.0	1.2	292	4	1.4	0.4	3.5	148	0	0.0	0.0	2.5
	Related	295	74	25.1	20.2	30.4	292	72	24.7	19.8	30.0	148	40	27.0	20.1	34.9
	Grade 3 & Related	295	0	0.0	0.0	1.2	292	3	1.0	0.2	3.0	148	0	0.0	0.0	2.5
Fever (rectal temperature)	$\geq 38.0^\circ\text{C}$	295	68	23.1	18.4	28.3	292	54	18.5	14.2	23.4	148	10	6.8	3.3	12.1
	$> 38.5^\circ\text{C}$	295	10	3.4	1.6	6.1	292	13	4.5	2.4	7.5	148	4	2.7	0.7	6.8
	$> 39.0^\circ\text{C}$	295	4	1.4	0.4	3.4	292	6	2.1	0.8	4.4	148	1	0.7	0.0	3.7
	$> 39.5^\circ\text{C}$	295	1	0.3	0.0	1.9	292	4	1.4	0.4	3.5	148	0	0.0	0.0	2.5
	$> 40.0^\circ\text{C}$	295	0	0.0	0.0	1.2	292	0	0.0	0.0	1.3	148	0	0.0	0.0	2.5
	$\geq 38.0^\circ\text{C}$ & Related	295	67	22.7	18.1	27.9	292	48	16.4	12.4	21.2	148	10	6.8	3.3	12.1
	$> 39.0^\circ\text{C}$ & Related	295	4	1.4	0.4	3.4	292	4	1.4	0.4	3.5	148	1	0.7	0.0	3.7
	$> 40.0^\circ\text{C}$ & Related	295	0	0.0	0.0	1.2	292	0	0.0	0.0	1.3	148	0	0.0	0.0	2.5

Specific solicited adverse events

Fever

A statistically significant increase in the incidence of *fever* ($\geq 38.0^\circ\text{C}$) was observed in infants when Synflorix was co-administered with standard infant vaccines such as DTPa/Hib, IPV and HBV, compared to their separate administration. The increase in the incidence of *fever* $\geq 38.0^\circ\text{C}$ was

significant for the first three doses of the primary vaccination course, whereas an increase in the incidence of fever > 39°C was only significant at the second dose. The differences in the incidence of fever ≥ 38.0°C and > 39°C were not significant after the booster vaccination. In the clinical trials, febrile reactions were moderate with rectal temperatures generally ≤ 39°C. The occurrence of grade 3 fever (> 40°C) was very low and comparable in the co-administration and control groups. Generally, the onset of fever was within 24 hours and of relatively short duration was < 72 hours.

Large swelling reactions (studies -002, -004, -007 and -022)

Large swelling reactions were reported by 7 (out of 2086) subjects after the booster dose. The onset of swelling occurred within three days after vaccination and all resolved within three days. In addition, large swelling reactions were reported by 32 (out of 2329) subjects at the site of the co-administered DTPa-based vaccine across all studies. Four (out of 300) subjects reported a large swelling reaction at the Synflorix injection site after catch-up immunization: one subject in the 12-23 months of age group and three subjects in the ≥ 24 months of age group.

Unsolicited adverse events by organ system or syndrome

Primary vaccination

The incidence of unsolicited AEs considered causally related to vaccination was 4.0% with the most frequently reported event injection site induration (1.3%).

Booster vaccination

Unsolicited AEs causally related to vaccination was 5.6% and most frequently reported was injection site induration (1.0%). The percentage of subjects reporting at least one causally related unsolicited AE was 4.2% for the Synflorix groups and 5.3% for the Prevenar group (RR=0.65 [0.40, 1.08]). Injection site induration was reported more often in the Prevenar group (RR=0.13 [0.04, 0.40], p=0.0001).

Catch up vaccination

The incidence of at least one unsolicited AE causally related to vaccination was 14.5% in the 7-11 months of age group, 12.2% in the 12-23 months group and 11.3% in the ≥ 24 months group. No cases of febrile or non-febrile convulsions were reported in the catch-up vaccination groups.

- Serious adverse event/deaths/other significant events

Incidence of Serious Adverse Events by Primary System Organ Class

Primary vaccination

The incidence of SAEs in Synflorix groups is summarised in Table 14. The SOC with the highest incidence of SAEs was “Infections and infestations” (6.9%)

Table 14: Incidence of serious adverse events in primary studies presented by System Organ Class (TVC cohort)

Primary System Organ Class (CODE)	Synflorix Pool N = 4145	
	n	%
<i>At least one symptom</i>	374	9.0
Blood and lymphatic system disorders (10005329)	8	0.2
Congenital, familial and genetic disorders (10010331)	3	0.1
Eye disorders (10015919)	1	0.0
Gastrointestinal disorders (10017947)	37	0.9
General disorders and administration site conditions (10018065)	8	0.2
Hepatobiliary disorders (10019805)	1	0.0
Immune system disorders (10021428)	4	0.1
Infections and infestations (10021881)	287	6.9
Injury, poisoning and procedural complications (10022117)	27	0.7
Metabolism and nutrition disorders (10027433)	14	0.3
Musculoskeletal and connective tissue disorders (10028395)	1	0.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	2	0.0
Nervous system disorders (10029205)	11	0.3

Primary System Organ Class (CODE)	Synflorix Pool N = 4145	
	n	%
Psychiatric disorders (10037175)	4	0.1
Renal and urinary disorders (10038359)	2	0.0
Reproductive system and breast disorders (10038604)	1	0.0
Respiratory, thoracic and mediastinal disorders (10038738)	42	1.0
Skin and subcutaneous tissue disorders (10040785)	13	0.3
Vascular disorders (10047065)	2	0.0

For Prevenar controlled trials the incidence of SAEs was within the same range in both groups. The number of subjects reporting at least one SAE in Synflorix groups was 300 (9.8%), and 96 in Prevenar groups (9.0%).

Booster vaccination

The incidence of SAEs by SOC reported throughout the study period in booster studies evaluating the Synflorix vaccine is described in Table 15. The SOC with the highest incidence of SAEs was “Infections and infestations” (2.0%).

Table 15: Incidence of serious adverse events in booster studies presented by System Organ Class (Total vaccinated cohort)

Primary System Organ Class (CODE)	Synflorix Pool N = 3725	
	n	%
<i>At least one symptom</i>	123	3.3
Blood and lymphatic system disorders (10005329)	1	0.0
Gastrointestinal disorders (10017947)	7	0.2
General disorders and administration site conditions (10018065)	2	0.1
Infections and infestations (10021881)	76	2.0
Injury, poisoning and procedural complications (10022117)	16	0.4
Metabolism and nutrition disorders (10027433)	4	0.1
Musculoskeletal and connective tissue disorders (10028395)	2	0.1
Nervous system disorders (10029205)	11	0.3
Respiratory, thoracic and mediastinal disorders (10038738)	19	0.5
Skin and subcutaneous tissue disorders (10040785)	2	0.1

In Prevenar controlled studies 74 subjects, i.e. 3.5% in Synflorix groups, and 18 subjects, i.e. 4.0%, in the Prevenar group reported at least one SAE. The SOC with the highest incidence of SAEs was “Infections and infestations” (2.3% and 3.1%, respectively).

Catch-up vaccination

The incidence of SAEs by SOC reported throughout the study period in catch-up groups was 4.0% in the 7-11Mo group, 1.3% in the 12-23Mo group and 0.0% in the ≥ 24 Mo group. Also in these groups the SOC with the highest incidence of SAEs was “Infections and infestations”.

Deaths

In completed primary vaccination studies 2 died out of the 4145 vaccinated subjects in the Synflorix groups and 1 out of the 1072 subjects in the Prevenar groups. None of the fatalities was considered by the investigator to be causally related to vaccination.

No fatal SAEs were reported in any of the study groups in completed booster vaccination studies. No fatal SAEs were reported in completed catch-up vaccination study groups.

Other Significant Adverse Events

Apnoea

Altogether 4 cases were reported from completed studies, 3 in the Synflorix group and one from the Prevenar group. All cases were full-term born babies.

From the ongoing studies were a total of thirteen case reports received where time to onset of *apnoea* or apnoeic attacks varied from 7 hrs to 54 days after vaccination. Only one case was considered to be possibly related and that child had received blinded vaccine. All subjects received multiple vaccines which may have contributed to the ADRs. In none of the cases in ongoing studies the investigator and the applicant considered that there was any reasonable possibility that apnoea may have been caused by the investigational product.

The findings in the present application support the warning in the SPC for Synflorix sections 4.4 and 4.8 although reports on the experience of apnoea also in full-term babies justifies continuous monitoring of all cases of apnoea and/or apnoeic attacks and subsequently accounting for in cumulative tables in future PSURs.

Break-through infections

Any case of severe pneumonia, AOM, sepsis and/or meningitis in vaccinated individuals should be subject to detailed diagnosis. The results from the ongoing study 10PN-PD-DiT-028, COMPAS will contribute to the evaluation of the possible risk of break-through infections. The Company commits (RMP, post-marketing study) to perform a 5-year IPD surveillance study in a country that would routinely use Synflorix and where this country has a nationwide pneumococcal disease surveillance system.

Reports on meningitis or meningo/encephalitis caused by pneumococci

Seven reports of meningitis or meningoencephalitis, were received. Three came from completed studies and 4 from ongoing studies. In one of these cases, meningitis was reported to be caused by pneumococci. However, culture results were not provided in this case. The other cases were reported to be viral (3), suspected bacterial (1), aseptic (1) and non-specified (1) in nature.

The applicant committed to provide the CHMP with a study plan for a surveillance study. The pharmaco-vigilance plan includes the plan for a post marketing study to monitor for possible serotype replacement and break-through infection/vaccine failure. This is expected to last for 3-5 years.

The company defines in the post-licensure surveillance, a vaccine breakthrough as the occurrence of an IPD case caused by a vaccine serotype reported in a fully vaccinated child, with an onset more than 14 days after the last dose (or more than 7 days if the last dose is a booster dose). The definition of a fully vaccinated child will be according to the appropriate-for-age schedule in line with the posology section of the SPC. The definition of a breakthrough case has been included in the surveillance protocol. For pneumonia and AOM, a similar case definition of a breakthrough case will be used, provided that they are bacteriologically confirmed.

- Laboratory findings

No specific laboratory findings. Results were provided for data on immune response only.

- Safety in special populations

Data from 10PN-PD-DIT studies in different populations have been compared with regard to possible differences in the safety profiles in relation to ethnicity. White Caucasian children, all from Poland, were vaccinated at the ages of 2-4-6 months while children of Asian Heritage all came from the Philippines. The South Asian children were vaccinated at an earlier age according to the 6-10-14 week's schedule. The Polish children were concomitantly vaccinated with DTPw-HBV/Hib+IPV vaccine while the Philippino children received DTPw.

With regard to the local solicited symptoms *redness* and *swelling* the incidence was significantly higher after primary doses in the Polish children (2-4-6 months vaccination group) as compared to the children from the Philippines. Concerning general solicited symptoms were higher incidences observed for all solicited symptoms – except for *fever* - in Synflorix vaccinees in Poland. The

differences in safety profile may be related to the differences in vaccination schedules and/or the co-administered vaccines. It has to be noted that both vaccination groups received Pw i.e. pertussis whole cell vaccine. The trends observed for Synflorix between the populations were also observed for Prevenar.

Ongoing studies in Latin America (Mexico) and in Africa will provide more data about whether the safety profile of Synflorix would be similar irrespective of ethnicity. Results from the studies were expected as of 2009.

As the vaccine is not intended for use in adults, information on the effects in pregnancy and lactation is not available.

- Safety related to drug-drug interactions and other interactions

Effect of prophylactic paracetamol on reactogenicity

The incidence of *pain* seemed to be lower in the group with prophylactic paracetamol (10Pn-AP group, 17.9%) than in the group without prophylactic paracetamol (10PnNAP group 28.6%). *Irritability* was the most frequently reported solicited general AE in both groups, but less frequently in the 10Pn-AP group than in the 10PnNAP group. The incidences of reports on overall/dose grade 3 solicited general AEs considered to be causally related to vaccination (maximum of 1.5%) were low.

Primary objective of reduction in febrile reactions $\geq 38.0^{\circ}\text{C}$ when paracetamol is administered compared to non- prophylactic administration of paracetamol was met with since the lower limit of the 95% CI of the difference (10PnNAP group minus 10Pn-AP group), in terms of percentage of subjects with *fever* $\geq 38.0^{\circ}\text{C}$ (rectal temperature) within 4 days (days 0 to 3) after at least one vaccination, was higher than 0% (15.5%).

Study 10PN-PD-DIT-014 (=booster of study 10PN-PD-DIT-010) submitted during the procedure assessed the impact of prophylactic antipyretic medication on booster vaccination with Synflorix. Results demonstrated that the administration of paracetamol as prophylactic antipyretic treatment in the 24 hours following booster vaccination with Synflorix co-administered with the DTPa-HBV-IPV/Hib vaccine, significantly reduced the incidence of febrile reactions with rectal temperature $\geq 38.0^{\circ}\text{C}$ (36.0% of subjects the AP-AP group versus 58.1% of subjects in the NAP-pre group). The primary objective was reached as the lower limit of the 95% CI for the difference between groups (NAP-pre minus AP-AP) in terms of the percentage of subjects reporting *fever* with rectal temperature $\geq 38.0^{\circ}\text{C}$ was above the pre-defined limit of 0% (LL of 11.78%).

The prophylactic administration of paracetamol also reduced the percentage of subjects reporting *pain* after booster vaccination. The percentage of subjects reporting unsolicited adverse events and medically attended visits for unsolicited adverse events was in the same range for the AP-AP, AP-NAP and NAP groups. Up to the data lock point, two subjects in the AP-AP group reported a serious adverse event after booster vaccination. None of these serious adverse events were assessed by the investigator to be causally related to vaccination and both resolved without sequels.

In summary it was shown that the administration of antipyretic paracetamol treatment in the 24 hours following booster vaccination significantly reduced the incidence of febrile reaction in the vaccinated subjects. Furthermore, the number of subjects reporting post booster vaccination pain was reduced. No specific safety data for the pneumococcal conjugate unprimed MenACWY-TT groups were retrieved by this study.

Additional solicited AEs specific to co-administered human rotavirus vaccine

In study 10PN-PD-DiT-010 human rotavirus vaccine (Rotarix) was co-administered with Synflorix and Infanrix hexa at 3 and 4 months of age. Therefore, *diarrhoea* and *vomiting* were monitored as solicited general symptoms.

Additional solicited AEs specific to co-administered MMRV vaccine

In study 10PN-PD-DIT-022, MMRV vaccine (Priorix-Tetra) was co-administered with Synflorix or Infanrix hexa. Subjects were randomized (1:1:1). Occurrence of *rash/exanthema*, *parotid/salivary gland swelling* and any sign of *meningism* including *febrile convulsions* reported within a 43 day follow-up period was solicited. In the 4 day follow-up period, the incidence of *fever* (any and $>39^{\circ}\text{C}$) was lower in the two MV groups than in the 10Pn-Hx control group after dose 1 and 2. For any *fever* the difference was significant for the 10Pn-MV group compared to the 10Pn-Hx control group after

dose 1. *Fever* (any and $>39^{\circ}\text{C}$) was reported more commonly after the first dose of MMRV vaccine than after the second dose in groups that received two MMRV doses.

Primary vaccination

One case of *febrile convulsions* was reported as SAE in the Synflorix group (4,145 subjects) within the 31 day follow-up period after primary vaccine dose. This event was considered possibly causally related to study vaccines by the investigator. No *febrile convulsions* were reported in the Prevenar group (1,072 subjects) within the same time window.

Non-febrile convulsions were reported by 5 subjects (out of 4,145) in Synflorix groups and by 1 subject (out of 1,072) in Prevenar groups within the 31 day follow-up period after each primary vaccine dose. Two cases, both reported as non-serious unsolicited AEs in the Synflorix group, of which 1 newly reported after 1 October 2007, were considered to be causally related to study vaccination. After the 31 day post-vaccination period, one subject (out of 4,145) in the Synflorix groups reported *non-febrile convulsions*. Compared to the initial file, 2 new cases were reported as non-serious unsolicited AEs within the 31 day follow-up period in the Synflorix group.

Booster vaccination

None of the subjects in booster vaccination groups reported *non-febrile convulsions*. The cases of *febrile convulsions* has significantly increased compared to the initial file (3,725 subjects compared to 2,086 subjects in October 2007). On the day of vaccination 2 subjects (out of 3,725) reported *febrile convulsions* after the booster dose of Synflorix. Both were considered to be causally related by the investigator and were described in the initial file.

Three reports on *febrile convulsions* (one after primary and two after booster vaccination) occurred in temporal association with Synflorix administration and were considered to be possibly related to the vaccination. Two cases received Infanrix hexa and one case received Tritanrix-HepB/Hib and Poliorix concomitantly. A total of 14 non-related cases (7 after primary and 7 after booster vaccination) of *fever convulsions* occurred between 13 days and 13 months after Synflorix vaccination. The prolonged time to onset and concurrent febrile diseases made the causal relationship unlikely. However, the fact that 3 cases of *febrile convulsions* could be considered related to vaccination justified its enclosure in section 4.8 of the SPC.

Two possibly related *non-febrile convulsions* have been reported in close temporal association with administration of Synflorix. These subjects had received concomitant injections of Infanrix hexa and Tritanrix-HepB/Hib, respectively.

The number of related cases of febrile and non-febrile convulsions is small, but nevertheless the events are to be noted. The Company has committed to within routine post-marketing pharmacovigilance continuously monitor and cumulatively report all such adverse events.

- Discontinuation due to adverse events

Table 16: Number of subjects withdrawn from primary, booster and catch-up Synflorix vaccination groups (total vaccinated cohort) due to SAE of AE

Study	N subjects vaccinated		N subjects completed		Number of subjects withdrawn			
	10Pn	Ctrl	10Pn	Ctrl	SAE		AE	
					10Pn	Ctrl	10Pn	Ctrl
Primary vaccination								
001	1235	415	1214	409	5	1	5	2
002*	351	-	348	-	1	-	1	-
003	70	64	68	64	0	0	0	0
005	119	121	117	120	0	0	0	0
010	459	-	456	-	1	-	0	-
011	1158	390	1123	376	2	0	1	0
012	603	203	594	199	2	1	1	0
013*	150	-	145	-	0	-	3	-
015	286	-	270	-	1	-	0	-
Total	4431	1193	4335	1168	12	2	11	2
Booster vaccination								
002*	345	-	342	-	0	-	1	-
004	397	150	395	149	0	0	1	0
007	1020	92	1018	91	0	0	0	0
013* <6m	145	-	141	-	0	-	0	-
013* 7-11m	145	-	145	-	0	-	0	-
014	414	-	414	-	0	-	0	-
017	1080	357	1074	356	0	0	0	0
022	324	-	320	-	0	-	1	-
Total	3870	599	3849	596	0	0	3	0
Catch-up vaccination in 013*								
7-11m	150	-	146	-	0	-	1	-
12-23m	150	-	142	-	0	-	1	-
≥ 24m	150	-	148	-	0	-	0	-
Total	450	-	436	-	0	-	2	-

N vaccinated = number of subjects that received at least one dose of Synflorix or control ; N completed = number of subjects that completed the last study visit

N withdrawn = number of subjects that did not complete the last study visit, including the reason why.

* Study 002 and 013 included both primary and booster or catch-up study groups; the numbers of subjects are the numbers for the relevant phases/groups.

The overall withdrawal rate observed in Synflorix vaccine recipients was very low (1.2%). The majority of the subjects withdrew from the trials for reasons other than AEs or SAEs.

- Post marketing experience

Not applicable

- Supportive studies and data (booster, catch-up) submitted during the procedure

Study **10PN-PD-DIT-012** assessed safety of Synflorix when co-administered with DTPw-HBV/Hib vaccine for 3-dose primary vaccination in two schedules (EPI [6-10-14 weeks] and 2-4-6 months) in approximately 600 subjects. The primary objective of the study was reached as Synflorix, when co-administered with DTPw-HBV/Hib and OPV or IPV vaccines did not induce more fever than Prevenar.

In all groups high overall/dose incidences of adverse events (solicited or unsolicited, general or local) were reported with high incidences of grade 3 local adverse events. This reactogenicity profile is in line with previous experience with DTPw vaccines. Although the incidence of fever was high in both schedules, only one case of grade 3 fever was reported in the 2-4-6 months of age schedule. Low incidences of unsolicited adverse events were observed in both schedules (reporting following 21% to 28% of the vaccine doses). Fifty subjects reported at least one SAE. No fatal SAEs were reported. Two of the reported SAEs were assessed to be causally related to vaccination and led to withdrawal. All SAEs except for one case resolved without sequels.

Study **10PN-PD-DIT-013 assessed** safety data of a booster dose of Synflorix after a 2-dose catch-up immunisation in 7-11 months and after a 3-dose primary course (3-4-5 months). It has been submitted during the procedure. High incidences of any adverse event (solicited and unsolicited, general and local) after each dose were reported in all study groups including the <6Mo control group i.e. ~ 86%-95 %. The most frequently recorded adverse reaction reported was pain although predominantly in 12-23-Mo and \geq 24-Mo groups. This is in line with previous reports with Prevenar. In general, there was no increase in the overall incidence of adverse events with successive doses for the groups receiving more than one dose. None of the reported SAEs were assessed to be causally related to vaccination.

Study **10PN-PD-DIT-017** (=booster of study 10PN-PD-DIT-011) assessed safety of a booster dose of Synflorix when co-administered with DTPa-HBV-IPV or DTPa-HBV-IPV/Hib, Hib-MenC or MenC vaccines. A booster dose of Synflorix, when co-administered with a DTPa-combined and MenC or Hib-MenC vaccines at 11 to 18 months of age did not give raise to any new or significant safety signals.

Data from 28929 doses of 11-valent formulations in 27 clinical studies were also assessed. The observed percentage of subjects that reported unsolicited adverse events (any, grade 3 and with causal relationship to vaccination) following vaccination with an 11-valent vaccine formulation was within the same range as following vaccination with Prevenar or a non-pneumococcal control vaccine. The results from these studies do not include any specific issues indicating safety signals. The safety profile is similar to that of both Prevenar and Synflorix and thus provides additional reassurance of the safety of Synflorix.

- Discussion on clinical safety

Overall, more than 4000 subjects received a primary course of Synflorix and more than 3500 subjects received it as a booster dose. Additionally a large clinical study is ongoing (COMPAS) with target enrolment of 24,000 healthy male and female infants and another large phase III/IV study enrolling approximately 100,000 subjects is planned.

Comparison of the safety of Synflorix and the licensed 7-valent pneumococcal conjugate vaccine (Prevenar) indicates that the reactogenicity profiles of the two vaccines are very similar. No statistically significant differences were observed in terms of the percentage of subjects reporting any solicited local or general symptom (any or grade 3) with the exception of *pain* and *swelling* > 20 mm following primary vaccination which was of borderline significance (lower limit of the 95% CI on the RR = 1.00). Importantly there was no difference between groups in terms of *pain* of grade 3 intensity, nor in terms of *fever* \geq 38.0°C, >39.0°C or >40.0°C. The general experience of *pain* increased by age. There was no evidence for any increased risk for the occurrence of specific unsolicited adverse events following primary, booster or catch-up vaccination with Synflorix compared to Prevenar.

The overall incidence of solicited AEs was lower in the groups receiving paracetamol, principally regarding *pain* but also *irritability*. No prospective controlled studies have investigated the impact of prophylactic administration of paracetamol on the immune responses of DTPa-based and conjugate vaccines. It is speculated that ibuprofen, which also exerts peripheral effects, might potentially impact immune responses in a greater magnitude than paracetamol. This potential negative effect of ibuprofen requires to be investigated in controlled randomised studies. The applicant has committed to investigate the issue with a study plan regarding the effect of the vaccine- induced immune response of ibuprofen.

An increased risk of febrile convulsions has been observed when Prevenar was co-administered with DTPw compared to the control receiving MenC conjugate vaccine co-administered with DTPw. No increased risk was identified in subjects who had received DTPa concomitantly with Synflorix. One case of febrile convulsion was reported within the 31 day follow-up period after primary vaccination. None of the subjects in booster vaccination groups reported non-febrile convulsions. Febrile convulsions occur mainly beyond 3 months of age, with peak incidence around 18 months of age. Therefore a warning statement recommending prophylactic antipyretics for children with seizure

disorders or with a prior history of febrile seizure disorders and in particular, for those receiving DTPw based vaccines concomitant with Synflorix was included in the SPC section 4.4. The applicant committed to continuously monitor such adverse events within routine post-marketing pharmacovigilance and cumulatively report all.

No specific unsolicited adverse reactions deserving close monitoring were defined except for febrile and non-febrile convulsions. Individuals in risk groups for pneumococcal infection e.g. with neurological disease, asplenia, severe chronic disease, iatrogenic or disease related immunosuppression, HIV infection or after recent use of immunoglobulin have so far not been studied in the present development program.

A reported fatal case of sepsis and meningitis was diagnosed to be caused by pneumococci, although no bacteriological confirmation was performed. The investigator considered that there was no reasonable possibility that the pneumococcal meningitis and septic shock could have been caused by the vaccine. The study is still blinded i.e. the exact vaccine received by the subject remains unknown. The possibility of a break-through infection could not be excluded.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The Rapporteur 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 17: Summary of the risk management plan for Synflorix

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
Potential risk		
Febrile convulsions.	<p>Results of additional pooling of clinical data are presented in RMP version 3 (Data lock point 15 June 2008)</p> <p>Soliciting convulsions (both febrile and non-febrile) during booster phase of COMPAS clinical trial</p> <p>Monitoring of reporting incidence of cases of febrile convulsions through PSURs</p>	<p>Febrile convulsions are part of section 4.8 of the proposed EU SPC. The healthcare professional is informed of the possibility of febrile convulsions after the administration of Synflorix. This is a rare adverse event where sub-population has been identified that has a higher risk.</p> <p>Section 4.4. of the proposed EU SPC states: “Prophylactic antipyretic medication is recommended: for all children receiving Synflorix simultaneously with vaccines containing whole cell pertussis because of higher rate of febrile reactions (see section 4.8). for children with seizure disorders or with a prior history of febrile seizures.”</p> <p>Antipyretic treatment should be initiated according to local treatment guidelines.</p>
Possible serotype replacement of disease isolates	<ul style="list-style-type: none"> • GSK is exploring the feasibility to conduct a post-marketing surveillance study which will monitor IPD/breakthrough infection/vaccine failure/possible serotype replacement/herd immunity/antibiotic resistant strains. The duration of the study would be 5 years, with the duration dependent on continued use by the study region of Synflorix. The Company will support the enhancement of epidemiological surveillance for the identification and monitoring of Invasive Pneumococcal Disease in a country that would routinely use Synflorix, when the following conditions will be met: <ul style="list-style-type: none"> - the vaccination coverage in this country is sufficient to meet the main objectives of the post-licensure study in a timely manner. - this country has a nationwide pneumococcal disease surveillance system -this country has a minimum incidence of pneumococcal disease to allow surveillance of breakthrough infection/vaccine failure/possible serotype replacement in a timely manner. 	NA

<p>Apnoea in full term and premature infants</p>	<p>Final results of study 10PN-PD-DIT-015 are presented in the RMP version 3 section 1.2.2.2.1. and Annex 7</p> <p>Study 10PN-PD-DIT-016 BST: 015</p> <p>Post-marketing cases in preterm/low birth weight infants and full term babies will be discussed in PSURs</p>	<p>Section 4.4 of the proposed EU SPC states : “The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.”</p> <p>This adequately informs treating physicians and, at this stage, allows to manage the risk for apnoea in this sub-set of vulnerable children.</p>
<p>Possible breakthrough infections/ Vaccine failure</p>	<p>Routine pharmacovigilance</p> <p>Cases suggestive of lack of efficacy will be discussed in a separate PSUR section</p> <p>Planned study 10PN-PD-DIT-043</p> <ul style="list-style-type: none"> • GSK is exploring the feasibility to conduct a post-marketing surveillance study which will monitor IPD/breakthrough infection/vaccine failure/possible serotype replacement/herd immunity/antibiotic resistant strains. The duration of the study would be 5 years, with the duration dependent on continued use by the study region of Synflorix. The Company will support the enhancement of epidemiological surveillance for the identification and monitoring of Invasive Pneumococcal Disease in a country that would routinely use Synflorix, when the following conditions will be met: • the vaccination coverage in this country is sufficient to meet the main objectives of the post-licensure study in a timely manner. • this country has a nationwide pneumococcal disease surveillance systems • -this country has a minimum incidence of pneumococcal disease to allow surveillance of breakthrough infection/vaccine failure/possible serotype replacement in a timely manner. 	<p>Section 4.4 of the proposed EU SPC states: “As with any vaccine, Synflorix may not protect all vaccinated individuals against invasive pneumococcal disease or otitis media caused by the serotypes in the vaccine. Protection against otitis media caused by pneumococcal serotypes in the vaccine is expected to be substantially lower than protection against invasive disease. In addition, as otitis media is caused by many micro-organisms other than the Streptococcus pneumoniae serotypes represented in the vaccine, the overall protection against otitis media is expected to be limited (see section 5.1)”</p> <p>This adequately informs treating physicians and, at this stage, allows to manage the risk in this patient population.</p>

<p>Unforeseen safety signals arising in the post-authorisation period</p>	<ul style="list-style-type: none"> • Routine signal evaluation practices (see section 2.1.1 of RMP version 3) • Within the framework of study 10PN-PD-DIT-043, Finnish hospitalization database registry data from subjects enrolled in the study (approximately 100,000 subjects vaccinated with Synflorix) will be available to further evaluate unforeseen safety signals arising during the post-authorisation period. 	<p>NA</p>
<p>Identified interaction</p>		
<p>Paracetamol (prophylactic setting)</p>	<ul style="list-style-type: none"> • Results of study 10PN-PD-DIT-014 BST:010 are provided in the RMP version 3 section 1.2.5.2. and Annex 11b • The Company would in principle be willing to look further into the feasibility to conduct additional studies. However, the Company also is of the opinion that this is an overarching issue which should be discussed in the context of other pneumococcal vaccines (class effect). • Study 10PN-PD-DIT-050 (prophylactic and delayed ibuprofen) 	<p>Section 4.4 of the proposed EU SPC states “Prophylactic administration of antipyretics before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions. However, data suggest that the prophylactic use of paracetamol might reduce the immune response to Synflorix. The clinical relevance of this observation, as well as the impact of antipyretics other than paracetamol on the immune response to Synflorix remains unknown.”</p> <p>This adequately informs prescribers and patients of an issue for which, at this stage, no further preventive measures can be taken.</p>

<ul style="list-style-type: none"> Potential hyporesponsiveness following a dose of 23-valent pneumococcal polysaccharide vaccine (23PPV) 	<p>Study 10PN-PD-DIT-061 (ext 10PN-PD-DIT-008)</p>	<p>As several countries recommend a dose of 23-valent plain polysaccharide vaccine (PPV23) in high risk children above 2 years of life, the Company proposes to align the statement in section 4.4 (Special warnings and precautions for use), with the statement present in Prevenar SPC, namely:</p> <p>“The immune response elicited after two doses of Synflorix in children 12-23 months of age is comparable to the response elicited after three doses in infants (see section 5.1). The immune response to a booster dose after two doses in children aged 12-23 months has not been evaluated, but a booster dose may be needed to ensure optimal individual protection.</p> <p>However, a 2-dose schedule in children aged 12-23 month children with high risk of pneumococcal disease (such as children with sickle-cell disease, asplenia, HIV infection, chronic illness or who are immunocompromised) may not be sufficient to provide optimal protection. In these children, a 23-valent pneumococcal polysaccharide vaccine should be given ≥ 2 years of age, whenever recommended. The interval between the pneumococcal conjugate vaccine (Synflorix) and the 23-valent pneumococcal polysaccharide vaccine should not be less than 8 weeks. There are no data available to indicate whether the administration of pneumococcal polysaccharide vaccine to Synflorix primed children may result in hyporesponsiveness to further doses of pneumococcal polysaccharide or to pneumococcal conjugate vaccine.”</p>
<p>Inactivated poliovirus type 2 interaction</p>	<p>Routine pharmacovigilance</p>	<p>Section 4.5 of the proposed EU SPC states: “Clinical studies demonstrated that the immune responses and the safety profiles of the co-administered vaccines were unaffected, with the exception of the inactivated poliovirus type 2 response, for which inconsistent results were observed across studies (seroprotection ranging from 78% to 100%). The clinical relevance of this observation is not known.”</p> <p>This adequately informs prescribers and patients of an issue for which, at this stage, no further preventive measures can be taken.</p>
<p>Missing information</p>		
<p>Clinical data on preterm/low birth weight infants.</p>	<p>Study 10PN-PD-DIT-015. Study 10PN-PD-DIT-016 BST: 015 Post-marketing cases in preterm/low birth infants will be discussed in PSURs</p>	<p>NA</p>

Clinical data on immunocompromised/ immunodeficient subjects including HIV-positive subjects.	Study 10PN-PD-DIT-034. PSUR monitoring.	Section 4.4 of the proposed EU SPC states: “Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to vaccination.” Section 4.5 of the proposed EU SPC states: “As with other vaccines it may be expected that in patients receiving immunosuppressive treatment an adequate response may not be elicited.” This adequately informs treating physicians and, at this stage, allows to manage the risk in this patient population.
Data in children with sickle cell disease, asplenia and nephrotic syndrome.	Routine pharmacovigilance practices Special patient groups (i.e. at-risk sub-populations to be discussed in separate PSUR section)	Section 4.4 of the proposed EU SPC states: “Safety and immunogenicity data in children with increased risk for pneumococcal infections (sickle cell disease, congenital and acquired splenic dysfunction, HIV-infected, malignancy, nephrotic syndrome) are not available.” This adequately informs treating physicians and, at this stage, allows to manage the risk in this patient population.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

During the evaluation of Synflorix four quality major objections were identified. Satisfactory responses have been provided to resolve them. Other minor concerns have been adequately addressed, and some commitments are made by the applicant and follow-up measures are defined to provide further information post-approval. In conclusion, all quality issues are resolved.

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

Synflorix was demonstrated to induce an immune response to all ten serotypes and protein D in all 3-dose primary vaccination schedules (2-3-4, 2-3-5 and 2-4-6 months) as well as in EPI schedule. The vaccine induced a functional immune response as measured by opsonophagocytic (OPA) assay. The majority of subjects who received a 3-dose primary series reached the ELISA threshold ≥ 0.20 $\mu\text{g/ml}$ (at least 93%) and the seroprotective OPA titre $\geq 1:8$ (at least 76%), except for certain serotypes. The immunogenicity data indicate a good priming effect of the 3-dose schedule and an anamnestic response following a booster dose. The presence of an immune memory was demonstrated by a challenge dose with 23-valent pneumococcal polysaccharide vaccine. Co-administration with different paediatric vaccines was assessed and did not result in negative interference on the immune response with the exception of poliovirus type 2, for which, inconsistent results were observed across studies.

Comparative clinical studies in the 10PN-PD-DIT program reveal that the immunogenicity profiles differ somewhat between Synflorix and Prevenar. Overall, data on the 7 common serotypes indicate that Synflorix is less immunogenic, with the exception of serotypes 19F and 18C. The low immunogenic serotypes with the 10-valent vaccine are serotypes 6B and 23F, as measured by the ELISA, and serotypes 1 and 5, as measured by OPA. The clinical consequences of the reduced immunogenicity are not known, but may result in breakthrough infections and shorter term persistence of vaccine efficacy. Post-licensure surveillance will be undertaken to further clarify the clinical consequences of the reduced immunogenicity.

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 has been performed and was considered to be satisfactory.

Risk-benefit assessment

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.
- no additional risk minimisation activities were required beyond those included in the product information.

Benefits

The introduction of Prevenar (7-valent pneumococcal conjugate vaccine) in the childhood immunisation program in the US in the year 2000 have resulted in a dramatic decline in rates of IPD 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 (70-75%) and in other continents (50-65%). Synflorix (with the additional serotypes 1, 5 and 7F) is expected to provide an increased coverage of at least two-thirds serotypes responsible for IPD in children aged <5 years in virtually all countries studied, and more than 80% of isolates in Western Europe. Synflorix includes serotype 1 which has been associated with complicated pneumonia and pleural empyemas.

The impact of Synflorix on overall IPD was estimated by the applicant taking into account the serotype-specific effectiveness values for Prevenar, the distribution of serotypes causing IPD in individual countries, and serotype-specific immunological differences between Synflorix and Prevenar observed in direct comparative studies. With a vaccine efficacy estimate using the percentage responders with ELISA antibody concentrations $\geq 0.20\mu\text{g/ml}$, Prevenar would be estimated to prevent a mean of 66% (range 42-79%) of IPD in young children across the different European countries included in the calculations, and Synflorix would prevent a mean of 74% (range 60-83%) of IPD.

The overall impact of Prevenar on AOM remains limited (6-7% against overall AOM). AOM is the most frequent bacterial infection infancy and a more efficacious vaccine would result in a substantial public health benefit. Synflorix has the potential to provide protection against AOM caused by NTHi due to the use of protein D. A protection against AOM due to both pneumococcal and NTHi would have a significant impact on the burden of middle ear disease

Uncertain benefits include the efficacy of Synflorix against serotype 1 in IPD and against serotype 1 and 5 in AOM. The post-primary and post-booster functional immune responses to vaccine serotypes 1 and 5 were low. Based on the OPA response it could be expected that the level of protection conferred by Synflorix against type 1 and type 5 IPD will be in the range of the one observed for Prevenar against serotypes 6A (VE:76%) and 19F (VE: 89%), respectively. After the booster dose strong anamnestic responses were induced against serotypes 1 and 5, which may enhance protection in older children. Even with an efficacy against these serotypes that is somewhat lower than for other serotypes, the vaccine would still represent a substantial benefit, in particular in countries in which these serotypes represent a large proportion of disease. Post-licensure surveillance will be undertaken to further clarify effectiveness of Synflorix against pneumococcal disease due to serotypes 1 and 5..

Further uncertain benefits include the partial cross-protection against serotypes 6A and 19A which is not convincingly supported by the data provided so far.

Risks

The safety profile of Synflorix is comparable to the licensed pneumococcal vaccine Prevenar and no new significant risks could be identified. Synflorix is commonly associated with a range of local and systemic adverse reactions. These adverse events are not often of severe intensity and the safety profile would not preclude the use of Synflorix for primary vaccination, booster vaccination or catch-up vaccination.

Serotype replacement is considered as an important potential risk that has been included in the risk management plan. Risk minimization measures are in place.

Synflorix may induce suboptimal vaccine efficacy to certain vaccine serotypes with a risk of breakthrough infections and only short term persistence of efficacy. FUM are in place to investigate this further.

No data has been presented for the use of Synflorix in populations at high risk for pneumococcal infection Any use in these populations may not provide satisfactory protection with a risk of breakthrough infections. The applicant committed to perform studies in high risk populations.

Balance

The overall B/R of Synflorix is considered favourable.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Synflorix for the “active immunisation against invasive disease and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks up to 2 years of age. See sections 4.4 and 5.1 for information on protection against specific pneumococcal serotypes. The use of Synflorix should be determined on the basis of official recommendations taking into consideration the impact of invasive disease in different age groups as well as the variability of serotype epidemiology in different geographical areas“ was favourable and therefore recommended the granting of the marketing authorisation.