



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Pneumococcal polysaccharide conjugate vaccine 10-valent adsorbed

Proprietary Product Name: Synflorix

Sponsor: GlaxoSmithKline Australia Pty Ltd

October 2012

TGA Health Safety
Regulation

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I. Introduction to product submission

Submission details

<i>Type of Submission</i>	Major Variation (Extension of Indication)
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	13 March 2012
<i>Active ingredient(s):</i>	Pneumococcal polysaccharide conjugate vaccine, 10-valent adsorbed
<i>Product Name(s):</i>	Synflorix
<i>Sponsor's Name and Address:</i>	GlaxoSmithKline Pty Ltd 436 Johnston Street Abbotsford Victoria 3067
<i>Dose form(s):</i>	Solution for Injection
<i>Strength(s):</i>	1 µg of Pneumococcal polysaccharide serotypes 1*, 5*, 6B*, 7F*, 9V*, 14* and 23F* and 3 µg of Pneumococcal polysaccharide serotypes 4*, 18C and 19F
<i>Container(s):</i>	Injection vial and Pre-filled syringe
<i>Pack size(s):</i>	1's and 10's
<i>Approved Therapeutic use:</i>	Active immunisation of infants and children from the age of 6 weeks up to 5 years against disease caused by Streptococcus pneumonia serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (including invasive disease, pneumonia and acute otitis media).
<i>Route(s) of administration:</i>	Intramuscular (IM) injection
<i>Dosage:</i>	0.5 mL
<i>ARTG Number (s)</i>	AUST R 149004 and AUST R 148981

Product background

Synflorix is a 10-valent pneumococcal conjugate vaccine containing polysaccharides of the pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14 and 23F conjugated individually to PD [a highly conserved protein of Non Typeable *Haemophilus influenzae* (NTHi)], serotype 18C conjugated to tetanus toxoid and serotype 19F conjugated to diphtheria toxoid.

The currently approved indication in Australia is

“Active immunisation of infants and children from the age of 6 weeks up to 2 years against disease caused by Streptococcus pneumonia serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (including invasive disease, pneumonia and acute otitis media)”.

This AusPAR describes the application by the sponsor for the indications to include *active immunisation of infants and children from age of 6 weeks to 5 years.*

This submission also seeks to add an *alternative 2* dose primary vaccination schedule in the age group 6 weeks to 6 months with first dose at 2 months of age, an interval of 2 months between the 2 doses and a booster dose at least 6 months after the last primary dose (*2+1 schedule*). The recommendation applies to infants from 6 weeks to 6 months of age based on the currently approved indication and implies use in routine childhood primary vaccination program.

The currently approved vaccination schedule in this age group is 3 dose primary series with an interval of at least 1 month between the doses (*3+1 schedule*). A booster dose is recommended at least 6 months after the last priming dose. The proposed changes include modification to state that the first dose is usually given at 2 months of age but may be given as early as 6 weeks of age. The proposed text in the Dosage & Administration section of the Product Information (PI) also states that 3+1 schedule provides optimal protection and that 2+1 schedule is an alternative regimen.

The extension up to 5 years of age is intended to provide dose recommendations in unvaccinated children from 7 months up to 5 years of age (‘catch up’) as follows:

Infants aged 7 to 11 months: Two doses at interval of at least one month between the doses. A third dose is recommended in 2nd year of life with an interval of at least 2 months (from the last dose).

Children aged 12 to 23 months: Two doses at an interval of at least 2 months between the doses. The need for a further booster dose has not been established.

Children aged 24 months to 5 years: Two doses with interval of at least 2 months between the doses. This implies that a booster is not required.

Dosage forms and strengths

The following dosage forms and strengths are currently registered:

Synflorix is available as a 0.5 mL suspension in a pre-filled syringe for 1 dose with a plunger stopper. Each 0.5 mL of Synflorix contains 1 µg of Pneumococcal polysaccharide serotypes 1*, 5*, 6B*, 7F*, 9V*, 14* and 23F* and 3 µg of Pneumococcal polysaccharide serotypes 4*, 18C and 19F adsorbed on to Aluminium phosphate (0.5 mg Al³⁺). Synflorix also contains about 9-16µg of Protein D carrier protein, 5-10 µg of tetanus toxoid carrier protein and 3-6 µg of diphtheria toxoid carrier protein.

The registered formulation contains sodium chloride (NaCl) and water for injection. Synflorix does not contain a preservative.

No new dosage forms or strengths are proposed.

Dosage and administration

The vaccine is given by intramuscular (IM) injection. The preferred sites are anterolateral aspect of the thigh in children under 12 months of age or the deltoid muscle of the upper arm in children over 12 months of age.

In order to update the PI for Synflorix, the wording of the Dosage and Administration section will be changed to include option of 2-dose primary series in addition to the already approved 3-dose primary series

Regulatory status

The following table summarises the international registration status of Synflorix™.

Table 1. International Regulatory Status.

Country	Approval for the 2-dose primary schedule	Approval for the Catch-up 2-5 year olds
Canada	10 July 2011	10 July 2011
New Zealand	14 April 2011	14 April 2011
EU (European Medicines Agency)	24 January 2011	8 August 2011

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

Introduction

Clinical rationale

The current PI of Synflorix states in Dosage and Administration section that the vaccination schedule for infants from 6 weeks to 6 months of age consists of 4 vaccine doses, that is, a 3-dose primary course followed by a booster dose at least 6 months after the last primary dose. However, in many countries, a 2-dose primary vaccination schedule in infants followed by a booster dose in the second year of life has been introduced into

national immunisation program^{1,2}). Effectiveness of a 2+1 vaccination schedule in infants as part of routine immunisation programs has been demonstrated for Prevenar (7-valent PCV) in Norway, Italy, the UK, Canada and the US^{3,4,5}. Since its approval in October 2008, Synflorix has been selected for use in national or regional immunisation programs using a 2+1 vaccination schedule in five Swedish regions, Finland, Quebec and Mexico.

The sponsor proposed to update the Australian PI *Dosage and Administration* section with a recommendation for use of Synflorix with 2+1 schedule in routine infant immunisation programs based on the availability of immunogenicity data following primary vaccination and booster vaccination in subjects receiving Synflorix according to a 2+1 or 3+1 schedule, as well as of new immunological data from study Study 46, demonstrating the persistence of antibodies elicited by either 2+1 or 3+1 vaccination for 2-3 years after a booster dose at 11-12 months of age and an anamnestic response to an additional challenge dose (long-term immune response). In addition to this evaluation of the persistence and immune memory post booster vaccination, the immunogenicity of Synflorix following primary vaccination but prior to the booster vaccination data (short term immune response) has been assessed by post-hoc comparison of immune responses after 2 primary doses of Synflorix or Prevenar. Due to the shortness of time since licensure of Synflorix and its introduction in routine immunisation programs, there are currently no effectiveness data available. However, the direct impact of vaccination with Synflorix on invasive pneumococcal disease may be predicted based on the principles underlying the WHO licensure criteria for new pneumococcal vaccines, head to head immunogenicity data for Synflorix and Prevenar, effectiveness data and the IPD serotype distribution in individual countries.

The following table contains a list of the abbreviations used throughout this AusPAR and their meanings.

Table 2. List of clinical Abbreviations used in this AusPAR. Table continued across two pages.

Abbreviation	Meaning
10Pn-2d group	Vaccination group including subjects previously Vaccinated with Synflorix according to a 2+1 schedule.
10Pn-3d group	Vaccination group including subjects previously vaccinated with the Synflorix vaccine according to a 3+1 schedule.

¹ Rose M, Zielen S. Impact of infant immunization programs with pneumococcal conjugate vaccine in Europe. *Expert Rev Vaccines*. 2009 8(10):1351-1364.

² Isaacman DJ, McIntosh ED, Reinert RR. Burden of invasive pneumococcal disease and serotype distribution among *Streptococcus pneumoniae* isolates in young children in Europe: impact of the 7-valent pneumococcal conjugate vaccine and considerations for future conjugate vaccines. *Int J Infect Dis*. 2010 14(3):197-209.

³ Vestrheim DF, Lovoll O, Aaberge IS et al, Effectiveness of a 2+1 dose schedule pneumococcal conjugate vaccination program on invasive pneumococcal disease among children in Norway; *Vaccine* 2008; 26: 3277-3281.

⁴ De Wals P, Bolduc D, Boulianne N, et al. Impact of a three-Dose Pneumococcal Conjugate Vaccine Program on the Epidemiology of Pneumococcal-Related Outcomes in the Province of Quebec, Canada (Abstract G-1003). In 47th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17-20, 2007; Chicago, IL, Abstract 277.

⁵ Kaye P, Andrews N, Slack N, et al, Impact of a Three-Dose Pneumococcal Conjugate Vaccine used in a 2-Dose Infant Priming plus Booster schedule in England and Wales (Abstract P3-118), 6th International Symposium on Pneumococci and Pneumococcal Diseases; June 8-12, 2008; Abstract 355.

Abbreviation	Meaning
AE	Adverse event
AOM	Acute Otitis Media
ATP	According-To-Protocol
CI	Confidence Interval
ELISA	Enzyme-Linked Immuno-Sorbent Assay
FHA	Filamentous Haemagglutinin
GMT	Geometric Mean Titre
IPD	Invasive pneumococcal disease
NTHi	Non Typeable <i>Haemophilus influenzae</i>
OPA	Opsonophagocytic Activity
PD	Protein D, a 42 kD cell-surface lipoprotein which is highly conserved among capsulated and unencapsulated strains of <i>H. influenzae</i>
Pn	Pneumococcal
PRN	pertactin
PRP	Purified polyribosylribitol phosphate
PT	Pertussis toxoid
PS	Polysaccharide
SAE	Serious Adverse Event
TT	Tetanus Toxoid
Vaccine specific	
DTPa	Diphtheria-tetanus-acellular pertussis
IPV	Inactivated poliovirus vaccine
Infanrix hexa™	GSK Biologicals' diphtheria-tetanus-acellular pertussis-hepatitis B virus-inactivated polio and <i>Haemophilus influenzae</i> type b vaccine (DTPa-HBV-IPV/Hib), referred to throughout the text as Infanrix hexa
Hib-MenC	<i>Haemophilus influenzae</i> type b (Hib)-meningococcal serogroup (MenC)-tetanus conjugate (Hib-MenC) vaccine
Hib	<i>Haemophilus influenzae</i> type b
HBV	Hepatitis B virus

Abbreviation	Meaning
10Pn-PD-DiT	GSK Biologicals' liquid 10-valent pneumococcal conjugate vaccine with Protein D, diphtheria and tetanus toxoids as protein carriers and containing pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F

Scope of the clinical submission

This application has 2 separate clinical data packages to support an alternative 2+1 infant vaccination schedule (in addition to the current 3+1 schedule) and to support a 2-dose catch-up vaccination for children between 2 and 5 years of age.

The 2+1 schedule is supported by 3 clinical trials, two of which have been previously evaluated (10PN-PD-DIT-002 (Study 002) and the Prevenar head to head comparison study 10PN-PD-DIT-011 (Study 011)); the more recent Study 10PN-PD-DIT-046 (Study 046) is the 2-3 years follow-up of Study 002 and demonstrates long term protection following vaccination with the 2+1 schedule.

Two clinical studies (10PN-PD-DIT-013 (Study 013) and Study 046) were submitted to support a 2 dose catch-up schedule for children 2 to 5 years of age. Study 013 included catch-up vaccination schedules for three age groups, that is, 7-11 months of age, 12-23 months of age and ≥ 24 months of age. The previous version of the PI included the posology for the first two age groups based on this study. Together with the new data from Study 046, results of Study 013 provide the complete dataset available in children from 2 to 5 years of age.

In summary, the submission contained the following clinical information:

- **Studies to support 2+1 schedule in infants:** Studies 002, 011 and 046
- **Studies to support 2 dose catch-up schedule for children 2 to 5 years of age:** Studies 013 and 046

Paediatric data

The submission involved only patients aged < 5 years of age and hence all the data is in the paediatric patients.

Good clinical practice (GCP)

All studies were conducted in compliance with GCP guidelines and had adequate ethics approval.

Pharmacokinetics

Biopharmaceutic studies are not required for vaccines, as outlined in the TGA adopted EU guideline *Note for Guidance on Clinical Evaluation of New Vaccines*⁶.

Pharmacodynamics

No specific pharmacokinetic or pharmacodynamic assessments other than the measurement of antibody titres and cell mediated immunity (as outlined below) have been performed.

⁶ CPMP/EWP/463/97 <http://www.tga.gov.au/pdf/euguide/vwp16465305enfin.pdf>

Efficacy

Alternative 2+1 infant vaccination schedule {Indication 1}

The immunogenicity of Synflorix following a 2-dose primary vaccination schedule in subjects less than 6 months of age was evaluated in Studies 002 and -011. Study 002 conducted in Slovakia, Denmark, Norway and Sweden was part of the initial registration file in Europe and compared the post primary vaccination and post booster immunogenicity following a 2+1 and 3+1 schedules for Synflorix. A post-hoc analysis of Study 011 (conducted in Germany, Poland and Spain) was performed upon request of CHMP during file review and provides a head to head comparison between Synflorix and Prevenar following two vaccine doses administered according to a 2, 4, 6 month schedule. The recent Study 046 conducted in Slovakia and Sweden assessed the persistence and immunological memory following 2+1 and 3+1 vaccination and is the follow-up of study 002.

Results of Studies 002 and 011 are presented in this report although these have been evaluated previously by the TGA. They provide data of short term immune response with the 2+1 schedule while new data from Study 046 support the claim of a long lasting protection following 2+1 schedule.

Pivotal efficacy studies

Study 002

Study design, objectives, locations and dates

This was an open, randomised, Phase IIIa study to evaluate the safety and immunogenicity of Synflorix (10-valent pneumococcal conjugate vaccine), when administered according to a 2-4-11 months (2 primary doses and 1 booster dose) vaccination schedule. The primary objective was to assess the immune response elicited by Synflorix vaccine after second dose administered according to a 2-4-11 months vaccination schedule with co-administration of DTPa combined vaccine. The secondary objectives were to assess : the post dose 3 immune response elicited by the vaccine administered at 2, 3, 4 and 11 months of age (3+1 schedule) with co-administration of DTPa combined vaccine at 2, 4 and 11 months of age; the persistence of pneumococcal antibodies elicited by the vaccine prior to booster vaccination at 11 months of age; the immune response elicited by a booster dose of vaccine following 2 doses at 2, 4 months of age or 3 doses at 2, 3 and 4 months of age when co-administered with DTPa combined vaccine at 11 months of age; the safety and reactogenicity of vaccine administered according to a 2-4-11 or 2-3-4-11 months vaccination schedule with co-administration of DTPa combined vaccine and the safety, reactogenicity and immune response of DTPa combined vaccine at 2, 4 and 11 months of age.

The study was conducted at 10 centres in Denmark (1 centre), Norway (2 centres), Slovakia (4 centres) and Sweden (3 centres) from 5 January 2006 to 25 January 2007.

Inclusion and exclusion criteria

The main inclusion criteria were male or female aged between 8 and 16 weeks (56-120 days) at the time of the first vaccination; born after a gestation period of 36 to 42 weeks and free of obvious or serious health problems as established by medical history and clinical examination before entering into the study. The main exclusion criteria were infants with previous vaccination against diphtheria, tetanus, pertussis, polio, hepatitis B, *Haemophilus influenzae* type b, and/or *S. pneumoniae* history of or intercurrent diphtheria, tetanus, pertussis, hepatitis B, polio, *Haemophilus influenzae* type b disease, and/or invasive pneumococcal diseases or history of allergic disease or reactions.

Study treatments

Details of treatment administered and schedules are provided in Table 3. All the vaccines were administered intramuscularly on the thighs. The administration of DTPa-HBV-IPV/Hib or DTPa-IPV/Hib vaccines was dependent on the national recommendations. Therefore, the analysis of anti-HBs antibodies was done only for those countries where DTPa-HBV-IPV/Hib vaccine was co administered (that is, Slovakia and Sweden).

Table 3. Vaccine dosage and administration.

Group	Visit	Age	Vaccine	Dose	Route ¹	Site ²	Side ³
2-dose priming group	1	8-16 weeks	DTPa combined vaccine 10Pn-PD-DiT	1	IM	T	L
	3	4 months	DTPa combined vaccine 10Pn-PD-DiT	2	IM	T	L
	5	11 months	DTPa combined vaccine 10Pn-PD-DiT	3	IM	T	L
3-dose priming group	1	8-16 weeks	DTPa combined vaccine 10Pn-PD-DiT	1	IM	T	L
	2	3 months	10Pn-PD-DiT	2	IM	T	R
	3	4 months	DTPa combined vaccine 10Pn-PD-DiT	2	IM	T	L
	5	11 months	DTPa combined vaccine 10Pn-PD-DiT	3	IM	T	L

1. Intramuscular (IM)

2. Thigh (T)

Efficacy variables and outcomes

Antibody concentrations against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (measured by 22F-inhibition ELISA⁷), Opsonophagocytic activity (OPA⁸) against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F and antibody concentrations against Protein D⁹ were measured one month post dose 2 (2-4-11 months schedule) or 1 month postdose 3 (2-3-4-11 months schedule), prior to and one month post booster dose. Antibody concentrations against all components of the DTPa combined vaccine, one month post dose 2, prior to and one month post booster dose of DTPa combined vaccine.

The primary endpoint was anti-pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody concentrations $\geq 0.20 \mu\text{g/mL}$, one month after the administration of the second dose (in a 2-4-11 months of age vaccination schedule).

The secondary endpoints were:

⁷ Pneumococcal serotype specific total IgG antibodies (antibodies against the vaccine serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F and the cross-reactive serotypes 6A and 19A) were each measured by 22F-inhibition ELISA. The antibody concentration was determined by logistic log comparison of the ELISA curves with a standard reference serum 89-SF available from the US Food and Drug Administration (FDA) for which concentration of IgG and IgM to the pneumococcal serotypes were known in $\mu\text{g/mL}$. The cut-off of the assay was $0.05 \mu\text{g/mL}$.

⁸ S. pneumoniae opsonophagocytic activity against the vaccine pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) and the cross-reactive serotypes (6A and 19A) was measured by a killing-assay using a HL 60 cell line [Romero-Steiner, 1997]. The results were presented as the dilution of serum (opsonic titre) able to sustain 50 % killing of live pneumococci under the assay conditions. The cut-off of the assay was an opsonic titre of 8.

⁹ Anti-PD antibodies were determined using an ELISA assay developed by GSK Biologicals. Concentration of specific PD antibodies was determined, using a standard reference serum. The cut-off of the assay was 100 EL.U/mL.

- Anti-pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody concentrations $\geq 0.20 \mu\text{g/mL}$ one month after the administration of the third dose (in a 2-3-4-11 months of age vaccination schedule), and before the booster dose and one month after the booster dose;
- Opsonophagocytic activity against all pneumococcal serotypes and Anti-PD antibody concentrations.

Seropositivity status, defined as:

- Anti-pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody concentrations $\geq 0.05 \mu\text{g/mL}$.
- Opsonophagocytic activity against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F ≥ 8 and Anti-PD antibody concentrations $\geq 100 \text{ EL.U/mL}$.

Exploratory endpoints were antibody concentrations and Opsonophagocytic activity against the cross-reactive pneumococcal serotypes 6A and 19A one month after the administration of the second dose (in a 2-4-11 months of age vaccination schedule) or the third dose (in a 2-3-4-11 months of age vaccination schedule), before and one month after the booster dose of Synflorix vaccine.

Seropositivity status, defined as:

- Anti-pneumococcal cross-reactive serotypes 6A and 19A antibody concentrations $\geq 0.05 \text{ U/mL}$.
- Opsonophagocytic activity against the cross-reactive pneumococcal serotypes 6A and 19A ≥ 8 .

Other efficacy endpoints were assessed one month after the administration of the second dose, and before the booster dose, and one month after the booster dose of DTPa combined vaccine and included:

- Anti-diphtheria and anti-tetanus toxoids, anti-PRP, anti-PT, anti-FHA and anti-PRN, anti-HBs antibody concentrations and anti-polio type 1, 2 and 3 titres¹⁰.

Seropositivity status, defined as:

- Anti-PT, anti-FHA and anti-PRN antibody concentrations $\geq 5 \text{ EL.U/mL}$.
- Seroprotection status, defined as:
 - Anti-diphtheria toxoid antibody concentrations $\geq 0.1 \text{ IU/mL}$.
 - Anti-tetanus toxoid antibody concentrations $\geq 0.1 \text{ IU/mL}$.
 - Anti-PRP antibody concentrations $\geq 0.15 \mu\text{g/mL}$.
 - Anti-PRP antibody concentrations $\geq 1.0 \mu\text{g/mL}$.
 - Anti-HBs antibody concentrations $\geq 10 \text{ mIU/mL}$.
- Anti-polio type 1, type 2 and type 3 titres ≥ 8 . Booster vaccine response to PT, FHA and PRN, one month after the administration of the booster dose of DTPa combined

¹⁰ Antibodies against the Hib polysaccharide PRP were measured by the ELISA technique. The assay cut-off was $0.15 \mu\text{g/mL}$. IgG antibodies against pertussis components pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) was measured by ELISA. The cut-off of the test was 5 EL.U/mL . Anti-diphtheria and anti-tetanus antibody concentrations were measured by ELISA and expressed in international units per mL (IU/mL), with respect to a reference serum. It is generally accepted that for both diphtheria and tetanus, antibody concentrations $\geq 0.01 \text{ IU/mL}$, as measured by *in vivo* neutralization tests were protective.

vaccine was defined as appearance of antibodies in subjects who are seronegative (that is, with concentrations < 5 EL.U/mL) just before booster dose and at least two-fold increase of prevaccination antibody concentrations in those who are seropositive (that is, with concentrations \geq 5 EL.U/mL) just before booster dose.

Randomisation and blinding methods

A randomisation list was generated at GSK Biologicals, Rixensart, Belgium using a standard SAS (Statistical Analysis System) program and was used to number the vaccines. A randomisation blocking scheme (1:1 ratio) was used to ensure that balance between treatments was maintained: a treatment number identified uniquely the vaccine doses to be administered to the same subject. The treatment allocation at the investigator site was performed using a central randomisation system on Internet. The randomisation algorithm used a minimisation procedure accounting for centre. The actual treatment number used for first vaccination of the subject was recorded by the investigator in the eCRF.

Due to the differences in the vaccination schedules between the 2-dose and the 3-dose priming groups it was not possible to blind the investigators, parents/guardians and the study was open.

Analysis populations

All analyses were done in the Total vaccinated¹¹ and the ATP (According To Protocol)¹² cohorts.

The intervals between study visits that were considered for inclusion in the ATP cohort for immunogenicity were 56-84 days between Visits 1 and 3, 28-48 days between Visits 3 and 4, 196-217 days between Visits 3 and 5 and 28-49 days between Visits 5 and 6.

Sample size

The target sample size was 300 eligible subjects (150 in each group) to be considered for the total analysis and safety. Considering up to 10% non evaluable subjects, this corresponded to 135 subjects per group (270 in total) for the according-to-protocol (ATP) analysis of immunogenicity. Considering the sample size of 135 evaluable subjects per group, the probability that the upper limit of the 95% CI for the group difference (3-dose priming group minus 2-dose priming group) in percentage of subjects with pneumococcal antibody concentrations \geq 0.2 μ g/mL for each single pneumococcal serotype, one month post dose 2 (2-dose priming group) or one month post dose 3 (3-dose priming group) of 10-valent pneumococcal conjugate vaccine, was below a limit of delta (δ).

Comments: The study appeared to be better powered to detect differences between the 3-dose and 2-dose priming groups for only certain pneumococcal serotypes.

Furthermore, the study did not appear to be designed as a non inferiority study.

Statistical methods

Geometric mean antibody concentrations/titres (GMCs/GMTs), seropositivity, seroprotection and vaccine response rates (as applicable) were calculated with their 95% confidence interval (CI) for each group, each antigen/serotype and at each applicable blood sampling time point. Distribution of antibody concentrations/titres were displayed

¹¹ Total vaccinated cohort for analysis of immunogenicity included vaccinated subjects for whom data concerning immunogenicity endpoint measures were available. all vaccinated subjects (i.e. who had received at least one dose of study vaccine during the primary vaccination course or the booster dose)

¹² ATP cohort for analysis of immunogenicity included all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures were available. These included subjects for who assay results were available for antibodies against at least one study vaccine antigen component and at least one blood sampling time point.

using tables and/or reverse cumulative curves for each group, each antigen/serotype and at each applicable blood sampling time point; Geometric mean ratios of opsonophagocytic titre/ELISA antibody concentration were tabulated with 95% CIs for each pneumococcal serotype at each blood sampling time point.

Participant flow

A total of 351 subjects (175 subjects in the 2-dose priming group and 176 subjects in the 3-dose priming group) were enrolled in the study and received at least one dose of study vaccine. A maximum of 85 subjects (24.2%) were enrolled in a single study centre. Overall, 342 out of 351 enrolled subjects completed the study (173 subjects in the 2-dose priming group and 169 subjects in the 3-dose priming group). One subject (in 3-dose priming group) was withdrawn due to a SAE. Two subjects (one each in the 2-dose and 3-dose priming group) were withdrawn due to a non serious AE (Table 4)

Table 4. Study 002.

Number of subjects vaccinated, completed and withdrawn with reason for withdrawal during the whole study period (Total vaccinated cohort)

	10Pn_2d	10Pn_3d	Total
Number of subjects vaccinated	175	176	351
Number of subjects completed	173	169	342
Number of subjects withdrawn	2	7	9
Reasons for withdrawal :			
Serious Adverse Event	0	1	1
Non-serious adverse event	1	1	2
Protocol violation	0	0	0
Consent withdrawal (not due to an adverse event)	1	2	3
Migrated/moved from study area	0	1	1
Lost to follow-up (subjects with incomplete vaccination course)	0	1	1
Lost to follow-up (subjects with complete vaccination course)	0	1	1
Others	0	0	0

10Pn_2d = 10Pn-PD-DiT (2-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)

10Pn_3d = 10Pn-PD-DiT (2-3-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)

Vaccinated = number of subjects who were vaccinated in the study

Completed = number of subjects who completed last study visit

Withdrawn = number of subjects who did not come for the last visit

Major protocol violations/deviations

Out of the 351 subjects in the Total vaccinated cohort, 343 (97.7%) met the eligibility criteria for the inclusion in the ATP cohort for safety and 312 (88.9%) met the eligibility criteria for the inclusion in the ATP cohort for immunogenicity; 8 subjects were eliminated from both the ATP cohort for safety and the ATP cohort for immunogenicity because they received vaccine(s) forbidden by the protocol¹³. In addition, 31 subjects were eliminated from the ATP cohort for immunogenicity mainly due to non-compliance with vaccination schedule (n=12), blood sampling schedule (n=11) and missing serological data (n=4).

Baseline data

Mean weight at birth was 3.6 kg, mean age at first vaccination was 12.1 weeks, 48.7% were female and the population was predominantly White Caucasian (97.8%). The demographic profile was comparable between the 2-dose and 3-dose priming groups, with respect to mean weight at birth, age, gender and race. The mean age at which the primary and booster vaccine doses were administered was 12.0, 20.8 weeks and 11.1 months

¹³ 1 subject received a Tuberculosis BCG vaccine, four subjects received Hepatitis A vaccine, one subject was administered MMR vaccine and 2 subjects received Hepatitis B vaccine.

respectively for the 2-dose priming group and 12.2, 16.7, 21.4 weeks and 11.2 months respectively for the 3-dose priming group. This corresponds to a 3-5-11 and 3-4-5-11 months vaccination schedule rather than 2-4-11 and 2-3-4-11 months vaccination schedule.

Results for the primary efficacy outcome

In the ATP analysis, one month post primary vaccination, at least 92.8% of subjects in the 2-dose priming group and 96.1% of subjects in the 3-dose priming group had antibody concentrations $\geq 0.2 \mu\text{g/mL}$ for each vaccine pneumococcal serotype with the exception of serotypes 6B and 23F (Table 5). Prior to booster vaccination, at least 86.4% of subjects in the 2-dose priming group and 94.6% of subjects in the 3-dose priming group still had antibody concentrations $\geq 0.05 \mu\text{g/mL}$ for each vaccine pneumococcal serotype. One month post booster vaccination, the observed percentages of subjects with antibody concentrations $\geq 0.2 \mu\text{g/mL}$ against each vaccine pneumococcal serotype were in the same ranges in both groups (almost 100% for both groups), except for serotype 6B (which was higher in the 3-dose compared with the 2-dose priming group: 92% versus 82%). Robust increases in antibody GMCs for each vaccine pneumococcal serotype were observed in both groups, from pre booster to one month post booster time point.

Table 5. Study 002. Seropositive rates and GMCs for Anti-1, Anti-4, Anti-5, Anti-6B, Anti-7F, Anti-9V, Anti-14, Anti-18C, Anti-19F and Anti-23F antibodies.

ATP cohort for immunogenicity

Antibody	Group	Timing	N	$\geq 0.05 \mu\text{g/mL}$						$\geq 0.2 \mu\text{g/mL}$				GMC		
				n	%	95% CI		n	%	95% CI		value	95% CI			
				LL	UL	LL	UL	LL	UL	LL	UL					
ANTI-1	10Pn_2d	Pii(M3)	153	153	100	97.6	100	149	97.4	93.4	99.3	1.03	0.90	1.18		
		Pii(M9)	149	146	98.0	94.2	99.6	77	51.7	43.4	59.9	0.21	0.19	0.24		
		Piii(M10)	156	156	100	97.7	100	155	99.4	96.5	100	1.85	1.59	2.15		
	10Pn_3d	Piii(M3)	151	151	100	97.6	100	149	98.7	95.3	99.8	1.23	1.07	1.42		
		Piii(M9)	147	146	99.3	96.3	100	101	68.7	60.5	76.1	0.30	0.26	0.34		
		Piv(M10)	147	147	100	97.5	100	147	100	97.5	100	1.88	1.62	2.17		
ANTI-4	10Pn_2d	Pii(M3)	153	153	100	97.6	100	150	98.0	94.4	99.6	1.37	1.21	1.55		
		Pii(M9)	152	152	100	97.6	100	120	78.9	71.6	85.1	0.40	0.35	0.46		
		Piii(M10)	155	155	100	97.6	100	155	100	97.6	100	3.06	2.68	3.49		
	10Pn_3d	Piii(M3)	153	153	100	97.6	100	152	99.3	96.4	100	1.71	1.47	1.99		
		Piii(M9)	149	149	100	97.6	100	137	91.9	86.4	95.8	0.64	0.56	0.73		
		Piv(M10)	147	147	100	97.5	100	147	100	97.5	100	3.47	3.03	3.98		
ANTI-5	10Pn_2d	Pii(M3)	152	152	100	97.6	100	146	96.1	91.6	98.5	1.32	1.14	1.52		
		Pii(M9)	148	147	99.3	96.3	100	121	81.8	74.6	87.6	0.43	0.37	0.50		
		Piii(M10)	155	155	100	97.6	100	155	100	97.6	100	2.65	2.31	3.03		
	10Pn_3d	Piii(M3)	149	149	100	97.6	100	149	100	97.6	100	1.85	1.63	2.10		
		Piii(M9)	149	149	100	97.6	100	133	89.3	83.1	93.7	0.59	0.51	0.68		
		Piv(M10)	147	147	100	97.5	100	147	100	97.5	100	3.21	2.81	3.67		
ANTI-6B	10Pn_2d	Pii(M3)	149	108	72.5	64.6	79.5	83	55.7	47.3	63.8	0.19	0.15	0.24		
		Pii(M9)	154	133	86.4	79.9	91.4	101	65.6	57.5	73.0	0.28	0.23	0.35		
		Piii(M10)	156	143	91.7	86.2	95.5	138	88.5	82.4	93.0	1.12	0.88	1.41		
	10Pn_3d	Piii(M3)	149	131	87.9	81.6	92.7	94	63.1	54.8	70.8	0.31	0.25	0.38		
		Piii(M9)	148	140	94.6	89.6	97.6	111	75.0	67.2	81.7	0.44	0.36	0.54		
		Piv(M10)	147	142	96.6	92.2	98.9	142	96.6	92.2	98.9	1.85	1.54	2.22		
ANTI-7F	10Pn_2d	Pii(M3)	153	153	100	97.6	100	148	96.7	92.5	98.9	1.28	1.13	1.46		
		Pii(M9)	151	151	100	97.6	100	135	89.4	83.4	93.8	0.55	0.49	0.63		
		Piii(M10)	156	156	100	97.7	100	156	100	97.7	100	2.81	2.51	3.15		
	10Pn_3d	Piii(M3)	152	152	100	97.6	100	151	99.3	96.4	100	2.14	1.90	2.40		
		Piii(M9)	149	149	100	97.6	100	146	98.0	94.2	99.6	0.92	0.81	1.05		
		Piv(M10)	147	147	100	97.5	100	147	100	97.5	100	3.88	3.45	4.37		
ANTI-9V	10Pn_2d	Pii(M3)	152	152	100	97.8	100	142	93.4	88.2	96.8	0.92	0.81	1.05		
		Pii(M9)	153	152	99.3	96.4	100	133	86.9	80.5	91.8	0.52	0.46	0.60		
		Piii(M10)	156	156	100	97.7	100	155	99.4	96.5	100	2.95	2.59	3.37		
	10Pn_3d	Piii(M3)	153	152	99.3	96.4	100	152	99.3	96.4	100	1.47	1.29	1.68		
		Piii(M9)	149	149	100	97.6	100	142	95.3	90.6	98.1	0.87	0.77	0.99		
		Piv(M10)	147	147	100	97.5	100	147	100	97.5	100	3.97	3.49	4.50		
ANTI-14	10Pn_2d	Pii(M3)	152	151	99.3	96.4	100	146	96.1	91.6	98.5	1.72	1.45	2.05		
		Pii(M9)	151	149	98.7	95.3	99.8	140	92.7	87.3	96.3	0.77	0.64	0.93		
		Piii(M10)	158	156	100	97.7	100	155	99.4	96.5	100	4.19	3.62	4.85		
	10Pn_3d	Piii(M3)	152	152	100	97.6	100	152	100	97.6	100	2.57	2.22	2.97		
		Piii(M9)	149	149	100	97.6	100	147	98.7	95.2	99.8	1.53	1.27	1.85		
		Piv(M10)	147	147	100	97.5	100	145	98.6	95.2	99.8	5.47	4.68	6.40		

Antibody	Group	Timing	N	≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
				n	%	95% CI		n	%	95% CI		value	95% CI	
ANTI-18C	10Pn_2d	P1I(M3)	152	152	100	97.6	100	146	96.1	91.8	98.5	1.26	1.06	1.51
		P1I(M9)	154	153	99.4	96.4	100	133	86.4	79.9	91.4	0.59	0.50	0.69
		P1I(M10)	156	156	100	97.7	100	156	100	97.7	100	6.24	5.43	7.18
	10Pn_3d	P1I(M3)	153	152	99.3	96.4	100	152	99.3	96.4	100	3.42	2.87	4.07
		P1I(M9)	149	149	100	97.6	100	144	96.6	92.3	98.9	1.14	0.96	1.35
		P1V(M10)	147	147	100	97.5	100	146	99.3	96.3	100	7.20	6.08	8.52
ANTI-19F	10Pn_2d	P1I(M3)	152	148	97.4	93.4	99.3	141	92.8	87.4	96.3	2.43	1.97	2.98
		P1I(M9)	153	151	98.7	95.4	99.8	140	91.5	85.9	95.4	1.04	0.87	1.25
		P1I(M10)	158	156	100	97.7	100	150	96.2	91.8	98.8	5.58	4.85	6.69
	10Pn_3d	P1I(M3)	152	150	98.7	95.3	99.8	146	96.1	91.6	98.5	4.43	3.60	5.45
		P1I(M9)	149	148	99.3	96.3	100	143	96.0	91.4	98.5	1.70	1.41	2.04
		P1V(M10)	147	147	100	97.5	100	144	98.0	94.2	99.6	6.95	5.92	8.17
ANTI-23F	10Pn_2d	P1I(M3)	153	139	90.8	85.1	94.9	106	69.3	61.3	76.5	0.38	0.30	0.47
		P1I(M9)	151	138	91.4	85.7	95.3	108	71.5	63.6	78.6	0.32	0.26	0.40
		P1I(M10)	154	152	98.7	95.4	99.8	148	96.1	91.7	98.6	2.41	1.98	2.94
	10Pn_3d	P1I(M3)	152	147	96.7	92.5	98.9	118	77.6	70.2	84.0	0.52	0.42	0.63
		P1I(M9)	148	141	95.3	90.5	98.1	116	78.4	70.9	84.7	0.44	0.36	0.54
		P1V(M10)	147	145	98.6	95.2	99.8	141	95.9	91.3	98.5	2.78	2.31	3.35

10Pn_2d = 10Pn-PD-DiT (2-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)

10Pn_3d = 10Pn-PD-DiT (2-3-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)

GMC = geometric mean antibody concentration

N = number of subjects with available results

n/% = number/percentage of subjects with concentration within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

P1I(M3) = One month after dose 2 (for the 2 primary doses group)

P1I(M9) = Before booster dose (for the 2 primary doses group)

P1I(M10) = One month after booster dose (for the 2 primary doses group)

P1I(M3) = One month after dose 3 (for the 3 primary doses group)

P1I(M9) = Before booster dose (for the 3 primary doses group)

P1V(M10) = One month after booster dose (for the 3 primary doses group)

Results for other efficacy outcomes

Secondary efficacy results: One month post primary vaccination, at least 82.6% of subjects in the 2-dose priming group and 90.8% of subjects in the 3-dose priming group had an opsonophagocytic activity ≥ 8 against each vaccine pneumococcal serotype except for serotypes 1 and 6B. One month post booster vaccination, the observed percentages of subjects with opsonophagocytic activity ≥ 8 against each vaccine pneumococcal serotypes were in the same ranges in both study groups except for serotypes 5 and 6B. A trend for higher post primary OPA GMTs was observed following the 3-dose primary vaccination course compared to the 2-dose primary vaccination course. This trend was also observed post booster vaccination except for serotype 1, for which the observed OPA GMTs were in the same range for both groups (Table 6).

Table 6. Study 002

Seropositivity rates and GMTs for OPSONO-1, OPSONO-4, OPSONO-5, OPSONO-6B, OPSONO-7F, OPSONO-9V, OPSONO-14, OPSONO-18C, OPSONO-19F and OPSONO-23F (ATP cohort for immunogenicity)

Antibody	Group	Timing	N	≥ 8			95% CI		GMT		
				n	%		LL	UL	value	LL	UL
OPSONO-1	10Pn_2d	PII(M3)	130	79	60.8	51.8	69.2	21.9	16.4	29.1	
		PII(M9)	136	13	9.6	5.2	15.8	5.1	4.5	5.8	
		PIII(M10)	131	106	80.9	73.1	87.3	109.9	76.1	158.7	
	10Pn_3d	PIII(M3)	132	83	62.9	54.0	71.1	26.5	19.8	35.4	
		PIII(M9)	134	21	15.7	10.0	23.0	6.7	5.4	8.3	
		PIV(M10)	126	98	77.8	69.5	84.7	100.6	68.9	146.9	
OPSONO-4	10Pn_2d	PII(M3)	134	134	100	97.3	100	462.6	410.4	521.4	
		PII(M9)	104	41	39.4	30.0	49.5	13.8	9.7	19.6	
		PIII(M10)	125	121	96.8	92.0	99.1	634.6	496.3	811.3	
	10Pn_3d	PIII(M3)	132	131	99.2	95.9	100	758.9	647.8	888.9	
		PIII(M9)	114	48	42.1	32.9	51.7	18.6	12.7	27.2	
		PIV(M10)	101	100	99.0	94.6	100	1204.0	990.7	1463.2	
OPSONO-5	10Pn_2d	PII(M3)	132	109	82.6	75.0	88.6	48.3	37.7	61.8	
		PII(M9)	133	60	45.1	36.5	54.0	9.9	8.1	12.0	
		PIII(M10)	133	116	87.2	80.3	92.4	102.1	75.8	137.6	
	10Pn_3d	PIII(M3)	130	118	90.8	84.4	95.1	68.4	54.0	86.5	
		PIII(M9)	135	58	41.5	33.1	50.3	10.7	8.6	13.4	
		PIV(M10)	121	118	97.5	92.9	99.5	157.2	123.1	200.7	
OPSONO-6B	10Pn_2d	PII(M3)	125	93	74.4	65.8	81.8	157.8	104.7	237.8	
		PII(M9)	121	65	53.7	44.4	62.8	56.1	34.9	90.4	
		PIII(M10)	132	107	81.1	73.3	87.4	220.3	146.9	330.3	
	10Pn_3d	PIII(M3)	126	112	88.9	82.1	93.8	379.6	272.4	529.1	
		PIII(M9)	124	72	58.1	48.9	66.9	62.9	40.2	98.5	
		PIV(M10)	103	93	90.3	82.9	95.2	468.5	311.6	704.3	
OPSONO-7F	10Pn_2d	PII(M3)	127	115	90.6	84.1	95.0	844.8	591.4	1206.7	
		PII(M9)	113	75	66.4	56.9	75.0	148.5	89.5	246.4	
		PIII(M10)	128	128	100	97.2	100	1843.4	1494.2	2274.1	
	10Pn_3d	PIII(M3)	131	129	98.5	94.6	99.8	2176.5	1759.2	2692.7	
		PIII(M9)	126	104	82.5	74.8	88.7	380.6	253.0	572.6	
		PIV(M10)	109	109	100	96.7	100	3290.6	2709.1	3996.8	
OPSONO-9V	10Pn_2d	PII(M3)	134	134	100	97.3	100	875.1	732.0	1046.1	
		PII(M9)	120	115	95.8	90.5	98.6	266.8	205.1	347.1	
		PIII(M10)	129	129	100	97.2	100	1068.1	874.7	1304.2	
	10Pn_3d	PIII(M3)	132	132	100	97.2	100	1343.4	1130.8	1596.0	
		PIII(M9)	134	131	97.8	93.6	99.5	322.2	256.4	405.1	
		PIV(M10)	109	109	100	96.7	100	1706.9	1438.5	2025.3	
OPSONO-14	10Pn_2d	PII(M3)	132	130	98.5	94.6	99.8	692.6	559.1	858.0	
		PII(M9)	102	58	56.9	46.7	66.6	52.1	32.4	84.0	
		PIII(M10)	107	107	100	96.6	100	835.5	672.1	1038.5	
	10Pn_3d	PIII(M3)	131	131	100	97.2	100	1125.3	946.2	1338.3	
		PIII(M9)	123	97	78.9	70.6	85.7	157.3	108.5	228.1	
		PIV(M10)	101	101	100	96.4	100	1280.7	1054.5	1555.5	

Table 6 continued. Study 002

Antibody	Group	Timing	N	≥ 8			95% CI		GMT		
				n	%		LL	UL	value	LL	UL
OPSONO-18C	10Pn_2d	P1I(M3)	134	111	82.8	75.4	88.8	56.2	42.9	73.7	
		P1I(M9)	122	30	24.6	17.2	33.2	8.3	6.5	10.7	
		P1III(M10)	136	133	97.8	93.7	99.5	330.0	259.1	420.3	
	10Pn_3d	P1III(M3)	131	126	96.2	91.3	98.7	218.6	176.1	271.4	
		P1III(M9)	126	62	49.2	40.2	58.3	16.9	12.5	22.8	
		P1IV(M10)	130	128	98.5	94.6	99.8	490.8	395.3	609.4	
OPSONO-19F	10Pn_2d	P1I(M3)	131	114	87.0	80.0	92.3	101.0	74.9	136.0	
		P1I(M9)	130	83	63.8	55.0	72.1	16.5	12.9	21.1	
		P1III(M10)	131	126	96.2	91.3	98.7	251.3	193.4	326.6	
	10Pn_3d	P1III(M3)	128	120	93.8	88.1	97.3	356.7	263.2	483.4	
		P1III(M9)	134	105	78.4	70.4	85.0	31.6	24.5	40.8	
		P1IV(M10)	129	124	96.1	91.2	98.7	734.7	568.3	949.8	
OPSONO-23F	10Pn_2d	P1I(M3)	131	113	86.3	79.2	91.6	489.7	342.6	700.0	
		P1I(M9)	112	83	74.1	65.0	81.9	190.7	115.2	315.6	
		P1III(M10)	134	124	92.5	86.7	96.4	1047.3	748.1	1466.3	
	10Pn_3d	P1III(M3)	129	126	97.7	93.4	99.5	1233.7	991.7	1534.7	
		P1III(M9)	133	96	72.2	63.7	79.6	150.7	95.9	236.8	
		P1IV(M10)	121	119	98.3	94.2	99.8	1528.9	1171.2	1996.0	

10Pn_2d = 10Pn-PD-DiT (2-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)
 10Pn_3d = 10Pn-PD-DiT (2-3-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)

GMT = geometric mean titre

N = number of subjects with available results

n/% = number/percentage of subjects with titre within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

P1I(M3) = One month after dose 2 (for the 2 primary doses group)

P1I(M9) = Before booster dose (for the 2 primary doses group)

P1III(M10) = One month after booster dose (for the 2 primary doses group)

P1III(M3) = One month after dose 3 (for the 3 primary doses group)

P1III(M9) = Before booster dose (for the 3 primary doses group)

P1IV(M10) = One month after booster dose (for the 3 primary doses group)

One month post primary vaccination, at least 20% and 42.7% of subjects in both groups (2-dose and 3-dose priming) had antibody concentrations $\geq 0.2 \mu\text{g/mL}$ against the cross-reactive pneumococcal serotypes 6A and 19A respectively, whatever the group. Prior to the booster dose, at least 69.9% and 79.2% of subjects in both groups still had antibody concentrations $\geq 0.05 \mu\text{g/mL}$ against the cross-reactive pneumococcal serotypes 6A and 19A, respectively. One month post booster vaccination, at least 63.6% and 81.4% of subjects had antibody concentrations $\geq 0.2 \mu\text{g/mL}$ against the cross-reactive pneumococcal serotypes 6A and 19A, respectively (Table 7).

Table 7. Study 002

**Seropositivity rates and GMCs for ANTI-6A and ANTI-19A antibodies
(ATP cohort for immunogenicity)**

Antibody	Group	Timing	N	$\geq 0.05 \mu\text{g/mL}$			$\geq 0.2 \mu\text{g/mL}$			GMC				
				n	%	95% CI	n	%	95% CI	value	95% CI	95% CI		
ANTI-6A	10Pn_2d	P1I(M3)	150	78	52.0	43.7	60.2	30	20.0	13.9	27.3	0.06	0.05	0.08
		P1I(M9)	146	102	69.9	61.7	77.2	46	31.5	24.1	39.7	0.11	0.09	0.14
		P1III(M10)	154	132	85.7	79.2	90.8	98	63.6	55.5	71.2	0.34	0.26	0.44
	10Pn_3d	P1III(M3)	146	96	65.8	57.5	73.4	35	24.0	17.3	31.7	0.09	0.07	0.11
		P1III(M9)	148	113	76.4	68.7	82.9	69	46.6	38.4	55.0	0.16	0.13	0.20
		P1IV(M10)	147	135	91.8	86.2	95.7	107	72.8	64.8	79.8	0.54	0.41	0.70
ANTI-19A	10Pn_2d	P1I(M3)	150	120	80.0	72.7	86.1	64	42.7	34.6	51.0	0.14	0.12	0.17
		P1I(M9)	149	118	79.2	71.8	85.4	63	42.3	34.2	50.6	0.14	0.12	0.17
		P1III(M10)	156	147	94.2	89.3	97.3	127	81.4	74.4	87.2	0.73	0.58	0.92
	10Pn_3d	P1III(M3)	150	131	87.3	80.9	92.2	80	53.3	45.0	61.5	0.19	0.16	0.24
		P1III(M9)	147	129	87.8	81.3	92.6	76	51.7	43.3	60.0	0.20	0.16	0.24
		P1IV(M10)	147	142	96.6	92.2	98.9	122	83.0	75.9	88.7	0.87	0.69	1.11

10Pn_2d = 10Pn-PD-DiT (2-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)

10Pn_3d = 10Pn-PD-DiT (2-3-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)

One month post primary vaccination, at least 39.8% and 12.8% of subjects had opsonophagocytic activity ≥ 8 against the cross-reactive pneumococcal serotypes 6A and 19A, respectively, in both groups. One month post booster vaccination, at least 57.1% and

24.4% of subjects had opsonophagocytic activity ≥ 8 against the cross-reactive pneumococcal serotypes 6A and 19A, respectively, in both groups (Table 8).

Table 8. Study 002

**Seropositivity rates and GMTs for OPSONO-6A and OPSONO-19A
(ATP cohort for immunogenicity)**

Antibody	Group	Timing	N	≥ 8		95% CI		GMT		
				n	%	LL	UL	value	LL	UL
OPSONO-6A	10Pn_2d	PII(M3)	128	51	39.8	31.3	48.9	19.6	13.7	28.2
		PII(M9)	107	54	50.5	40.6	60.3	37.9	23.9	60.3
		PIII(M10)	105	60	57.1	47.1	66.8	54.9	34.4	87.6
	10Pn_3d	PIII(M3)	121	69	57.0	47.7	66.0	41.0	27.9	60.1
		PIII(M9)	110	48	43.6	34.2	53.4	26.5	17.2	40.6
		PIV(M10)	105	72	68.6	58.8	77.3	109.7	69.3	173.4
OPSONO-19A	10Pn_2d	PII(M3)	133	17	12.8	7.6	19.7	5.5	4.8	6.5
		PII(M9)	134	2	1.5	0.2	5.3	4.2	3.9	4.6
		PIII(M10)	119	29	24.4	17.0	33.1	8.7	6.6	11.6
	10Pn_3d	PIII(M3)	130	46	35.4	27.2	44.2	15.8	11.2	22.3
		PIII(M9)	133	5	3.8	1.2	8.6	4.6	4.0	5.2
		PIV(M10)	116	54	46.6	37.2	56.0	27.2	18.0	41.2

10Pn_2d = 10Pn-PD-DiT (2-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)

10Pn_3d = 10Pn-PD-DiT (2-3-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)

One month post primary vaccination, 98.0% of subjects in the 2-dose priming group and all subjects in the 3-dose priming group were seropositive for antibodies against Protein D (≥ 100 EL.U/mL). Prior to the booster dose, 90.1% of subjects in the 2-dose priming group and 95.3% of subjects in the 3-dose priming group remained seropositive for anti-PD antibodies whereas one month post-booster vaccination, all subjects except one in the 2-dose priming group had anti-PD antibodies ≥ 100 EL.U/mL.

One month post primary vaccination, the observed difference between the two groups (3-dose priming group minus 2-dose priming group) in terms of the percentage of subjects with ELISA antibody concentrations ≥ 0.2 μ g/mL was below 6% for each vaccine pneumococcal serotype except for serotypes 6B and 23F for which 7.38% and 8.35% differences were observed respectively.

One month post primary vaccination, the observed difference between the two groups (3-dose priming group minus 2-dose priming group) in terms of the percentage of subjects with opsonophagocytic activity ≥ 8 was below 9% for all the vaccine pneumococcal serotypes except for serotypes 6B, 18C and 23F for which differences of 14.5%, 13.4% and 11.4% were observed respectively (Table 9). One month post booster the observed percentages of subjects with pneumococcal antibody concentrations ≥ 0.2 μ g/mL were in the same ranges in both groups for all vaccine serotypes except serotype 6B (which was higher in the 3-dose group). In addition, the observed percentages of subjects with opsonophagocytic activity ≥ 8 were in the same ranges in both study groups for all serotypes except serotypes 5 and 6B. All subjects except one in the 2-dose priming group had an anti-PD antibody concentration ≥ 100 EL.U/m (Table 9).

Table 9. Study 002

Difference between groups in percentage of subjects with ELISA antibody concentrations greater or equal to 0.2 microgram/mL, one month post-primary vaccination, for pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (ATP cohort for immunogenicity)

Antibody	10Pn_2d group		10Pn_3d group		Post-primary difference in % \geq 0.2 μ g/mL (10Pn_3d minus 10Pn_2d)		
	N	%	N	%	%	95 % CI LL	UL
ANTI-1	153	97.4	151	98.7	1.29	-2.39	5.37
ANTI-4	153	98.0	153	99.3	1.31	-1.83	5.03
ANTI-5	152	96.1	149	100	3.95	1.39	8.34
ANTI-6B	149	55.7	149	63.1	7.38	-3.76	18.35
ANTI-7F	153	96.7	152	99.3	2.61	-0.70	6.85
ANTI-9V	152	93.4	153	99.3	5.93	2.14	11.12
ANTI-14	152	96.1	152	100	3.95	1.43	8.34
ANTI-18C	152	96.1	153	99.3	3.29	-0.09	7.77
ANTI-19F	152	92.8	152	96.1	3.29	-2.05	9.04
ANTI-23F	153	69.3	152	77.6	8.35	-1.57	18.17

10Pn_2d = 10Pn-PD-DiT (2-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)

10Pn_3d = 10Pn-PD-DiT (2-3-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)

N = number of subjects with available results

% = percentage of subjects with pneumococcal antibody concentrations \geq 0.2 μ g/mL

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Other efficacy analysis

Immune response to the co-administered DTPa combined vaccines: One month post primary vaccination, at least 97.4% of subjects had seroprotective antibody concentrations \geq 0.1 IU/mL against diphtheria in both groups, whereas 100% of subjects in both groups reached seropositive antibody levels against tetanus. One month post booster vaccination, all subjects in both groups reached seroprotective antibody levels against diphtheria and tetanus. The observed GMCs for antibodies against diphtheria and tetanus were higher in the 3-dose priming group than the 2-dose priming group.

For each of the pertussis antigens, at least 97.9% of subjects in both the 2-dose and 3-dose priming groups had antibody concentrations \geq 5 EL.U/mL one month post primary vaccination. One month post booster vaccination, all subjects in both groups were seropositive for antibodies against the three pertussis antigens. The observed booster vaccine response for anti-PT, anti-FHA and anti-PRN antibodies ranged from 96.4% to 99.3% in the 2-dose priming group and from 93.5% to 98.6% in the 3-dose priming group.

The analysis of the response to the HBs antigen was done by country and for Slovakia and Sweden only as the hepatitis B containing hexavalent combination vaccine DTPa-HBV-IPV/Hib was co administered during the study only in these countries. One month post primary vaccination, 97.3% and 94.7% of subjects in the 2-dose and 3-dose priming group respectively had seroprotective anti-HBs antibody concentrations (\geq 10 mIU/mL). One month post booster vaccination, all subjects in both groups had reached seroprotective antibody levels against hepatitis B.

One month post primary vaccination, a seroprotective immune response against poliovirus type 1 (titres \geq 8 ED₅₀) was observed in 95.7% and 91.2% of the subjects in the 2-dose and 3-dose priming groups, respectively. For poliovirus type 2 the seroprotection rates were 91.5% and 78.0% while for poliovirus type 3 the seroprotection rates were 100% and 98.2% in the 2-dose and 3-dose priming groups, respectively. Prior to the booster dose, the observed percentage of subjects with titres \geq 8 against polioviruses

ranged from 47.5% to 72.7% whereas one month post booster vaccination all subjects in each group reached seroprotective levels.

The seroprotection rates and GMCs for antibodies against the Hib antigen showed that one month post primary vaccination, at least 88.4% of subjects in the 2-dose priming group and 95.9% in the 3-dose priming group had anti-PRP antibody concentration ≥ 0.15 $\mu\text{g}/\text{mL}$. One month post booster vaccination, at least 97.4% in the 2-dose priming group and 97.3% of subjects in the 3-dose priming group had reached anti-PRP antibody level ≥ 1 $\mu\text{g}/\text{mL}$.

Comments: A trend for higher post primary pneumococcal and anti-PD antibody GMCs and OPA GMTs was observed following 3 primary doses of 10Pn-PD-DiT vaccine compared to the 2-dose primary schedule. The biggest differences between both schedules were observed for serotypes 6B and 23F in terms of percentage of subjects with ELISA antibodies ≥ 0.2 $\mu\text{g}/\text{mL}$ and for serotypes 6B, 18C and 23F in terms of OPA seropositivity. The clinical relevance of this difference was not evaluated and would be of concern especially since some of the serotypes (6B and 23F) are associated with more severe IPD.

Prior to the booster dose at 11 months of age, the biggest differences between both schedules were also observed for serotypes 6B and 23F in terms of percentage of subjects with ELISA antibodies ≥ 0.05 $\mu\text{g}/\text{mL}$ and for serotypes 7F, 14, 18C and 19F in terms of OPA seropositivity (observed difference $>10\%$).

In both schedules an increase of pneumococcal antibody GMCs and OPA GMTs was observed following the booster dose of 10Pn-PD-DiT vaccine as compared to the level observed post primary vaccination and prior to the booster dose. Post booster antibody GMCs and OPA GMTs seemed to be higher following the 3-dose primary vaccination course compared to the 2-dose priming with the exception of serotype 1. This observed difference tended to be bigger for OPA GMTs, possibly indicating that the third primary vaccination dose might contribute to an improved quality of the induced antibodies.

One month post primary vaccination, the seroprotection/seropositivity rate was at least 91.2% in both groups for antibodies against each of the co administered antigens except polio-2 (at least 78%) and PRP (at least 88.4%, for the 0.15 $\mu\text{g}/\text{mL}$ cut-off). One month post-booster vaccination, the seroprotection/seropositivity rate was at least 97.3% for antibodies against each of the co administered antigens. For diphtheria and tetanus the observed GMCs were higher in the 3-dose priming group than in the 2-dose priming group, although for DTPa combination vaccines a 2-dose primary vaccination schedule + booster was used in both study groups.

Study 011

A Phase IIb randomised, open, controlled study to assess the safety, reactogenicity and immunogenicity of Synflorix vaccine when co-administered with DTPa-combined and MenC or Hib-MenC vaccines in children as a 3-dose primary immunisation course during the first 6 months of age. The study was conducted in 44 centres in Germany, 14 centres in Spain and 7 centres in Poland from 12 June 2006 to 23 April 2007.

The primary objective of the study was to demonstrate that Synflorix vaccine, when administered as a 3-dose primary vaccination course was non-inferior¹⁴ to Prevenar, both co administered with DTPa-HBV-IPV and Hib-MenC vaccines, in terms of post immunisation febrile reactions with rectal temperature $> 39.0^{\circ}\text{C}$.

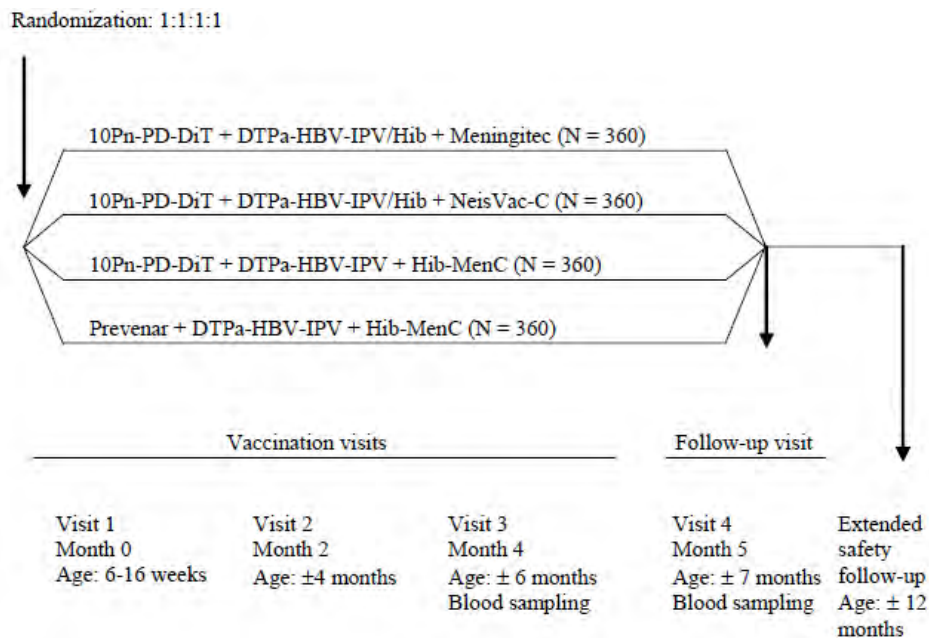
The secondary objectives were as follows :

¹⁴ Criteria for safety: Non-inferiority was demonstrated if the upper limit of the 95% CI of the difference (10Pn-PD-DiT + Hib-MenC group minus Prevenar + Hib-MenC group), in terms of percentage of subjects with rectal temperature $>39.0^{\circ}\text{C}$, was lower than 10%.

- to assess the safety and reactogenicity of Synflorix vaccine when co administered with DTPa-combined and MenC or Hib-MenC vaccines;
- to evaluate, one month post dose 3, the immunogenicity Synflorix vaccine, when co-administered with DTPa-combined and MenC or Hib-MenC vaccines;
- to evaluate two months post dose 2, the immunogenicity of the GSK Biologicals Hib-MenC conjugate vaccine when co-administered with Synflorix vaccine or Prevenar and DTPa-HBV-IPV vaccines and
- to evaluate, one month post dose 3, the immunogenicity of DTPa-HBV-IPV and Hib-MenC vaccines when co administered with Synflorix vaccine or Prevenar.

The study design is outlined in Figure 1. The mean age at the time of first vaccination was 8.1 weeks (SD \pm 2.23 weeks). For the Total vaccinated cohort, the mean age at first vaccination was 8.4 weeks. Most of the subjects were White/Caucasian (95.6%) and 49.7% of the subjects were female.

Figure 1. Study PN011. Study design



Comments: The original study design did not provide any information regarding safety or efficacy of Synflorix versus Prevenar after the proposed 2+1 (2 priming and 1 booster) vaccination schedule. Hence, results of the comparison between the 3+1 schedule of Synflorix versus Prevenar are not repeated here as it was discussed in the earlier submission. However, a post hoc analysis of the immunogenicity data measured 2 months after the second vaccine dose was performed to provide comparative data with Prevenar for the proposed new 2+1 dosing schedule. Results of this post hoc analysis were only provided in the sponsor's Clinical Summary of Efficacy.

The percentage of subjects with antibody concentration ≥ 0.20 ug/ml after the second dose was within the same range for both vaccines with the exception of serotypes 6B (64% for Synflorix versus 31% for Prevenar), and 18C (higher for Prevenar 98% versus 87%) (Table 10). The corresponding percentage for serotype 23F was 75% for both vaccines.

Table 10. Post hoc analysis 2 months after the second dose. Synflorix versus Prevenar.

Study 011: Seropositivity rates and GMCs for ANTI-1, ANTI-4, ANTI-5, ANTI-6B, ANTI-7F, ANTI-9V, ANTI-14, ANTI-18C, ANTI-19F and ANTI-23F antibodies (Pooled 10Pn groups, ATP cohort for immunogenicity)

Antibody	Group	Timing	N	≥ 0.2 µg/mL			GMC			
				n	%	95% CI	value	95% CI		
						LL	UL		LL	UL
ANTI-1	10Pn	Pii(M4)	153	146	95.4	90.8	98.1	0.78	0.66	0.88
		Piii(M5)	516	494	95.7	93.6	97.3	1.07	0.98	1.15
	Prev	Pii(M4)	51	2	3.9	0.5	13.5	0.11	0.10	0.12
		Piii(M5)	170	1	0.6	0.0	3.2	0.10	0.10	0.10
ANTI-4	10Pn	Pii(M4)	169	166	98.2	94.9	99.6	1.23	1.07	1.41
		Piii(M5)	516	512	99.2	98.0	99.8	1.85	1.73	1.97
	Prev	Pii(M4)	168	185	99.4	96.7	100	2.02	1.79	2.29
		Piii(M5)	170	170	100	97.9	100	2.78	2.46	3.14
ANTI-5	10Pn	Pii(M4)	152	147	96.7	92.5	98.9	1.17	1.02	1.36
		Piii(M5)	516	514	99.6	98.6	100	1.84	1.73	1.96
	Prev	Pii(M4)	50	1	2.0	0.1	10.6	0.11	0.09	0.12
		Piii(M5)	168	4	2.4	0.7	6.0	0.10	0.10	0.10
ANTI-6B	10Pn	Pii(M4)	167	107	64.1	56.3	71.3	0.34	0.28	0.40
		Piii(M5)	517	465	89.9	87.0	92.4	0.86	0.78	0.94
	Prev	Pii(M4)	166	51	30.7	23.8	38.3	0.16	0.14	0.18
		Piii(M5)	169	157	92.9	87.9	96.3	1.31	1.10	1.55
ANTI-7F	10Pn	Pii(M4)	151	149	98.7	95.3	99.8	1.27	1.10	1.46
		Piii(M5)	517	514	99.4	98.3	99.9	2.54	2.38	2.70
	Prev	Pii(M4)	49	3	6.1	1.3	16.9	0.11	0.10	0.13
		Piii(M5)	169	5	3.0	1.0	6.8	0.10	0.10	0.11
ANTI-9V	10Pn	Pii(M4)	166	158	95.2	90.7	97.9	0.92	0.80	1.04
		Piii(M5)	517	508	98.3	96.7	99.2	1.68	1.56	1.80

Antibody	Group	Timing	N	≥ 0.2 µg/mL			GMC			
				n	%	95% CI	value	95% CI		
						LL	UL		LL	UL
	Prev	Pii(M4)	166	161	97.0	93.1	99.0	2.24	1.82	2.62
		Piii(M5)	169	167	98.8	95.8	99.9	3.17	2.76	3.65
ANTI-14	10Pn	Pii(M4)	170	168	98.8	95.8	99.9	2.09	1.82	2.41
		Piii(M5)	517	517	100	99.3	100	3.62	3.36	3.91
	Prev	Pii(M4)	166	163	98.2	94.6	99.6	2.63	2.18	3.16
		Piii(M5)	169	168	99.4	96.7	100	5.96	5.03	7.06
ANTI-18C	10Pn	Pii(M4)	170	148	87.1	81.1	91.7	1.21	0.99	1.48
		Piii(M5)	517	512	99.0	97.8	99.7	2.81	2.57	3.08
	Prev	Pii(M4)	166	162	97.6	93.9	99.3	1.79	1.54	2.08
		Piii(M5)	169	167	98.8	95.8	99.9	3.00	2.64	3.42
ANTI-19F	10Pn	Pii(M4)	170	163	95.9	91.7	98.3	2.17	1.83	2.57
		Piii(M5)	517	511	98.8	97.5	99.6	4.45	4.11	4.83
	Prev	Pii(M4)	165	164	99.4	96.7	100	2.10	1.82	2.43
		Piii(M5)	170	170	100	97.9	100	2.56	2.29	2.86
ANTI-23F	10Pn	Pii(M4)	170	128	75.3	68.1	81.6	0.47	0.39	0.55
		Piii(M5)	517	490	94.8	92.5	96.5	1.16	1.06	1.26
	Prev	Pii(M4)	166	126	75.9	68.7	82.2	0.49	0.41	0.59
		Piii(M5)	169	159	94.1	89.4	97.1	2.45	2.02	2.96

10Pn = pooled analysis of Synflorix + DTPa-HBV-IPV/Hib + Meningitec + Pn-Neis = Synflorix + DTPa-HBV-IPV/Hib + NeisVac-C + Pn-HibC = Synflorix + DTPa-HBV-IPV + Hib-MenC

Prev = Prevenar + DTPa-HBV-IPV + Hib-MenC

GMC = geometric mean antibody concentration

N = number of subjects with available results

n/% = number/percentage of subjects with concentration within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Pii(M4) = two months after dose II Piii(M5) = one month after dose III

Antibody GMCs were similar in both groups with the exception of 6B (which was higher for Synflorix) and 4, 9V, 14 and 18C (which were higher for Prevenar). For each of the serotypes common to both vaccines, the OPA GMTs and the percentage of subjects reaching OPA titres ≥ 8 after the second dose was within the same range for both vaccines, with the exception of serotypes 6B, 19F and 23F for which responses were higher with Synflorix. The OPA GMTs against serotype 18C were similar for both vaccines with a higher OPA seropositivity rate in the Prevenar group (75% versus 61%) (Table 11).

Table 11. Post hoc analysis 2 months after the second dose- Synflorix versus Prevanar

Study 011: Seropositivity rates and GMTs for OPSONO-1, OPSONO-4, OPSONO-5, OPSONO-6B, OPSONO-7F, OPSONO-9V, OPSONO-14, OPSONO-18C, OPSONO-19F and OPSONO-23F (Pooled 10Pn groups, ATP cohort for immunogenicity)

Antibody	Group	Timing	N	≥ 8			GMT			
				n	%	95% CI LL UL	value	95% CI LL UL		
OPSONO-1	10Pn	PIII(M4)	133	67	50.4	41.6	59.2	15.2	11.9	19.4
		PIII(M5)	491	255	51.9	47.4	56.4	20.6	17.6	24.2
	Prev	PIII(M4)	46	0	0.0	0.0	7.7	4.0	4.0	4.0
		PIII(M5)	156	2	1.3	0.2	4.6	4.2	3.9	4.5
OPSONO-4	10Pn	PIII(M4)	148	143	96.6	92.3	98.9	239.1	199.3	287.0
		PIII(M5)	472	468	99.2	97.8	99.8	706.8	647.8	771.2
	Prev	PIII(M4)	155	149	96.1	91.8	98.6	241.6	200.5	291.1
		PIII(M5)	154	154	100	97.6	100	826.2	779.5	1100.4
OPSONO-5	10Pn	PIII(M4)	131	97	74.0	65.7	81.3	24.3	19.4	30.5
		PIII(M5)	475	424	89.3	86.1	91.9	79.5	69.5	91.0
	Prev	PIII(M4)	46	0	0.0	0.0	7.7	4.0	4.0	4.0
		PIII(M5)	153	3	2.0	0.4	5.6	4.2	4.0	4.5
OPSONO-6B	10Pn	PIII(M4)	148	93	62.8	54.5	70.6	94.2	81.9	143.3
		PIII(M5)	446	378	84.8	81.1	88.0	403.7	331.2	492.2
	Prev	PIII(M4)	148	51	34.9	27.2	43.3	22.8	15.2	34.4
		PIII(M5)	151	147	97.4	93.4	99.3	1575.3	1230.8	2016.0
OPSONO-7F	10Pn	PIII(M4)	133	129	97.0	92.5	99.2	1218.2	946.7	1567.7

Antibody	Group	Timing	N	≥ 8			GMT			
				n	%	95% CI LL UL	value	95% CI LL UL		
	Prev	PIII(M5)	471	464	98.5	97.0	99.4	2536.3	2248.1	2861.4
		PII(M4)	42	0	0.0	0.0	8.4	4.0	4.0	4.0
		PIII(M5)	138	21	15.2	9.7	22.3	8.7	6.3	11.9
OPSONO-9V	10Pn	PIII(M4)	147	145	98.6	95.2	99.8	675.4	537.9	848.0
		PIII(M5)	461	458	99.3	98.1	99.9	1077.9	965.0	1204.0
	Prev	PIII(M4)	154	153	99.4	96.4	100	658.4	543.0	798.3
		PIII(M5)	150	149	99.3	96.3	100	1305.0	1046.3	1627.6
OPSONO-14	10Pn	PIII(M4)	147	143	97.3	93.2	99.3	385.9	307.4	484.4
		PIII(M5)	481	467	97.1	95.2	98.4	818.9	725.9	923.7
	Prev	PIII(M4)	154	145	94.2	89.2	97.3	432.2	334.4	558.5
		PIII(M5)	154	151	98.1	94.4	99.6	1539.4	1230.2	1926.2
OPSONO-18C	10Pn	PIII(M4)	142	86	60.6	52.0	68.7	22.4	16.9	29.6
		PIII(M5)	475	454	95.6	93.3	97.2	192.9	171.2	217.3
	Prev	PIII(M4)	154	115	74.7	67.0	81.3	22.8	18.6	28.0
		PIII(M5)	149	149	100	97.6	100	212.8	174.9	258.9
OPSONO-19F	10Pn	PIII(M4)	151	127	84.1	77.3	89.5	65.8	51.3	84.5
		PIII(M5)	481	459	95.4	93.2	97.1	310.9	268.6	359.8
	Prev	PIII(M4)	156	106	67.9	60.0	75.2	19.3	15.7	23.9
		PIII(M5)	147	133	90.5	84.5	94.7	52.0	40.8	66.4
OPSONO-23F	10Pn	PIII(M4)	149	144	96.6	92.3	98.9	860.4	670.1	1104.7
		PIII(M5)	448	419	93.5	90.8	95.6	1049.8	888.0	1241.1
	Prev	PIII(M4)	150	133	88.7	82.5	93.3	556.6	397.6	779.1
		PIII(M5)	148	147	99.3	96.3	100	5469.2	4410.2	6782.6

10Pn = Pooled analysis of Pn-Men = Synflorix+ DTPa-HBV-IPV/Hib + Meningitec + Pn-Neis = Synflorix+ DTPa-HBV-IPV/Hib + NeisVac-C + Pn-HibC = Synflorix+ DTPa-HBV-IPV + Hib-MenC ; Prev = Prevanar + DTPa-HBV-IPV + Hib-MenC

GMT = geometric mean titre

N = number of subjects with available results

n/% = number/percentage of subjects with titre within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PII(M4) = two months after dose II PIII(M5) = one month after dose III

Results for the immune response to pneumococcal serotypes one month after the third dose of Synflorix versus Prevanar are summarised in Tables 12 and 13. As the 3+1 dosing schedule has already been approved, these are not discussed here again.

Table 12. Study 011. Immunogenicity comparisons 1 months after 3rd dose of Synflorix and Prevanar (3+1 schedule)

Percentage of subjects with antibody concentrations ≥ 0.2 $\mu\text{g/mL}$ and antibody GMCs (22F-inhibition ELISA) against pneumococcal serotypes (ATP cohort for immunogenicity)										
Antibody	Group	Timing	N	≥ 0.2 $\mu\text{g/mL}$				GMC		
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
ANTI-1	Pn-Men	PIII(M5)	169	163	96.4	92.4	98.7	1.17	1.03	1.33
	Pn-Neis	PIII(M5)	174	170	97.7	94.2	99.4	1.09	0.96	1.24
	Pn-HibC	PIII(M5)	173	161	93.1	88.2	96.4	1.00	0.86	1.15
	Pr-HibC	PIII(M5)	170	1	0.6	0.0	3.2	0.03	0.03	0.03
ANTI-4	Pn-Men	PIII(M5)	169	169	100	97.8	100	1.88	1.70	2.09
	Pn-Neis	PIII(M5)	174	173	99.4	96.8	100	1.96	1.76	2.19
	Pn-HibC	PIII(M5)	173	170	98.3	95.0	99.6	1.70	1.52	1.92
	Pr-HibC	PIII(M5)	170	170	100	97.9	100	2.78	2.46	3.14
ANTI-5	Pn-Men	PIII(M5)	169	169	100	97.8	100	1.96	1.78	2.17
	Pn-Neis	PIII(M5)	174	174	100	97.9	100	1.87	1.69	2.08
	Pn-HibC	PIII(M5)	173	171	98.8	95.9	99.9	1.69	1.49	1.91
	Pr-HibC	PIII(M5)	168	4	2.4	0.7	6.0	0.03	0.03	0.04
ANTI-6B	Pn-Men	PIII(M5)	169	159	94.1	89.4	97.1	0.96	0.82	1.12
	Pn-Neis	PIII(M5)	175	155	88.6	82.9	92.9	0.85	0.72	1.01
	Pn-HibC	PIII(M5)	173	151	87.3	81.4	91.9	0.71	0.59	0.86
	Pr-HibC	PIII(M5)	169	157	92.9	87.9	96.3	1.32	1.12	1.57
ANTI-7F	Pn-Men	PIII(M5)	169	169	100	97.8	100	2.82	2.54	3.14
	Pn-Neis	PIII(M5)	175	174	99.4	96.9	100	2.57	2.32	2.86
	Pn-HibC	PIII(M5)	173	171	98.8	95.9	99.9	2.25	1.98	2.55
	Pr-HibC	PIII(M5)	169	5	3.0	1.0	6.8	0.04	0.03	0.04
ANTI-9V	Pn-Men	PIII(M5)	169	167	98.8	95.8	99.9	1.77	1.58	2.00
	Pn-Neis	PIII(M5)	175	171	97.7	94.3	99.4	1.72	1.52	1.95
	Pn-HibC	PIII(M5)	173	170	98.3	95.0	99.6	1.58	1.40	1.77
	Pr-HibC	PIII(M5)	169	167	98.8	95.8	99.9	3.17	2.75	3.64
ANTI-14	Pn-Men	PIII(M5)	169	169	100	97.8	100	3.75	3.25	4.31
	Pn-Neis	PIII(M5)	175	175	100	97.9	100	3.79	3.37	4.26
	Pn-HibC	PIII(M5)	173	173	100	97.9	100	3.36	2.91	3.88
	Pr-HibC	PIII(M5)	169	168	99.4	96.7	100	5.97	5.05	7.07
ANTI-18C	Pn-Men	PIII(M5)	169	167	98.8	95.8	99.9	2.43	2.07	2.84
	Pn-Neis	PIII(M5)	175	173	98.9	95.9	99.9	3.92	3.38	4.54
	Pn-HibC	PIII(M5)	173	172	99.4	96.8	100	2.34	2.01	2.71
	Pr-HibC	PIII(M5)	169	167	98.8	95.8	99.9	3.01	2.65	3.42
ANTI-19F	Pn-Men	PIII(M5)	169	166	98.2	94.9	99.6	4.93	4.28	5.68
	Pn-Neis	PIII(M5)	175	174	99.4	96.9	100	4.71	4.09	5.42
	Pn-HibC	PIII(M5)	173	171	98.8	95.9	99.9	3.81	3.32	4.37
	Pr-HibC	PIII(M5)	170	170	100	97.9	100	2.56	2.29	2.86
ANTI-23F	Pn-Men	PIII(M5)	169	162	95.9	91.7	98.3	1.30	1.13	1.49
	Pn-Neis	PIII(M5)	175	168	96.0	91.9	98.4	1.20	1.02	1.40
	Pn-HibC	PIII(M5)	173	160	92.5	87.5	95.9	0.96	0.82	1.13
	Pr-HibC	PIII(M5)	169	159	94.1	89.4	97.1	2.46	2.04	2.98

Pn-Men = 10Pn-PD-DiT + DTPa-HBV-IPV/Hib + Meningitec; Pn-Neis = 10Pn-PD-DiT + DTPa-HBV-IPV/Hib + NeisVac-C; Pn-HibC = 10Pn-PD-DiT + DTPa-HBV-IPV + Hib-MenC; Pr-HibC = Prevanar + DTPa-HBV-IPV + Hib-MenC; GMC = geometric mean antibody concentration; N = number of subjects with available results; n/% = number/percentage of subjects with concentration within the specified range; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; PIII(M5) = one month after dose III; Data source = Appendix table IIIA.

Table 13. Study 011. Immunogenicity comparisons 1 months after 3rd dose of Synflorix and Prevenar (3+1 schedule). Percentage of subjects with opsonophagocytic activity ≥ 8 and GMTs against pneumococcal serotypes (ATP cohort for immunogenicity).

Antibody	Group	Timing	N	≥ 8				GMT		
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
OPSONO-1	Pn-Men	PIII(M5)	162	88	54.3	46.3	62.2	23.9	17.9	32.0
	Pn-Neis	PIII(M5)	168	86	51.2	43.4	59.0	18.8	14.4	24.4
	Pn-HibC	PIII(M5)	161	81	50.3	42.3	58.3	19.7	14.9	26.1
	Pr-HibC	PIII(M5)	156	2	1.3	0.2	4.6	4.2	3.9	4.5
OPSONO-4	Pn-Men	PIII(M5)	154	154	100	97.6	100	697.4	617.8	787.3
	Pn-Neis	PIII(M5)	159	159	100	97.7	100	755.6	660.9	863.7
	Pn-HibC	PIII(M5)	159	155	97.5	93.7	99.3	669.8	553.8	810.0
	Pr-HibC	PIII(M5)	154	154	100	97.6	100	926.2	779.5	1100.4
OPSONO-5	Pn-Men	PIII(M5)	153	142	92.8	87.5	96.4	91.7	72.7	115.7
	Pn-Neis	PIII(M5)	163	141	86.5	80.3	91.3	71.4	56.5	90.4
	Pn-HibC	PIII(M5)	159	141	88.7	82.7	93.2	77.4	61.0	98.2
	Pr-HibC	PIII(M5)	153	3	2.0	0.4	5.6	4.2	4.0	4.5
OPSONO-6B	Pn-Men	PIII(M5)	148	130	87.8	81.5	92.6	459.1	334.2	630.8
	Pn-Neis	PIII(M5)	150	127	84.7	77.9	90.0	404.6	287.7	569.1
	Pn-HibC	PIII(M5)	148	121	81.8	74.6	87.6	354.2	243.4	515.3
	Pr-HibC	PIII(M5)	151	147	97.4	93.4	99.3	1575.3	1230.8	2016.0
OPSONO-7F	Pn-Men	PIII(M5)	149	149	100	97.6	100	2513.3	2106.1	2999.3
	Pn-Neis	PIII(M5)	164	162	98.8	95.7	99.9	2821.3	2297.9	3463.9
	Pn-HibC	PIII(M5)	158	153	96.8	92.8	99.0	2290.5	1802.3	2910.9
	Pr-HibC	PIII(M5)	138	21	15.2	9.7	22.3	8.7	6.3	11.9
OPSONO-9V	Pn-Men	PIII(M5)	153	152	99.3	96.4	100	1005.6	825.3	1225.2
	Pn-Neis	PIII(M5)	153	151	98.7	95.4	99.8	1108.8	905.9	1357.1
	Pn-HibC	PIII(M5)	155	155	100	97.6	100	1122.6	938.9	1342.3
	Pr-HibC	PIII(M5)	150	149	99.3	96.3	100	1305.0	1046.3	1627.6
OPSONO-14	Pn-Men	PIII(M5)	154	151	98.1	94.4	99.6	797.8	655.3	971.2
	Pn-Neis	PIII(M5)	167	162	97.0	93.2	99.0	879.0	709.1	1089.5
	Pn-HibC	PIII(M5)	160	154	96.3	92.0	98.6	779.9	628.1	968.3
	Pr-HibC	PIII(M5)	154	151	98.1	94.4	99.6	1539.4	1230.2	1926.2
OPSONO-18C	Pn-Men	PIII(M5)	155	150	96.8	92.6	98.9	174.9	144.1	212.3
	Pn-Neis	PIII(M5)	163	160	98.2	94.7	99.6	282.8	234.7	340.8
	Pn-HibC	PIII(M5)	157	144	91.7	86.3	95.5	142.7	113.8	179.1
	Pr-HibC	PIII(M5)	149	149	100	97.6	100	212.8	174.9	258.9
OPSONO-19F	Pn-Men	PIII(M5)	157	154	98.1	94.5	99.6	387.5	305.0	492.2
	Pn-Neis	PIII(M5)	165	155	93.9	89.1	97.1	298.4	230.3	386.7
	Pn-HibC	PIII(M5)	159	150	94.3	89.5	97.4	261.0	200.9	339.0
	Pr-HibC	PIII(M5)	147	133	90.5	84.5	94.7	52.0	40.8	66.4

Antibody	Group	Timing	N	≥ 8				GMT		
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
OPSONO-23F	Pn-Men	PIII(M5)	146	139	95.2	90.4	98.1	1066.0	811.9	1399.6
	Pn-Neis	PIII(M5)	156	148	94.9	90.1	97.8	1219.6	930.7	1598.2
	Pn-HibC	PIII(M5)	146	132	90.4	84.4	94.7	880.7	633.1	1225.1
	Pr-HibC	PIII(M5)	148	147	99.3	96.3	100	5469.2	4410.2	6782.6

Pn-Men = 10Pn-PD-DiT + DTPa-HBV-IPV/Hib + Meningitec; Pn-Neis = 10Pn-PD-DiT + DTPa-HBV-IPV/Hib + NeisVac-C; Pn-HibC = 10Pn-PD-DiT + DTPa-HBV-IPV + Hib-MenC; Pr-HibC = Prevenar + DTPa-HBV-IPV + Hib-MenC; GMT = geometric mean titre; N = number of subjects with available results; n/% = number/percentage of subjects with titre within the specified range; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; PIII(M5) = one month after dose III; Data source = Appendix table IIIA

Comments: Study 011 evaluated the immune responses in infants vaccinated with either Prevenar or Synflorix at 2, 4 and 6 months of age. A post hoc analysis of the immunogenicity data measured 2 months after the second vaccine dose was performed to provide comparative data with Prevenar. The percentage of subjects with antibody concentration >0.20 g/ml after the second dose was within the same range for both vaccines with the exception of serotypes 6B (64% for Synflorix versus 31% for Prevenar), and 18C (higher for Prevenar; 98% versus 87%). The corresponding percentage for serotype 23F was 75% for both vaccines. Antibody GMCs were similar in both groups with the exception of 6B (which was higher for Synflorix) and 4, 9V 14 and 18C (which were higher for Prevenar). For each of the serotypes common to both vaccines, the OPA GMTs

and the percentage of subjects reaching OPA titres > 8 after the second dose was within the same range for both vaccines with the exception of serotypes 6B, 19F and 23F for which responses were higher with Synflorix. The OPA GMTs against serotype 18C were similar for both vaccines with a higher OPA seropositivity rate in the Prevenar group (75% versus 61%).

Other efficacy studies

Long-term efficacy (Study 046):

Study design, objectives, location study dates

Study 46 was a Phase III, open, controlled, multi-centre, long-term follow-up study (of Study 002). The subjects were randomised in three parallel groups:

1. Synflorix 2+1 group: subjects previously vaccinated with Synflorix according to a 2+1 schedule, receiving one dose of Synflorix at 36-46 months of age,
2. Synflorix 3+1 group: subjects previously vaccinated with Synflorix according to a 3+1 schedule, receiving one dose of Synflorix at 36-46 months of age, and
3. Unprimed group: age matched subjects not previously vaccinated with any pneumococcal vaccine receiving two doses of Synflorix at 36-46 and 38-48 months of age.

The primary objectives were to assess the immune responses following children previously vaccinated with Synflorix according to either a 3+1 or a 2+1 vaccination schedule and to assess the immune responses following vaccination with a single dose in age matched unprimed children. Other study objectives included the assessment of antibody persistence 24-34 months following vaccination in Study 002 and evaluation of the safety, reactogenicity and immunogenicity of Synflorix when given as a 2-dose vaccination course to unprimed children in their fourth year of life.

The study was conducted at 7 centres in Slovakia and Sweden from 2 Dec 2008 to 2 July 2009.

Study treatment

The vaccine was administered by intramuscular injection in the right deltoid. Single dose in 36-46 month old primed children and 2 doses in age matched unprimed children. The duration of the study was approximately one month for each subject of the primed groups and approximately 3 months for each subject of the unprimed group.

Inclusion/ exclusion criteria

The main inclusion criteria were: Male or female subjects between and including 36-46 months of age at the time of vaccination; For primed subjects: having completed the full vaccination course with the 10Pn-PDDiT vaccine in Study 10PN-PD-DIT-002; Subjects for whom the investigator believed that their parent(s)/guardian(s) could and would comply with the requirements of the protocol; Written informed consent; Free of obvious health problems as established by medical history and clinical examination before entering into the study. The main exclusion criteria were: Use of any investigational or non registered product (drug or vaccine) within 30 days preceding the vaccination or planned use during the study period; Chronic administration (defined as more than 14 days) of immunosuppressants¹⁵ or other immune-modifying drugs within 6 months prior to the vaccination.; For primed subjects: administration of any pneumococcal vaccine since the

¹⁵ For corticosteroids, this meant prednisone, or equivalent, >0.5 mg/kg/day. Inhaled and topical steroids were allowed.

end of Study 10PN-PD-DIT-002; For unprimed subjects: previous vaccination with any pneumococcal vaccine; Administration of immunoglobulins and/or any blood products less than 6 months prior to the vaccination or planned use during the study period; Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required); History of reactions or allergic disease likely to be exacerbated by any component of the study vaccine; Acute disease¹⁶ at the time of vaccination.

Efficacy endpoints

The following were measured prior to, 7-10 days post dose 1 and one month post dose 2 (unprimed group only):

- Antibody concentrations against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (22F-inhibition ELISA);
- Opsonophagocytic activity (OPA) against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F;
- Antibody concentrations and opsonophagocytic activity (OPA) against cross-reactive pneumococcal serotypes 6A and 19A;
- Antibody concentrations against Protein D (ELISA). Quantification of memory B-cells that produce antibodies against vaccine pneumococcal serotypes 6B, 18C, 19F and 23F (Elispot assay), prior to and 7-10 days post dose 1.

Analysis populations, sample size, statistical methods

The analysis was performed on the ATP cohort for analysis of immunogenicity and on the ATP cohort for analysis of antibody persistence. Considering that approximately 85 subjects would be enrolled in the primed groups and 42 subjects would be enrolled in the unprimed group of the current study and considering that up to 10% of the subjects may be excluded from the ATP cohort for analysis of immunogenicity, there would be approximately 115 evaluable subjects in the current study (approximately 38 subjects in the 10Pn-2d primed group, 39 subjects in the 10Pn-3d primed group and 38 subjects in the unprimed group). Based on this sample size, Table 14 gives the width of the 95% confidence interval (95% CI) of the ELISA GMC ratio's (GMCs from the 10Pn-2d or 10Pn-3d group over GMCs from the unprimed group) for each of the 10 pneumococcal serotypes 7 to 10 days after the administration of the 10Pn-PD-DiT vaccine at 36 to 46 months of age.

¹⁶ Acute disease was defined as the presence of a moderate or severe illness with or without fever. All vaccines could be administered to persons with a minor illness such as diarrhoea or mild upper respiratory infection, provided the body temperature was <38°C (rectal measurement) or <37.5°C (for oral/axillary/tympanic measurements). In such cases, study entry was delayed until the illness had improved

Table 14. Study 046.

Estimated width of the 95% CI of the ELISA GMC ratio's (GMCs from 10Pn-2d or 10Pn-3d group over GMCs from the unprimed group) for each of the 10 pneumococcal serotypes, 7 to 10 days after vaccination at Day 0 with 10Pn-PD-DIT, using an ANOVA model (N=38 or 39/38 evaluable subjects in 10Pn-2d or 10Pn-3d /Unprimed group)

Antigens	Standard deviation of log (concentrations)*	Ratio** of 95%CI boundaries (N = 39 in 10Pn-3d group and N= 38 in unprimed group)	Ratio** of 95%CI boundaries (N = 38 in 10Pn-2d group and N= 38 in unprimed group)
4	0.42	2.37	2.39
6B	0.57	3.23	3.26
9V	0.52	2.91	2.94
14	0.82	5.40	5.46
18C	0.54	3.04	3.06
19F	0.53	2.98	3.00
23F	0.66	3.89	3.92
1	0.44	2.47	2.49
5	0.60	3.44	3.46
7F	0.33	1.96	1.97

* Standard deviation of log (concentrations) observed in the unprimed group from the Undeca-Pn-037 (104083) study.

** Ratio of 95%CI boundaries was calculated according to the following formula: $10^{2 \times \text{SD} \times \text{mean} + 1.96}$

Participant flow

Out of the 351 subjects vaccinated in the primary Study 002, 140 were planned to be enrolled in this current study and 110 effectively participated. Alongside, 62 subjects were enrolled in the unprimed group (31 in Sweden and 31 in the Slovak Republic). Among the 241 subjects from Study 002 who did not participate in this long term follow-up study (124 in the 10Pn-2d group and 117 in the 10Pn-3d group), 208 belonged to centres not willing to participate to the current study, 2 were not eligible, 9 were lost to follow-up and 22 subjects did not want to participate (not due to an adverse event).

Amongst the 110 subjects enrolled and vaccinated in the primed groups, 109 completed the study. All subjects enrolled in the unprimed group were vaccinated and completed the study.

Protocol violations/ deviations

None of the subjects were excluded from the ATP analysis for safety and from the ATP analysis for persistence. Among the 172 subjects who were enrolled and vaccinated, 5 subjects (1 in the 10Pn-2d group, 2 in the 10Pn-3d group and 2 in the unprimed group) were excluded from the ATP analyses of immunogenicity.

Baseline demographics

The mean age of the subjects of the ATP cohort for immunogenicity was 38.8 months (SD = 2.35). The ATP cohort for immunogenicity was composed of 53.3 % males and 97.6 % of the subjects were Caucasians.

Immunogenicity results

Persistence of anti-pneumococcal antibodies and opsonophagocytic activity prior to vaccination in 4th year of life: Despite the decline in vaccine pneumococcal polysaccharide antibody concentrations observed 24-36 months after the last vaccination in Study 10PN-PD-DIT-002, the observed percentage of subjects with vaccine pneumococcal antibody concentrations >0.05 ug/mL was at least 96.0% for each vaccine pneumococcal serotypes except for serotypes 1 (86.0%), 4 (83.7%), 6B (89.8%) and 23F (88.0%) in the 10Pn-2d group and was at least 96.6% in the 10Pn-3d group for each vaccine serotype. A trend of higher antibody GMCs was observed in the 10Pn-3d group compared to the 10Pn-2d group for all vaccine pneumococcal serotypes, except for serotype 19F. The observed

percentage of subjects with pneumococcal antibody concentrations ≥ 0.2 ug/mL also tended to be higher in the 10Pn-3d group than in the 10Pn-2d group.

The observed percentage of subjects with an OPA titre ≥ 8 , 24-36 months after vaccination in Study 002 in the 10Pn-2d group was at least 95.2% for serotypes 7F, 9V and 14, at least 66.7% for serotypes 19F and 23F and ranged from 12.5% to 48.8% for serotypes 1, 4, 5, 6B and 18C. In the 10Pn-3d group, this observed percentage was at least 98.1% for serotypes 7F, 9V and 14, at least 67.3% for serotypes 6B, 19F and 23F and ranged from 21.4% to 38.2% for serotypes 1, 4, 5 and 18C. A trend of higher OPA GMTs was observed in the 10Pn-3d group compared to the 10Pn-2d group for all serotypes except for serotype 4, 7F, 9V and 23F. The percentage of subjects with antibody concentrations ≥ 0.20 ug/ml at 24-36 months post vaccination ranged between 46.9% and 68.4% for the cross-reactive serotypes 6A and 19A using both schedules. The percentage of subjects in the 2+1 group with an OPA titre ≥ 8 was 58.5% for serotype 6A and 28.3% for serotype 19A and these OPA responses were comparable to those in the 3+1 group.

About 24-36 months after the booster vaccination in Study 002, the observed percentage of subjects with anti-PD antibody concentrations >100 EL.U/mL was 82.4% and 96.6% in the 10Pn-2d group and 10Pn-3d groups, respectively; GMCs tended to be higher for the 10Pn-3d group compared to the 10Pn-2d group.

Immune responses to the pneumococcal conjugate vaccine given in the 4th year of life for evaluation of immunological memory: Higher and rapid increases in anti-pneumococcal serotype-specific ELISA antibody GMCs and OPA GMTs were observed 7-10 days after vaccination with a single dose of 10Pn-PD-DiT vaccine in the subjects vaccinated previously according to a 2+1 or 3+1 schedule as compared to the unprimed age matched control group. About 7-10 days after the vaccination, the observed percentages of subjects with vaccine pneumococcal antibody concentrations ≥ 0.20 ug/mL were in the same range for both primed groups (at least 98.0% in the 10Pn-2d group and 100% in the 10Pn-3d group) and higher than in the unprimed group for most of the serotypes. The observed OPA GMTs in the primed groups were higher than in the unprimed group for most of the vaccine serotypes. For the cross reactive serotypes 6A and 19A, a robust and rapid increase in ELISA GMCs after the additional dose of Synflorix was also observed for both schedules and GMCs were higher than that observed in unprimed subjects. All subjects in the 2+1 group and 3+1 group had measurable antibodies against Protein D (> 100 EL.U/ml). The observed robust anamnestic immune responses were indicative of similar induction of immunological memory after previous vaccination according to a 2+1 or 3+1 vaccination schedule.

Immune responses following 2-dose catch-up vaccination with the pneumococcal conjugate vaccine during the 4th year of life: In the unprimed group, 7-10 days after the first vaccination, the observed percentage of subjects with vaccine pneumococcal antibody concentrations ≥ 0.2 ug/mL ranged from 26.7% to 100% depending on the serotype. One month after the second dose the observed percentage of subjects with vaccine pneumococcal antibody concentrations ≥ 0.2 ug/mL was 100% with the exception of serotypes 6B and 23F (93.3%).

In the unprimed group, 7-10 days after the first vaccination, the observed percentage of subjects with an opsonophagocytic activity titre ≥ 8 was at least 94.7% for all serotypes except for serotype 6B (77.8%) and serotype 19F (89.5%). One month after the second dose all subjects had an opsonophagocytic activity titre ≥ 8 for all serotypes except for serotypes 1 (89.3%), 5 (98.2%) and 6B (93.0%). In the unprimed group, 93.3% of subjects reached anti-PD antibody concentrations >100 EL.U/mL, 7-10 days after the first vaccination. One month after the second dose, 98.3% of subjects had anti-PD antibody concentrations >100 EL.U/mL and the anti-PD GMC was 960.4 EL.U/mL.

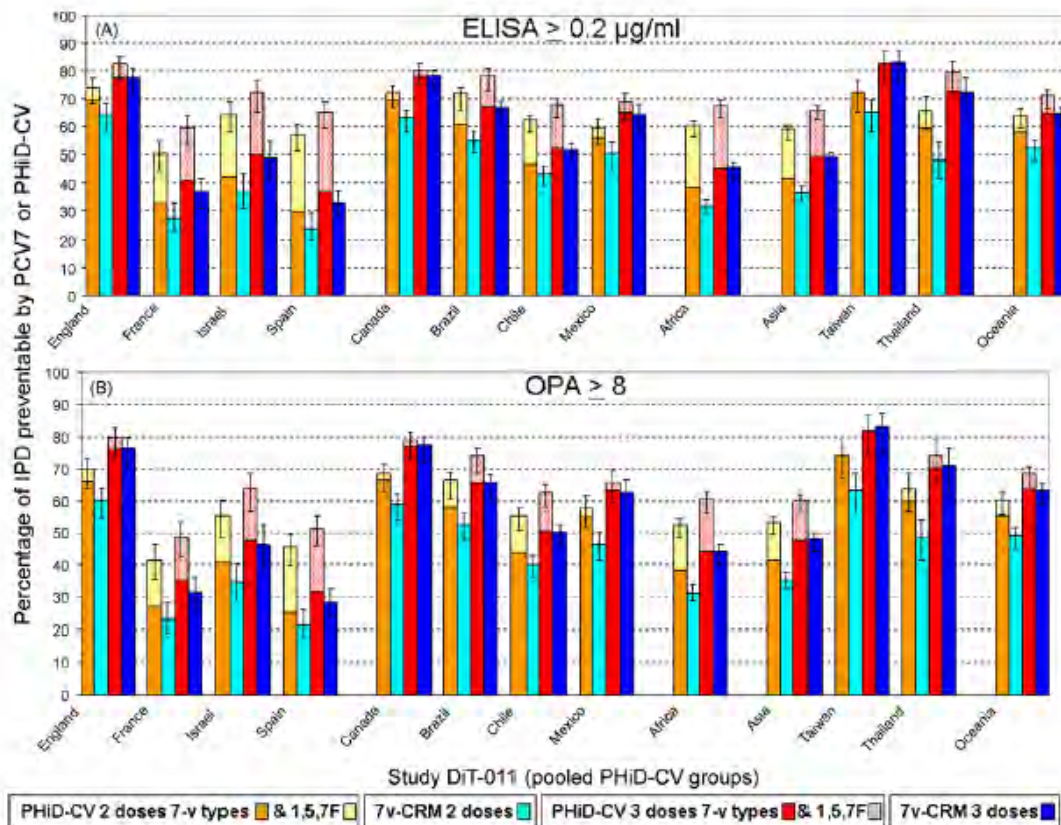
Analyses performed across trials (pooled analyses and meta-analyses)

Effectiveness data following vaccination of Synflorix according to a 2+1 schedule are currently not available. At the time of this evaluation, the time since licensure for countries that have implemented Synflorix has been too short to complete an evaluation of vaccine effectiveness. For instance, Study 10PN-PD-DIT-043 in Finland was still enrolling subjects and effectiveness results are not expected till end of 2012. However, the potential impact of Synflorix (and Prevenar) 2+1 versus 3+1 schedules on efficacy was estimated taking into account WHO licensure criteria for PCV and using an algorithm that considers Prevenar effectiveness data, epidemiology data for IPD for the countries considered in the analysis (several European countries including France, Spain and England) and the relative immunogenicity (ELISA and OPA) with Synflorix as derived from Study 011¹⁷.

A 2-dose primary series of Synflorix was predicted to prevent 50-74% and 42-74% of IPD by ELISA and OPA across all countries while a 2-dose primary series of Prevenar was predicted to prevent 18-65% and 19-63% of IPD respectively (Figure 2). For both vaccines across all countries studied, the 2-dose primary series was predicted to prevent slightly less IPD than a 3-dose primary series (4-14% less IPD for Synflorix and 6-26% less IPD for Prevenar).

Figure 2.

Percentage of IPD preventable by 2 or 3 doses of Synflorix or Prevenar based on % of ELISA/OPA responders in study 011 (Hausdorff, 2009)



¹⁷ Hausdorff WP, Dagan R, Beckers F, Schuerman L. Estimating the direct impact of new conjugate vaccines against invasive pneumococcal disease. *Vaccine*. 2009 27(52):7257-7269.

Comments: The effectiveness of a 2-dose primary course appeared to be greater with Synflorix than with Prevenar. There are, however, some limitations of using this modelling approach: herd protection and contribution of a booster dose are not considered. As a result, differences between 2 and 3 primary doses might disappear after administration of a booster dose and herd protection. However, the results from this modelling are consistent with post marketing surveillance data for Prevenar which suggest a substantial reduction in IPD with a 2+1 schedule, although possibly (at least in initial years) slightly less than that reported with a 3+1 schedule in the US¹⁸. For example, Prevenar demonstrated effectiveness in a 2+1 schedule in the United Kingdom (UK) (72%) and Norway (74%)^{3, 5}. In Quebec, Prevenar showed effectiveness >93% after 2-dose primary vaccination and 100% after booster dose⁴. Furthermore, it is important to note that Synflorix has 3 additional serotypes (1, 5, 6B, 7F, 9V, 14, 23F, 4, 18C and 19F) in addition to those in Prevenar (4, 6B, 9V, 14, 18C, 19F and 23F). However, the EU guideline on the clinical evaluation of new vaccines¹⁹ does state that efficacy studies are not always feasible.

Evaluator's conclusions on clinical efficacy for "alternative 2+1 infant vaccination schedule" (Indication 1)

The sponsor has produced a 10-valent conjugated pneumococcal vaccine that uses Protein D (PD) as carrier (10Pn-PD vaccine) and contains three additional serotypes to those in Prevenar (serotypes 1, 5 and 7F). However, Prevenar 13 has all serotypes in Synflorix and also has 3 additional serotypes (3, 6A, 19A) not included in Synflorix.

Populations evaluated across clinical studies were drawn from the paediatric population in which the proposed pneumococcal conjugate vaccine is recommended. Studies were conducted in healthy male and female children after checking eligibility criteria at study entry. In Studies 002 and 011, exclusion criteria aimed to prevent administration of the candidate vaccine to individuals with medical conditions that might potentially interfere with the evaluation of the immune response; those in whom previous exposure to the vaccine antigens through vaccination or disease would prevent interpretation of the results and those individuals at risk of possible adverse reactions to the vaccine. Studies 002, 011 and 046 were conducted in Denmark, Germany, Norway, Poland, Slovakia, Spain and Sweden. The majority (>90%) of subjects who participated in the clinical studies were White/Caucasian. Males and females were approximately equally represented in all studies. Overall, the study population was representative of the target patient population for Synflorix.

Antibody concentrations as measured by ELISA and opsonophagocytic activity (OPA) against all vaccine serotypes and vaccine related serotypes 6A and 19A were evaluated in all studies. In general, the analysis of the immunogenicity was performed on the ATP cohort for immunogenicity but in Study 046 the ATP cohort for persistence included all subjects in the ATP cohort for safety with assay data for at least one vaccine serotype or Protein D. The immune responses as measured by ELISA against the 10 vaccine serotypes and the vaccine related serotypes 6A and 19A were evaluated in terms of percentages of subjects reaching an antibody concentration of >0.20ug/ml, and the geometric mean antibody concentrations (GMC). The percentage of subjects reaching an OPA titre of 8 and the geometric mean OPA titres (GMT) against the 10 vaccine serotypes one month after

¹⁸ Whitney CG, Pilishvili T, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, Reingold A, Cieslak PR, Pilishvili T, Jackson D, Facklam RR, Jorgensen JH, Schuchat A; Active Bacterial Core Surveillance of the Emerging Infections Program Network. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. *Lancet* 2006; 368(9546):1495-502.

¹⁹Guideline on clinical evaluation of new vaccines. EMEA/ CHMP/ VWP/ 164653/ 2005.

vaccination in Studies 002 and 046 and two months post dose 2 in the post hoc analysis of Study 011, were assessed. These assay methods were well validated and acceptable as they were identical to the ones used for the registered Synflorix (3+1 schedule).

In Study 002, over 92% of infants primed with 2 doses reached the threshold of antibody concentration >0.2 µg/ml as measured by ELISA in all except serotypes 6B and 23F²⁰. Similar findings were observed for functional antibodies with all serotypes reaching OPA titres >8 in 82% or more of subjects except for serotypes 1 and 6B. There was no significant difference between the 2-dose and 3-dose groups in the percentage of subjects with antibody concentration of 0.2µg/ml (ELISA) but there were a lower percentage of subjects with OPA titres >8 in 2-dose primed subjects compared to 3-dose primed subjects for serotypes 6B, 18C and 23F (74.4%, 82.8%, 86.3% respectively for the 2-dose schedule and 88.9%, 96.2%, 97.7% respectively for the 3-dose schedule).

For most serotypes post primary ELISA GMCs were higher (no overlap of CIs) after the 3-dose priming than after the 2-dose priming, particularly for serotype 18C and to a lesser extent 19F. In the time period after primary and before booster vaccination (Study 046), a decline in ELISA GMCs was observed in both groups for all serotypes except 6B and 23F. Importantly, in the 2+1 schedule a robust increase in ELISA GMCs and OPA GMTs was observed for all serotypes after a booster dose indicating adequate priming, as observed when using the 3+1 schedule. The difference between groups became less marked after the booster dose for both ELISA and OPA but was still significant for the percentage of subjects reaching ELISA/OPA thresholds for serotypes 6B (ELISA) and 5 (OPA).

It is important to note that these findings are generally consistent with studies conducted with Prevenar which showed a reduced immune response with the 2+1 immunisation scheme compared to the 3+1 schedule with lower ELISA GMCs for 6B and 23F²¹.

To further evaluate a 2+1 schedule, data from Study 011 provide a head to head comparison of 2 primary doses of Synflorix versus Prevenar via a post hoc analysis of the immunogenicity data reported 2 months after the second dose (subjects were vaccinated at 2, 4 and 6 months of age)²². For all Prevenar serotypes, the observed percentage of subjects with ELISA antibody concentration >0.2µg/ml after the second dose was similar for both vaccines with the exception of serotypes 6B (which was higher for Synflorix), and 18C (which was higher for Prevenar). Antibody GMCs were similar in both groups but higher for Synflorix for 6B and higher for Prevenar for 4, 9V and 18C. The OPA GMTs and the percentage of subjects reaching OPA GMTs ≥8 after the second dose was higher in the Synflorix group for serotypes 6B and 19F and similar for the other serotypes common to both vaccines. However, these results must be interpreted with caution due to the post hoc nature of the analysis.

Studies on IPD effectiveness of Prevenar indicated that the lower immune response observed with the 2+1 schedule had no major impact on vaccine effectiveness^{4,3,5}.

²⁰ Silfverdal SA, Hogh B, Bergsaker MR, Skerlikova H, Lommel P, Borys D, Schuerman L. Immunogenicity of a 2-dose priming and booster vaccination with the 10-valent pneumococcal nontypeable Haemophilus influenzae Protein D conjugate vaccine. *Pediatr Infect Dis J*. 2009 28(10):276-282.

²¹ Givon-Lavi N, Greenberg D, Dagan R. Immunogenicity of CRM-conjugated 7-valent pneumococcal conjugate vaccine (PCV7) administered at 2 doses (4 and 6m) and 3-dose primary regimen (2, 4, 6m) with a booster at 12m. Abstract P3-049. In: 6th International Symposium on Pneumococci and Pneumococcal Diseases; June 8-12, 2008, Reykjavik, Iceland, Abstract 308.

²² Wysocki J, Tejedor JC, Grunert D, Konior R, Garcia-Sicilia J, Knuf M, Bernard L, Dieussaert I, Schuerman L. Immunogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae Protein D conjugate vaccine (PHiD-CV) when coadministered with different neisseria meningitidis serogroup C conjugate vaccines. *Pediatr Infect Dis J*. 2009 28(4):S77-88.

Modelling of the direct impact of 2+1 schedule on IPD indicated that two doses of Synflorix is expected to prevent at least as much and usually more IPD than two doses of Prevenar¹⁷. However, this modelling approach to determine efficacy of vaccines is confounded by herd protection and the fact that contribution of a booster dose are not considered.

Furthermore, the effects of lower percentage of patients with OPA titres >8 in 2-dose primed compared to 3-dose primed subjects for serotypes 6B, 18C and 23F on efficacy of vaccines and incidence of IPD was not evaluated and would need to be monitored in postmarketing studies as these serotypes are generally associated with more severe IPD²³.

The relatively recent licensure of Prevenar 13 (which has all the serotypes in Synflorix as well as 3 extra ones; 3, 6A and 19A) in December 2009 has not allowed GSK to perform a similar head to head comparison between Synflorix and Prevenar 13. However, a head to head study with Prevenar 13 (Study PCV13-501²⁴) conducted in Spain with a 2, 4, 6 primary vaccination schedule showed that the immune responses after two primary doses of Prevenar 13 were similar to those after two doses of Prevenar in terms of the number of subjects with ELISA antibody concentration >0.35ug/ml, as observed for Synflorix in Study 011, although the ELISA GMCs for all common serotypes following two doses of Prevenar13 were lower than those observed for Prevenar. From a second head to head study conducted in the UK with a 2+1 schedule (2, 4, 12 months) (PCV13-007²⁵, it was found that the OPA GMTs were higher for serotype 6B in subjects that received two doses of Prevenar 13, as observed for Synflorix in comparison with Prevenar. For other serotypes, OPA GMTs were either lower or similar to the GMTs following two doses of Prevenar. The ratios of the GMCs and GMTs elicited by two doses of Prevenar13 compared to two doses of Prevenar are also presented for each serotype. The decision to include the 2+1 vaccination schedule in the Posology section of the EU Summary of Product Characteristics of Prevenar 13 (also approved in Australia) in the context of routine immunisation programs was justified in part by the results from Studies PCV13-501 and PCV13-007. The sponsor believes that comparable data for Synflorix also support the inclusion of a 2+1 vaccination schedule in the *Dosage and Administration* section of the PI.

In long term Study 046, the persistence of the immune response was demonstrated 24-36 months after completion of the 2+1 or 3+1 vaccination course in Study 002. Although there was a trend towards lower antibody levels and functional responses for most serotypes at 24-36 months in the 2+1 primed children compared to 3+1 primed children, waning of immunity occurred at similar pace for both groups. A single dose of 10Pn-PD-DiT vaccine during the fourth year of life in subjects having been primed according to a 2+1 schedule or a 3+1 schedule elicited robust anamnestic immune response measured 7-10 days after vaccination indicative of similar induction of immunological memory after previous vaccination with 2+1 or 3+1 schedules.

Overall, there is enough data to suggest similar although slightly lesser immune response to the primary 2+1 dosing schedule compared to the 3+1 schedule. However, single dose of 10Pn-PD-DiT vaccine during the fourth year of life in subjects having been primed

²³ Matt Kalin. Pneumococcal serotypes and their clinical relevance. Thorax 1998; 53: 159-162.

²⁴ Diez-Domingo J, Gurtman A, Bernaola E, Gimenez-Sanchez F, Martinon-Torres F, Pineda-Solas V, Delgado A, Infante-Marquez P, Liang JZ, Giardina P, Gruber WC, Emini EA, Scott DA. Safety and Immunogenicity of a 13-Valent Pneumococcal Conjugate Vaccine in Healthy Infants and Toddlers Receiving Routine Vaccinations in Spain; 27th Annual Meeting of the European Society for Paediatric Infectious Disease (ESPID), June 9-13, 2009, Brussels, Belgium.

²⁵ Congress abstract Immune Response to Pcv13 with A Reduced Dosing Schedule
Author(s) : Paradiso,P.; Rodgers,G.; Thompson,A.; Tansey,S.; Gurtman,A.; Snape,M.; Pollard,A.; Esposito,S.; Principi,N.; ez-Domingo,J.; Gruber,W.; Emini,E.; Scott,D.; 007 5FAU - 007,500
Source : . 2010 ; () : 561 . Congress : 7th Biennial International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD7) Location : Tel Aviv; Israel Start date : 14/03/2010

according to a 2+1 schedule or a 3+1 schedule elicited robust anamnestic immune response measured 7-10 days after vaccination indicative of similar induction of immunological memory after previous vaccination with 2+1 or 3+1 schedules. In many countries including Australia, a 2-dose primary vaccination schedule in infants followed by a booster dose in the second year of life (with or without catch-up immunisation) has been introduced into the national immunisation program. Although the draft PI clearly states that it is preferred to give the 3+1 dosing schedule, the option of 2+1 would provide a convenient option for infants receiving 2-dose primary vaccination. The 2+1 dosing option has already been approved in Australia for Prevenar and Prevenar 13.

Two dose catch-up vaccination schedule for children 2 to 5 years of age

Pivotal efficacy studies

The biggest burden of disease caused by *Streptococcus pneumoniae* and Non-typeable *Haemophilus influenzae* (NTHi) occurs in the very young and the elderly. Most of the invasive disease cases as well as AOM and pneumonia in children occur below 5 years of age¹⁷. Currently, Synflorix is indicated for children below 2 years of age while the medical need goes beyond that age. The two other licensed pneumococcal conjugate vaccines (PCV7 and PCV13) are registered up to 5 years of age, recommending 1 dose between 2 and 5 years of age.

Study PN-PD-DIT-013

Study design, objectives, locations and dates

Study 13 was an open, controlled study with 4 parallel groups stratified according to age and with different vaccination schedules and blood sampling time points. *The primary objective* was to evaluate the immunogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine, when given as a catch-up immunisation in 3 age groups of children older than 7 months of age (7-11 months, 12-23 months and ≥ 24 months) with different schedules; infants <6 months of age served as the control group.

Secondary objectives included evaluation of:

1. Safety and reactogenicity of Synflorix vaccine when given as a catch-up immunisation in children older than 7 months (three age-groups with different schedules);
2. Immunogenicity, safety and reactogenicity of GSK Biologicals' DTPa-IPV/Hib vaccine when co administered with Synflorix vaccine as a 3-dose primary immunisation course in children before 6 months of age and as a booster dose in children 12-15 months of age.

The study was conducted at 10 centres in Finland from 18 September 2006 to 15 November 2007.

Inclusion and exclusion criteria

The study included male or female subjects aged 9-12 weeks (63-90 days), 7-11 months, 12-23 months and 24 months to 5 years in the <6 months old (Mo), 7-11 Mo, 12-23 Mo and >24 Mo groups, respectively. Other inclusion and exclusion criteria were similar to those in Study 002 (discussed above).

Study treatments

All vaccines were administered intramuscularly in the right (10Pn-PD-DiT vaccine) or the left (DTPa-IPV/Hib vaccine) thigh or deltoid (deltoid only used for children >12 months of age if muscle size was adequate).

Efficacy variables and outcomes

The main efficacy variables were: For the evaluation of immunogenicity of the appropriate schedule for catch-up vaccination, the following parameters were measured one month after the administration of the primary (<6 Mo and 7-11 Mo groups) or the full (12-23 Mo and >24 Mo groups) vaccination course, before and one month after the booster dose (<6 Mo and 7-11 Mo groups):

- Antibody concentrations against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F, 6A and 19A (22F-inhibition ELISA).
- Antibody concentrations against Protein D.
- Opsonophagocytic activity against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F, 6A and 19A.

The primary efficacy outcome was % of subjects with Anti-pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody concentrations $\geq 0.20 \mu\text{g}/\text{m}$, 1 month after the administration of the primary (<6 Mo and 7-11 Mo groups) or the full (12-23 Mo and ≥ 24 Mo groups) vaccination course with GSK Biologicals 10-valent pneumococcal conjugate vaccine.

Secondary endpoints were: The following were assessed at 1 month after the administration of the primary (<6 Mo and 7-11 Mo groups) or the full (12-23 Mo and ≥ 24 Mo groups) vaccination course, with GSK Biologicals 10-valent pneumococcal conjugate vaccine, and before and one month after the booster dose with Synflorix for the <6 Mo and 7-11 Mo groups:

- Antibody concentrations to pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F;
- Opsonophagocytic activity against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F;
- Antibody concentrations and
- Opsonophagocytic activity against cross-reactive pneumococcal serotypes 6A and 19A;
- Antibody concentrations to Protein D.

Seropositivity status was defined as:

- Anti-pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody concentrations $\geq 0.05 \mu\text{g}/\text{mL}$
- Opsonophagocytic activity against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F ≥ 8 .
- Anti-pneumococcal cross-reactive serotypes 6A and 19A antibody concentrations $\geq 0.05 \mu\text{g}/\text{mL}$.
- Opsonophagocytic activity against cross-reactive pneumococcal serotypes 6A and 19A ≥ 8 .
- Anti-PD antibody concentrations $\geq 100 \text{ EL.U}/\text{mL}$

Other exploratory endpoints: 1 month after the administration of the primary vaccination course, before and one month after the booster dose with GSK Biologicals. DTPa-IPV/Hib vaccine when co administered with Synflorix vaccine, for the <6 Mo group:

- Anti-diphtheria and anti-tetanus toxoids, anti-PRP, anti-PT, anti-FHA and anti-PRN, antibody concentrations, and anti-polio type 1, 2 and 3 titres.

Seropositivity status defined as:

- Anti-PT antibody concentrations ≥ 5 EL.U/mL.
- Anti-FHA antibody concentrations ≥ 5 EL.U/mL.
- Anti-PRN antibody concentrations ≥ 5 EL.U/mL.

Seroprotection status defined as:

- Anti-diphtheria toxoid antibody concentrations ≥ 0.1 IU/mL. – Anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/mL.
- Anti-PRP antibody concentrations ≥ 0.15 μ g/mL and ≥ 1.0 μ g/mL.
- Anti-polio type 1, 2 and 3 titres ≥ 8 .

Booster vaccine response to PT, FHA and PRN one month after the booster dose for the <6 Mo group; defined as appearance of antibodies in subjects who were seronegative prior to the booster dose (that is, with concentrations < 5 EL.U/mL) and at least two fold increase of pre booster vaccination antibody concentrations in those who were seropositive prior to the booster dose (that is, with concentrations ≥ 5 EL.U/mL).

Randomisation and blinding methods

The enrolment of about 600 subjects was performed to ensure equal distribution of the subjects across the four age strata (150 each in <6 Month, 7-11 Month, 12-23 Month and ≥ 24 Month age groups). The treatment allocation at the investigator site was performed using a central randomisation system on Internet in order to control/limit the number of subjects enrolled in each age group. A sub-randomisation of 200 subjects (50 subjects in each age group) was done for the opsonophagocytic activity serological testing. This was generated using a standard SAS® (Statistical Analysis System) program.

This study was conducted in an open manner because of the different vaccination schedules associated with the different age groups.

Analysis populations

The analysis of immunogenicity was performed on the Primary ATP cohort²⁶ (primary analysis) and the Primary Total vaccinated cohort²⁷. Similarly, analysis of immunogenicity for the booster dose was performed in the Booster ATP cohort and the Booster Total Vaccinated cohort.

Sample size

Considering the sample size of 135 evaluable subjects per age group, Table 15 shows the probability that for a specific pneumococcal serotype the upper limit of the 95% CI for a group difference [<6 Mo group (Post Vacc III (M3)) minus 7-11 Mo group (Post Vacc II (M2)) or <6 Mo group (Post Vacc III (M3)) minus 12-23 Mo group (Post Vacc II (M3)) or <6 Mo group (Post Vacc III (M3)) minus ≥ 24 Mo group (Post Vacc I (M1))] in percentage of subjects with pneumococcal antibody concentrations ≥ 0.2 μ g/mL will be below a limit of delta (δ).

²⁶ The Primary ATP cohort for analysis of immunogenicity included all evaluable subjects (that is, those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures were available. This included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component at least one blood-sampling timepoint (after dose 1 for ≥ 24 Mo group, dose 2 for 7-11 and 12-23 Mo groups, dose 3 for <6 Mo group).

²⁷The Primary Total Vaccinated cohort which included all vaccinated subjects (all subjects who received at least one primary dose).

Table 15. Study 013

Probability that the upper limit of the 95% CI for a group difference in percentage of subjects with pneumococcal antibody concentrations greater than or equal to 0.2 µg/mL be below a limit of (Delta), considering N = 135 subjects/age-group and various proportions.

True proportion in < 6Mo group *	True proportion in one of the 3 catch-up groups **	δ			
		5%	10%	15%	20%
99% (serotype 1, 4, 5, 7F and 14)	99% 95%	78.4% 5.7%	99.9% 62.0%	100% 99.0%	100% 99.9%
98% (serotype 19F)	98% 96%	62.8% 22.0%	99.5% 87.5%	100% 99.9%	100% 100%
97% (serotype 9V)	92% 88%	- -	35.3% 4.7%	88.3% 39.6%	99.7% 87.6%
96% (serotype 18C)	96% 91%	45.9% -	95.0% 32.5%	99.9% 84.7%	100% 99.4%
86% (serotype 23F)	86% 82%	21.4% 4.1%	63.7% 26.3%	93.1% 67.6%	99.6% 93.9%
85% (serotype 6B)	85% 82%	20.5% 6.4%	61.6% 33.3%	91.9% 74.1%	99.4% 95.8%

PASS 2005 (Standardized Asymptotic method), one-sided two group test of equivalence in proportions, alpha = 2.5%.

*Proportions based on 11Pn-PD&Di-001, 11Pn-PD&Di-007 and 11PN-PD-DIT-001 studies, for all serotypes, except for serotype 18C for which proportion was based on 11PN-PD-DIT-002 study.

**Proportions based on 11Pn-PD-019 and 11Pn-PD-025 studies

Statistical methods

For the evaluation of the immunogenicity of the different vaccination schedules a descriptive analysis based on GMCs and GMTs as well as seropositivity rates was performed for each of the pneumococcal serotypes, Protein D and the co administered antigens. In addition, an exploratory inferential analysis was performed for pneumococcal serotypes by comparing the percentages of subjects reaching an ELISA antibody concentration of 0.2 µg/ml.

Participant flow

Of the 600 subjects enrolled, 581 completed the primary vaccination course. Of the 290 subjects from the <6 Mo and 7-11 Mo groups enrolled, 286 completed the booster vaccination study.

Major protocol violations/deviations

Out of the 600 subjects in the Primary Total vaccinated cohort, 593 (98.8%) met the eligibility criteria for the inclusion in the Primary ATP cohort for safety and 540 subjects (90.0 %) met the eligibility criteria for the inclusion in the Primary ATP cohort for immunogenicity. Seven subjects were eliminated from both the Primary ATP cohort for Safety/ Immunogenicity because they received concomitant vaccines forbidden by the protocol; 53 subjects were eliminated from the Primary ATP cohort for immunogenicity (for non-compliance with vaccination schedules/ blood sampling intervals and missing serological data).

Among the 300 subjects from the <6 Mo and 7-11 Mo groups that were vaccinated during the primary vaccination course and that were planned to be enrolled, a total of 290 subjects (145 subjects in each group) received the booster dose of study vaccine and thus were part of the Booster Total vaccinated cohort. Among the 290 subjects enrolled for the booster vaccination, 286 completed the study: 141 in the < 6 Mo group and 145 in the 7-11 Mo group. No subjects discontinued due to a serious adverse event (SAE) or adverse event (AE). Overall, 14 subjects (all from the 7-11 Mo group) were eliminated from both the Booster ATP cohort for Safety and Immunogenicity because they received concomitant vaccines forbidden in the protocol and 21 subjects were eliminated from the Booster ATP cohort for immunogenicity.

Baseline data

In the Primary ATP cohort for immunogenicity, the mean age at the first vaccination dose was 10.9 weeks for the <6 Mo group, 8.3 months for the 7-11 Mo group, 17.9 months for the 12-23 Mo group and 36.4 months for the >24 Mo group. Overall 47.4% of the subjects were female. In all groups most of the subjects were White-Caucasian (99.1%).

Comments: It was observed that in the ≥ 24 Mo group most of the subjects were between 2 and 3 years of age while a smaller proportion of the group was between 3 and 5 years of age.

In the Booster ATP cohort for Immunogenicity, the mean age at the booster vaccination was 12.2 months for the <6 Mo group and 13.4 months for the 7-11 Mo group. Overall, 44.7% of the subjects were female. All subjects except two (one in each group) were White-Caucasian.

Results for the primary efficacy outcome

Post primary immune response to the pneumococcal vaccine: In the <6 Mo group, one month post dose 3, at least 93.8% of the subjects had antibody concentrations ≥ 0.2 $\mu\text{g}/\text{mL}$ for each of the vaccine pneumococcal serotypes except 6B (72.5%) and 23F (87.0%).

In the 7-11 Mo group one month post dose 2 (still to receive a third dose -booster dose at the age of 12-15 months), at least 95.6% of the subjects already had antibody concentrations ≥ 0.2 $\mu\text{g}/\text{mL}$ for each of the vaccine pneumococcal serotypes except 6B (51.1%) and 23F (70.4%). The observed antibody GMCs were lower for serotypes 6B, 9V and 23F and higher for serotypes 4, 18C and 19F compared to those observed for the same serotypes in the <6 Mo group (non-overlap of CIs).

For the 12-23 Mo group one month post dose 2, at least 97.7% of the subjects had antibody concentrations ≥ 0.2 $\mu\text{g}/\text{mL}$ for each of the vaccine pneumococcal serotypes except 6B (81.2%) and 23F (91.7%). The observed antibody GMCs were higher for serotypes 4, 7F, 14, 18C and 19F compared to those observed for the same serotypes in the <6 Mo group (non-overlap of CIs) and the observed percentage of subjects with ELISA antibody concentrations ≥ 0.2 $\mu\text{g}/\text{mL}$ was in the same range or higher for all vaccine serotypes compared to the <6 Mo control group.

For the ≥ 24 Mo group one month post dose 1, at least 91.4% of the subjects had antibody concentrations ≥ 0.2 $\mu\text{g}/\text{mL}$ for each of the vaccine pneumococcal serotypes except 6B (68.6%) and 23F (66.9%). The observed antibody GMCs were lower for serotypes 1, 5, 14 and 23F and higher for serotypes 4, 18C and 19F compared to those observed for the same serotypes in the <6 Mo group (non-overlap of CIs). The observed percentage of subjects with ELISA antibody concentrations ≥ 0.2 $\mu\text{g}/\text{mL}$ was lower for serotypes 14 and 23F and higher for serotype 19F compared to the <6 Mo control group (Table 16).

The immunogenicity results for the Primary Total vaccinated cohort were in line with those observed for the Primary ATP cohort for Immunogenicity.

Comments: In the catch-up immunisation groups, high responses were observed for serotypes 18C and 19F. These serotypes are conjugated to the TT and DT carrier respectively, for which children were previously primed during early childhood. This priming could have contributed to the observed higher responses for serotypes 18C and 19F. However, also high responses were observed for serotype 4, conjugated to Protein D, for which children were not previously primed.

Table 16. Study 013

Seropositivity rates and GMCs for ANTI-1, ANTI-4, ANTI-5, ANTI-6B, ANTI-7F, ANTI-9V, ANTI-14, ANTI-18C, ANTI-19F and ANTI-23F antibodies (Primary ATP cohort for immunogenicity)

Antibody	Group	Timing	N	≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
				n	%	95% CI		n	%	95% CI		value	95% CI	
ANTI-1	<6Mo	PIII(M3)	131	130	99.2	95.8	100	128	97.7	93.5	99.5	1.20	1.02	1.42
	7-11Mo	PII(M2)	135	135	100	97.3	100	135	100	97.3	100	1.19	1.05	1.35
	12-23Mo	PRE	133	30	22.6	15.8	30.6	2	1.5	0.2	5.3	0.03	0.03	0.04
		PII(M3)	133	133	100	97.3	100	132	99.2	95.9	100	1.22	1.06	1.40
	>=24Mo	PRE	139	70	50.4	41.8	58.9	10	7.2	3.5	12.8	0.05	0.04	0.06
	PI(M1)	140	139	99.3	96.1	100	135	96.4	91.9	98.8	0.77	0.66	0.89	
ANTI-4	<6Mo	PIII(M3)	131	131	100	97.2	100	128	97.7	93.5	99.5	1.84	1.57	2.15
	7-11Mo	PII(M2)	135	135	100	97.3	100	135	100	97.3	100	3.47	3.03	3.97
	12-23Mo	PRE	133	7	5.3	2.1	10.5	1	0.8	0.0	4.1	0.03	0.03	0.03
		PII(M3)	133	133	100	97.3	100	133	100	97.3	100	4.21	3.77	4.69
	>=24Mo	PRE	140	19	13.6	8.4	20.4	6	4.3	1.6	9.1	0.03	0.03	0.04
	PI(M1)	140	140	100	97.4	100	140	100	97.4	100	5.72	5.00	6.54	
ANTI-5	<6Mo	PIII(M3)	131	131	100	97.2	100	130	99.2	95.8	100	2.04	1.75	2.37
	7-11Mo	PII(M2)	135	135	100	97.3	100	134	99.3	95.9	100	1.72	1.51	1.96
	12-23Mo	PRE	133	51	38.3	30.1	47.2	6	4.5	1.7	9.6	0.04	0.04	0.05
		PII(M3)	133	133	100	97.3	100	131	98.5	94.7	99.8	1.80	1.57	2.06
	>=24Mo	PRE	140	90	64.3	55.8	72.2	23	16.4	10.7	23.6	0.08	0.06	0.09
	PI(M1)	138	138	100	97.4	100	135	97.8	93.8	99.5	1.16	0.99	1.36	
ANTI-6B	<6Mo	PIII(M3)	131	113	86.3	79.2	91.6	95	72.5	64.0	80.0	0.37	0.29	0.48
	7-11Mo	PII(M2)	135	109	80.7	73.1	87.0	69	51.1	42.4	59.8	0.21	0.16	0.26
	12-23Mo	PRE	133	21	15.8	10.0	23.1	4	3.0	0.8	7.5	0.03	0.03	0.04
		PII(M3)	133	126	94.7	89.5	97.9	108	81.2	73.5	87.5	0.53	0.43	0.65
	>=24Mo	PRE	137	76	55.5	46.7	64.0	36	26.3	19.1	34.5	0.08	0.07	0.11
	PI(M1)	140	133	95.0	90.0	98.0	96	68.6	60.2	76.1	0.38	0.30	0.47	

Table 16. continued.

Antibody	Group	Timing	N	≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
				n	%	95% CI		n	%	95% CI		value	95% CI	
ANTI-7F	<6Mo	PIII(M3)	131	131	100	97.2	100	130	99.2	95.8	100	2.03	1.76	2.33
	7-11Mo	PII(M2)	135	135	100	97.3	100	135	100	97.3	100	2.10	1.83	2.41
	12-23Mo	PRE	133	16	12.0	7.0	18.8	4	3.0	0.8	7.5	0.03	0.03	0.04
		PII(M3)	133	133	100	97.3	100	133	100	97.3	100	3.62	3.22	4.06
	>=24Mo	PRE	140	30	21.4	14.9	29.2	10	7.1	3.5	12.7	0.04	0.03	0.04
PI(M1)		140	140	100	97.4	100	140	100	97.4	100	2.60	2.25	3.01	
ANTI-9V	<6Mo	PIII(M3)	131	130	99.2	95.8	100	128	97.7	93.5	99.5	1.33	1.14	1.55
	7-11Mo	PII(M2)	135	134	99.3	95.9	100	129	95.6	90.6	98.4	0.91	0.78	1.07
	12-23Mo	PRE	133	12	9.0	4.7	15.2	4	3.0	0.8	7.5	0.03	0.03	0.03
		PII(M3)	133	133	100	97.3	100	130	97.7	93.5	99.5	1.50	1.30	1.73
	>=24Mo	PRE	139	37	26.6	19.5	34.8	13	9.4	5.1	15.5	0.04	0.04	0.05
PI(M1)		140	139	99.3	96.1	100	132	94.3	89.1	97.5	1.01	0.84	1.22	
ANTI-14	<6Mo	PIII(M3)	131	131	100	97.2	100	130	99.2	95.8	100	3.00	2.61	3.46
	7-11Mo	PII(M2)	135	135	100	97.3	100	132	97.8	93.6	99.5	2.30	1.95	2.72
	12-23Mo	PRE	132	42	31.8	24.0	40.5	19	14.4	8.9	21.6	0.05	0.04	0.07
		PII(M3)	133	133	100	97.3	100	132	99.2	95.9	100	4.24	3.64	4.95
	>=24Mo	PRE	136	94	69.1	60.6	76.8	35	25.7	18.6	33.9	0.12	0.09	0.16
PI(M1)		139	139	100	97.4	100	127	91.4	85.4	95.5	1.36	1.06	1.74	
ANTI-18C	<6Mo	PIII(M3)	131	130	99.2	95.8	100	127	96.9	92.4	99.2	1.84	1.50	2.26
	7-11Mo	PII(M2)	135	135	100	97.3	100	135	100	97.3	100	4.82	4.14	5.61
	12-23Mo	PRE	133	12	9.0	4.7	15.2	2	1.5	0.2	5.3	0.03	0.03	0.03
		PII(M3)	133	133	100	97.3	100	133	100	97.3	100	9.20	8.22	10.29
	>=24Mo	PRE	139	51	36.7	28.7	45.3	23	16.5	10.8	23.8	0.05	0.04	0.07
PI(M1)		140	140	100	97.4	100	140	100	97.4	100	4.65	4.06	5.31	
ANTI-19F	<6Mo	PIII(M3)	130	129	99.2	95.8	100	122	93.8	88.2	97.3	1.61	1.28	2.02
	7-11Mo	PII(M2)	135	132	97.8	93.6	99.5	129	95.6	90.6	98.4	3.36	2.68	4.20
	12-23Mo	PRE	132	26	19.7	13.3	27.5	14	10.6	5.9	17.2	0.04	0.03	0.05
		PII(M3)	133	133	100	97.3	100	131	98.5	94.7	99.8	5.45	4.63	6.41
	>=24Mo	PRE	139	87	62.6	54.0	70.6	64	46.0	37.6	54.7	0.20	0.14	0.28
PI(M1)		140	140	100	97.4	100	140	100	97.4	100	5.26	4.34	6.39	
ANTI-23F	<6Mo	PIII(M3)	131	124	94.7	89.3	97.8	114	87.0	80.0	92.3	0.62	0.50	0.76
	7-11Mo	PII(M2)	135	123	91.1	85.0	95.3	95	70.4	61.9	77.9	0.40	0.32	0.50
	12-23Mo	PRE	133	17	12.8	7.6	19.7	6	4.5	1.7	9.6	0.03	0.03	0.04
		PII(M3)	133	132	99.2	95.9	100	122	91.7	85.7	95.8	0.88	0.73	1.05
	>=24Mo	PRE	140	59	42.1	33.9	50.8	32	22.9	16.2	30.7	0.07	0.05	0.09
PI(M1)		139	131	94.2	89.0	97.5	93	66.9	58.4	74.6	0.37	0.30	0.47	

<6Mo = 10Pn-PD-DiT + DTPa-IPV/Hib (3, 4, 5 months)

7-11Mo = 10Pn-PD-DiT (7-11, 8-12 months)

12-23Mo = 10Pn-PD-DiT (12-23, 14-25 months)

>=24Mo = 10Pn-PD-DiT (24 months - 5 Years)

GMC = geometric mean antibody concentration

N = number of subjects with available results

n/% = number/percentage of subjects with concentration within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PIII(M3) = One month after dose 3 (<6Mo group)

PII(M2) = One month after dose 2 (7-11Mo group)

PRE = Before dose 1

PII(M3) = One month after dose 2 (12-23Mo group)

PI(M1) = One month after dose 1 (>=24Mo group)

Results for other efficacy outcomes

In a subset (about 50 subjects/group), one month post dose 3, at least 85.4% of the subjects in the <6 Mo group had an opsonophagocytic activity ≥ 8 for each of the vaccine pneumococcal serotypes except serotype 1 (54.5%) and 6B (76.3%). For the 7-11 Mo group one month post dose 2, at least 84.4% of the subjects already had an opsonophagocytic activity ≥ 8 against all of the vaccine pneumococcal serotypes except serotype 1 (45.8%), 5 (76.1%) and 6B (33.3%). The observed OPA GMTs for this age group were lower for serotype 6B and higher for serotype 18C compared to those observed for the <6 Mo group (non-overlap of CIs). For the 12-23 Mo group one month postdose 2, at

least 84.0% of the subjects had an opsonophagocytic activity ≥ 8 for each of the vaccine pneumococcal serotypes except serotypes 1 (45.1%) and 6B (75.5%). For this age group, higher OPA GMTs were observed for serotypes 9V and 18C than those observed for the same serotypes in the <6 Mo group (non-overlap of CIs). For the ≥ 24 Mo group one month post vaccination, at least 90.2% of the subjects had an opsonophagocytic activity ≥ 8 for each of the vaccine pneumococcal serotypes except serotypes 1 (46.3%), 5 (56.4%) and 6B (64.7%). The observed OPA GMTs was lower for serotype 5 and higher for serotypes 4, 9V, 18C and 19F compared to those observed for the same serotypes in the <6 Mo group (non-overlap of CIs).

In Study 013 post primary vaccination, the maximum observed difference in terms of percentage of subjects with ELISA pneumococcal antibody concentrations ≥ 0.2 $\mu\text{g}/\text{mL}$ between the <6 Mo group and the 7-11 Mo group (<6 Mo group minus 7-11 Mo group) was less than 2.2% for all the vaccine pneumococcal serotypes except 6B (difference of 21.4%) and 23F (16.7%). The maximum observed difference in terms of percentage of subjects with ELISA pneumococcal antibody concentrations ≥ 0.2 $\mu\text{g}/\text{mL}$ between the <6 Mo group and the 12-23 Mo group (<6 Mo group minus 12-23 Mo group) was 0.7% for all vaccine pneumococcal serotypes including serotypes 6B and 23F. The observed difference between the <6 Mo group and the ≥ 24 Mo group (<6 Mo group minus ≥ 24 Mo group) in terms of percentage of subjects with ELISA pneumococcal antibody concentrations ≥ 0.2 $\mu\text{g}/\text{mL}$ showed a maximum of 7.9% for all vaccine pneumococcal serotypes except 23F, for which the observed difference was 20.1%.

The GMCs of antibodies against the cross-reactive pneumococcal serotypes 6A and 19A were measured by 22F-inhibition ELISA; the percentage of subjects with pneumococcal antibody concentrations ≥ 0.05 $\mu\text{g}/\text{mL}$ and ≥ 0.20 $\mu\text{g}/\text{mL}$ for 6A and 19A were greater one month post dose 2 (12-23 Mo group) and one month post dose 1 (≥ 24 Mo group) compared to one month post dose 3 (<6 Mo group) and one month post dose 2 (7-11 Mo group). Similar results were observed for percentage of subjects with opsonophagocytic activity ≥ 8 .

After the primary vaccination the observed antibody responses (GMCs) against Protein D were lower in the three catch-up groups compared to those observed in the <6 Mo control group and seemed to be dose dependent.

In the <6Mo group, one month post dose 3, all subjects had antibody concentrations ≥ 0.1 IU/mL against diphtheria and tetanus antigens. One month post dose 3, all but one subject (who was seronegative for anti-PT antibodies) had antibody concentrations ≥ 5 EL.U/mL against each of the three pertussis antigens. Only a small number of subjects had sufficient serum volume remaining to allow performing the micro neutralisation assay for all 3 poliovirus antigens. These results should therefore be interpreted with caution. One month post dose 3, all subjects had titres ≥ 8 for polio 1 and polio 3 antigens and 81.3% of the subjects had titres ≥ 8 for polio 2 antigens. One month post dose 3, 98.5% of the subjects had anti-PRP antibody concentrations ≥ 0.15 $\mu\text{g}/\text{mL}$ and 75.0% of the subjects reached an anti-PRP antibody level of 1.0 $\mu\text{g}/\text{mL}$.

Immunogenicity results after booster vaccination (<6 Mo and 7-11 Mo group)

Persistence: Prior to booster vaccination in the <6 Mo and 7-11Mo groups, that is, 7-10 months after the primary vaccination, at least 95.6% of the subjects still had antibody concentrations ≥ 0.05 $\mu\text{g}/\text{mL}$ for each of the vaccine pneumococcal serotypes. In the time period after the primary and before the booster vaccination, a decline in antibody GMCs was observed for most of the serotypes, except for serotype 6B in <6Mo group and serotypes 6B, 14 and 23F in the 7-11 Mo group. A decline in antibody GMCs was observed in the time period after the primary and before the booster vaccination for most of the serotypes. For serotypes 6B and 23F an increase in antibody GMC and in the percentage of seropositive subjects (antibody concentrations ≥ 0.05 $\mu\text{g}/\text{mL}$) seemed to be observed

whereas for serotype 14 the post primary antibody GMC and the percentage of seropositive subjects were maintained.

Prior to booster vaccination, that is, 7-10 months after primary vaccination, the percentage of subjects with an opsonophagocytic activity ≥ 8 ranged from 14.3% (serotype 18C) to 100% (serotype 9V) in the <6 Mo group and was at least 71.0% (except for serotype 1 - 28.9%) in the 7-11 Mo group. In the time period after the primary and before the booster vaccination, a decline in OPA GMTs was observed for most of the serotypes. Prior to booster vaccination in the 7-11 Mo group, that is, 3-4 months after the primary vaccination at least. In the time period after the primary and before the booster vaccination, the OPA GMTs declined or were maintained for most of the serotypes, except for serotypes 6B and 23F.

Prior to the booster vaccination, 97-98% of the subjects in the <6 Mo and 7-11 groups still had anti Protein D antibody concentrations ≥ 100 EL.U/mL.

Booster response: One month post booster vaccination at least 96.4% of the subjects in the <6 Mo and 7-11 groups had antibody concentrations ≥ 0.20 $\mu\text{g/mL}$ for each of the vaccine pneumococcal serotypes. A 2 to 8 fold increase in antibody GMCs was observed from the pre booster to the one month post booster time point for each of the vaccine pneumococcal serotypes. Post booster vaccination, the observed antibody GMCs were lower for serotypes 9V and 23F and higher for serotypes 14, 18C and 19F compared to those observed for the same serotypes following booster vaccination in the <6 Mo group (non-overlap of CIs). However, the observed antibody GMCs exceeded those observed following primary vaccination in the control group for all serotypes.

One month post booster vaccination at least 90% of the subjects in the <6 Mo and 7-11 Mo groups had an opsonophagocytic activity ≥ 8 except for serotypes 1 (83.3%) and 6B (84.4%). For each of the vaccine pneumococcal serotypes substantial increases in OPA GMTs were observed compared to the pre booster time point as well as to the one month post primary vaccination time point. As already observed for ELISA, high OPA responses were observed for serotypes 18C and 19F in the 7-11Mo age group. For all serotypes the post booster OPA GMTs were higher compared to those observed one month post primary vaccination in the <6 Mo group. This trend for higher post booster OPA GMTs was also observed when comparing to the post booster OPA GMTs in the <6 Mo group except for serotypes 4, 14 and 23F.

The percentage of subjects with pneumococcal antibody concentrations ≥ 0.05 $\mu\text{g/mL}$ and ≥ 0.20 $\mu\text{g/mL}$, one month post booster vaccination were slightly higher in the (7-11Mo) group compared to the (<6 Mo) group. Both groups showed similar results at one month post dose 3 (<6 Mo group), one month post dose 2 (7-11 Mo group), prior to booster vaccination.

One month post booster vaccination all subjects in the <6 Mo group and all but 1 subject in the 7-11Mo group had anti-Protein D antibody concentrations ≥ 100 EL.U/mL. The observed antibody GMC in the 7-11 Mo group was lower than that observed in the <6 Mo group. This lower response might be due to the fact that subjects in the 7-11 Mo group received only three doses of pneumococcal conjugate vaccine while subjects in the <6 Mo group received four doses.

The maximum observed difference in terms of percentage of subjects with ELISA pneumococcal antibody concentrations ≥ 0.2 $\mu\text{g/mL}$ between the <6 Mo group and the 12-23 Mo group [<6 Mo (Post Vacc IV (M10) minus 12-23 Mo (Post Vacc II (M3))] was below 2.3% for all vaccine pneumococcal serotypes except for serotypes 6B and 23F for which the observed differences were 15.2% and 7.5% respectively.

The observed difference between the <6 Mo group and the ≥ 24 Mo group [<6 Mo (Post Vacc IV (M10) minus ≥ 24 Mo (Post Vacc I (M1))] in terms of percentage of subjects with

ELISA pneumococcal antibody concentrations $\geq 0.2 \mu\text{g/mL}$ showed a maximum of 8.6% for all vaccine pneumococcal serotypes except for serotypes 6B and 23F for which the observed difference was 27.8% and 32.4% respectively.

Persistence and booster immune response to the co administered DTPa-IPV/Hib vaccine:

In the <6Mo group, seropositivity/seroprotection/booster vaccine response rates for antibodies against the antigens contained in the co administered DTPa-IPV/Hib vaccine were in line with previous observations for this co administered vaccine.

The immunogenicity results for the Booster Total vaccinated cohort were in line with those observed for the Booster ATP cohort for immunogenicity.

Suboptimal response: The listing of the subjects with a suboptimal response²⁸ showed that one subject each in the 7-11 Mo (one month post booster vaccination) and the ≥ 24 Mo group (one month post vaccination) had antibody concentrations $< 0.05 \mu\text{g/mL}$ against the vaccine pneumococcal serotypes 6B and 23F.

Study 046

Study design, patient characteristics, efficacy/ immunological endpoints, statistical methods and the study results have been discussed previously in this report. However, results relevant to the proposed indication of '2-dose catch-up vaccination schedule for children 2 to 5 years of age are discussed in this section.

Immune responses following 2-dose catch-up vaccination with the pneumococcal conjugate vaccine during the fourth year of life:

In the unprimed group, 7-10 days after the first vaccination, the observed percentage of subjects with vaccine pneumococcal antibody concentrations $>0.2 \mu\text{g/mL}$ ranged from 26.7% to 100%, depending on the serotype. One month after the second dose, the observed percentage of subjects with vaccine pneumococcal antibody concentrations $> 0.2 \mu\text{g/mL}$ was 100% except for serotypes 6B and 23F (93.3%).

In the unprimed group, 7-10 days after the first vaccination, the observed percentage of subjects with an opsonophagocytic activity titre >8 , was at least 94.7% for all serotypes, except 6B (77.8%) and 19F (89.5%). One month after the second dose all subjects had an opsonophagocytic activity titre > 8 for all serotypes except 1 (89.3%), 5 (98.2%) and 6B (93.0%). In the unprimed group, 93.3% of subjects reached anti-PD antibody concentrations $>100 \text{ EL.U/mL}$ 7-10 days after the first vaccination. One month after the second dose 98.3% of subjects had anti-PD antibody concentrations $>100 \text{ EL.U/mL}$ and the anti-PD GMC was 960.4 EL.U/mL.

Consistent and robust increases in ELISA antibody GMCs and OPA GMTs were observed one month after the second dose of vaccine as compared to the pre vaccination status in unprimed subjects.

Other efficacy studies

Not applicable.

Analyses performed across trials (pooled analyses and meta-analyses)

Not applicable.

²⁸ Subjects with a suboptimal response were subjects with pneumococcal antibody concentration below $0.05 \mu\text{g/mL}$ for more than one serotype after completion of the complete vaccination course

Evaluator's conclusions on clinical efficacy for "2 dose catch-up vaccination schedule for children 2-5 years of age" (Indication 2)

Populations evaluated across clinical Studies 013 and 046 were drawn from the paediatric population in which pneumococcal conjugate vaccines is proposed to be used for 'catch-up vaccination in 2 to 5 year olds not previously vaccinated with pneumococcal vaccines'. Studies were conducted in healthy male and female children and exclusion criteria aimed to prevent administration of the candidate vaccine to individuals with medical conditions that might potentially interfere with the evaluation of the immune response; those in whom previous exposure to the vaccine antigens through vaccination or disease would prevent interpretation of the results and those individuals at risk of possible adverse reactions to the vaccine. Study 013 was conducted in Finland. Study 046 was performed in Slovakia and Sweden (while its preceding Study 002 was conducted in Denmark, Norway, Slovakia and Sweden). The majority (>90%) of subjects who participated in the clinical studies were White/Caucasian. Males and females were equally represented in all studies. All serological assays used to evaluate the anti-pneumococcal antibody and OPA responses were performed in GSK Biologicals' laboratory using standardised and validated procedures with adequate controls. Antibody concentrations as measured by ELISA and opsonophagocytic activity (OPA) against all vaccine serotypes and vaccine related serotypes 6A and 19A were evaluated in both studies. The analysis of the immunogenicity was performed on the ATP cohort for immunogenicity.

In *Study 013*, results in the <6 Mo group after a 3-dose primary vaccination and booster vaccination at 12-15 months of age in whom Synflorix is already approved showed expected immunogenicity results.

Results in the 7-11 Mo group, after the two-dose primary vaccination and booster vaccination at 12-15 months of age:

One month post-primary vaccination, antibody concentrations $\geq 0.2 \mu\text{g/mL}$ were measured in at least 95.6% of the subjects for each of the vaccine pneumococcal serotypes except for serotypes 6B (51.1%) and 23F (70.4%). The observed ELISA antibody GMCs were lower for serotypes 6B, 9V and 23F and higher for serotypes 4, 18C and 19F compared to those observed for the same serotypes in the <6 Mo control group (non-overlap of CIs). The observed percentage of subjects with ELISA antibody concentrations $\geq 0.2 \mu\text{g/mL}$ was also lower for serotypes 6B and 23F compared to the <6 Mo group. At one month post primary vaccination, at least 84.4% of the subjects had an opsonophagocytic activity ≥ 8 for each of the vaccine pneumococcal serotypes, except for serotypes 1 (45.8%), 5 (76.1%) and 6B (33.3%). The observed OPA GMTs were lower for serotype 6B and higher for serotype 18C than to those observed in the <6 Mo control group (non-overlap of CIs).

Prior to booster dose that is, 3 to 4 months after the completion of the three dose primary vaccination course at least 95.6% of the subjects still had antibody concentrations $\geq 0.05 \mu\text{g/mL}$ for each of the vaccine pneumococcal serotypes. Prior to the booster vaccination at least 71.0% of the subjects still had an opsonophagocytic activity ≥ 8 for each of the vaccine pneumococcal serotypes except serotype 1 (28.9%).

One month post-booster vaccination the observed ELISA antibody GMCs were lower for serotypes 9V and 23F and were higher for serotypes 14, 18C and 19F compared to those observed for the same serotypes following booster vaccination in the <6 Mo control group (non overlap of CIs). However, the observed antibody GMCs for all serotypes exceeded those observed following primary vaccination in the control group. The percentage of subjects with ELISA antibody concentrations $\geq 0.2 \mu\text{g/mL}$ was higher than that observed following primary vaccination in the <6 Mo control group and was in the same range compared to that observed following booster vaccination in the <6 Mo control group. One month post booster vaccination, at least 90.0% of the subjects had an opsonophagocytic activity ≥ 8 for each of the vaccine pneumococcal serotypes. For all vaccine pneumococcal

serotypes increases in OPA GMTs were observed compared to those noted at the pre booster and the one month post primary vaccination time points. For all serotypes the post booster OPA GMTs were higher compared to those observed one month post primary vaccination in the <6 Mo control group. This trend for higher post booster OPA GMTs was also observed when comparing to the post booster OPA GMTs in the <6 Mo control group except for serotypes 4, 14 and 23F.

Results in the 12-23 Mo group, after completed two-dose vaccination schedule:

One month post dose 2, antibody concentrations $\geq 0.2 \mu\text{g/mL}$ were measured in at least 97.7% of the subjects for each of the vaccine pneumococcal serotypes except for 6B (81.2%) and 23F (91.7%). The observed ELISA antibody GMCs in the 12-23 Mo group were higher for serotypes 4, 7F, 14, 18C and 19F compared to those observed for the same serotypes in the <6 Mo control group one month after the 3-dose primary vaccination (non-overlap of CIs). These remained significantly higher compared to the post booster antibody GMCs in the <6 Mo control group for serotypes 4, 18C and 19F whereas GMCs for antibodies against serotypes 6B, 9V and 23F were significantly lower compared to the post booster antibody GMCs in the <6 Mo control group (non-overlap of CIs). The percentage of subjects with ELISA antibody concentrations $\geq 0.2 \mu\text{g/mL}$ was lower for serotypes 6B and 23F compared to the post booster time point in the <6 Mo control group (non-overlap of CIs).

One month post dose 2, at least 84.0% of the subjects had an opsonophagocytic activity ≥ 8 for each of the vaccine pneumococcal serotypes except serotypes 1 (45.1%) and 6B (75.5%). The observed OPA GMTs were higher for serotypes 9V and 18C compared to those observed for the same serotypes in the <6 Mo control group one month after the 3-dose primary vaccination (non-overlap of CIs). The OPA GMTs observed post dose 2 were higher for serotypes 9V and 18C and lower for serotypes 1, 4, 5 and 23F compared to those observed post booster dose in the <6 Mo control group.

Results in the ≥ 24 Mo group, after single-dose vaccination schedule:

One month post dose 1, antibody concentrations $\geq 0.2 \mu\text{g/mL}$ were measured in at least 91.4% of the subjects for all pneumococcal serotypes except for serotypes 6B (68.6%) and 23F (66.9%). The observed ELISA antibody GMCs were lower for serotypes 1, 5, 14 and 23F and were higher for serotypes 4, 18C and 19F compared to those observed for the same serotypes in the <6 Mo control group one month after the 3-dose primary vaccination (non-overlap of CIs). These remained significantly higher compared to the post booster antibody GMCs in the <6 Mo control group for serotypes 4 and 19F, whereas GMCs for antibodies against serotypes 1, 5, 6B, 9V, 14 and 23F were significantly lower compared to the post booster antibody GMCs in the <6 Mo control group (non-overlap of CIs). The percentage of subjects with ELISA antibody concentrations $\geq 0.2 \mu\text{g/mL}$ was lower for serotypes 14 and 23F and higher for serotype 19F compared to the <6 Mo control group one month after the 3-dose primary vaccination (non-overlap of CIs). Compared to the post booster time point in the <6 Mo control group, the percentage of subjects with ELISA antibody concentrations $\geq 0.2 \mu\text{g/mL}$ was lower for serotypes 6B, 14 and 23F.

One month post dose 1, at least 90.2% of the subjects had an opsonophagocytic activity ≥ 8 for each of the vaccine pneumococcal serotypes except serotypes 1 (46.3%), 5 (56.4%) and 6B (64.7%). The OPA GMTs were lower for serotype 5 and were higher for serotypes 4, 9V, 18C and 19F compared to those observed for the same serotypes in the <6 Mo control group one month after the 3-dose primary vaccination (non-overlap of CIs). The same trend was observed compared to the post booster OPA GMTs in the <6 Mo control group.

In Study 013, a single dose of the 10-valent pneumococcal conjugate vaccine at ≥ 24 months of age did not seem to induce an acceptable immune response for some of the

pneumococcal vaccine serotypes. Therefore, an additional dose could be beneficial beyond the second year of life. A lower immune response was observed with a single dose for several serotypes compared to post dose 3 in infants less than 6 months of age, with a reduced proportion of subjects reaching an antibody concentration $>0.2 \mu\text{g/ml}$ for serotypes 14 and 23F. Lower ELISA GMCs were observed for serotypes 1, 5, 14 and 23F and higher GMCs were reported for 4, 18C and 19F. OPA GMT was lower for serotype 5 and the percentage of subjects reaching an OPA titer of 8 was lower for serotypes 1, 5 and 6B. The Protein D response was lower after one dose in the >24 Mo group compared to the response after 3 doses in the <6 Mo group.

Although in Study 046 no direct control group of infants receiving a 3-dose primary schedule was available, comparisons were made with the <6 Mo group in the preceding Study 002.

In Study 046 no direct control group of infants below 6 months receiving 3 primary doses of Synflorix was present. Therefore, the comparison of the 2-dose catch-up was made to the infant group that received 3-dose primary vaccination in the preceding Study 002. Without an immunological correlate for individual protection, the comparison of the immune response after catch-up vaccination in older children to those after a 3-dose primary schedule in infants below 6 months of age was justified because the catch-up vaccination can actually be seen as primary vaccination in older children. The immune response after catch-up vaccination should therefore be at least as good as after 3 doses in infants below 6 months. However, the 3-dose primed group in Study 002 was vaccinated according to a 3, 4, 5 month schedule, despite the protocol defined vaccination schedule of 2, 3 and 4 months. A limitation of such comparison is that the groups were vaccinated at different points in time as there was approximately a 2 year interval between studies.

In Study 046, two doses resulted in higher GMCs and GMTs compared to a 3-dose primary vaccination course for each of the pneumococcal serotypes and similar response to Protein D. Although acknowledging the limitations when comparing results between different studies (such as control groups with different schedules, different age at first dose and different countries), the immune responses after 2 doses in Study 046 in unprimed subjects were clearly higher than those in Study 013, not only for the pneumococcal serotypes but also for Protein D.

Overall, there was evidence to suggest an adequate immune response following '2-dose catch-up vaccination with Synflorix in children aged 2 to 5 years not previously immunised with pneumococcal vaccine'.

Safety

Studies providing evaluable safety data

The main conclusions on safety of Synflorix administered according to a 2+1 schedule were derived from Studies 002 and 046 and are summarised below. Analysis of the reactogenicity and safety of Synflorix was not performed in the post hoc analysis in Study 011. Furthermore, data on safety in catch-up groups aged 7-11 months, 12-23 months and ≥ 24 months were compared to the control group of <6 months in Study 013. The assessment of safety and reactogenicity of Synflorix administered according to a 2+1 or 3+1 schedule was part of the secondary objectives in Study 002. The safety and reactogenicity of the additional dose of Synflorix administered at 36-46 months of age in primed children was a secondary objective of Study 046.

The adverse events (AEs) were recorded in the Diary cards by the subject's parents/guardians and transcribed in the electronic Case Report Form (eCRF) by the study investigator.

Safety and reactogenicity were evaluated as follows:

- Local AEs (pain, redness and swelling at injection site) were solicited during a 4 day follow-up period (Day 0-Day 3) after each vaccination visit;
- General AEs (drowsiness, fever, irritability/fussiness and loss of appetite) were solicited during a 4-day follow-up period (Day 0-Day 3) after each vaccination visit;
- Other AEs (that is, non serious and unsolicited) were followed-up for a period of 31 days (Day 0-Day 30) after each vaccination visit;
- Serious AEs (SAEs) were followed throughout the whole study period.

The analysis of reactogenicity and safety was performed on the total vaccinated cohort for all studies. The total vaccinated cohort included all subjects with documented vaccine administration.

The following analyses were performed:

- Incidence of solicited and/or unsolicited local and general AEs were calculated with 95% CI after each vaccine dose and overall, according to the intensity and causal relationship to vaccination;
- Incidence of each local and each general solicited AE during the 4 day post vaccination period were calculated with exact 95% CI, after each vaccine dose and overall, according to the intensity and causal relationship to vaccination;
- The percentages of subjects and doses (each with 95% CI) with an unsolicited AE reported within 31 day post vaccination period were summarised according to the Medical Dictionary for Regulatory Activities (MedDRA) Prevalence of concomitant medication during the 4 day post-vaccination period, was computed with 95% CI after each vaccine dose and overall;
- Serious adverse events, large swelling reactions and withdrawals due to adverse event(s) during the whole period of the study were described in detail.

Table 17 lists the type and intensity grading of solicited local and general symptoms. Grade 3 fever was defined as rectal temperature $>40.0^{\circ}\text{C}$.

The evaluation of the safety of the catch-up vaccination schedules in both Studies 013 and 046 included the incidence of solicited local and general events (during 4 days post vaccination), the incidence of unsolicited events (during 31 days post vaccination), the use of concomitant antipyretics or medication and the occurrence of SAEs (during the whole study period). The intensity of each solicited symptom was graded according to a standard intensity scale except for fever (rectal temperature $>38^{\circ}\text{C}$ or axillary/oral/tympanic temperature $>37.5^{\circ}\text{C}$; grade 3 fever was defined as rectal temperature $>40.0^{\circ}\text{C}$ or axillary/oral/tympanic temperature $>39.5^{\circ}\text{C}$) (Table 17). Using his/her clinical judgement, the investigator assessed the intensity of each unsolicited event and the presence or absence of a possible causal relationship to vaccination according to criteria specified in the protocol. All solicited local symptoms were considered to be causally related to vaccination.

Table 17.

Local and general adverse events solicited during 10PN-PD-DIT studies and grading of intensity

Adverse Event	Intensity grade	Parameter
Symptoms solicited in all 10PN-PD-DIT studies		
Pain at injection site	0	Absent
	1	Minor reaction to touch
	2	Cried/protected on touch
	3	Cried when limb was moved/was spontaneously painful
Redness at injection site	*	Record greatest surface diameter in mm
Swelling at injection site*	*	Record greatest surface diameter in mm
Fever†	†	Record temperature in °C
Irritability/Fussiness	0	Behaviour as usual
	1	Cried more than usual/ no effect on normal activity
	2	Cried more than usual/ interfered with normal activity
	3	Cried and could not be comforted/ prevented normal activity
Drowsiness	0	Behaviour as usual
	1	Drowsiness easily tolerated
	2	Drowsiness that interfered with normal activity
	3	Drowsiness that prevented normal activity
Loss of appetite	0	Normal
	1	Ate less than usual/ no effect on normal activity
	2	Ate less than usual/ interfered with normal activity
	3	Did not eat at all

* The size of redness and swelling was graded at GSK Biologicals as follows: grade 0: absent, grade 1: >0 – ≤20 mm; grade 2: > 20 mm – ≤30 mm, grade 3: > 30 mm. † Fever was defined as rectal temperature ≥38°C or axillary/oral/tympenic temperature ≥37.5°C. Grade 3 fever was defined as rectal temperature >40.0°C or axillary/oral/tympenic temperature >39.5°C. Temperature was recorded in the evening. If temperature measurement was performed additionally at another time of day, the highest was recorded.

Pivotal studies that assessed safety as a primary outcome

Although the primary objective of Study 011 was to compare safety and reactogenicity of Synflorix with that of Prevenar, only the 3+1 dosing schedule (which is already approved) was evaluated. Post hoc analysis after the second dose was only done for immunogenicity and safety was not evaluated in this post-hoc analysis.

Patient exposure

2+1 vaccination schedule:

A total of 351 subjects (175 subjects in the 2-dose priming group and 176 subjects in the 3-dose priming group) were enrolled in Study 002 and received at least one dose of Synflorix. This study was conducted in 10 centres in 4 countries. Out of the 351 subjects in Study 002, 110 participated in the follow-up Study 046. In addition, Study 046 enrolled 62 subjects in the unprimed group. This study was conducted at 7 centres in two countries.

The mean age of the Total vaccinated cohort was 12.1±1.9 weeks in Study 002 and 38.8 ± 2.4 months in Study 046. The cohort was composed of approximately 52% males in both studies. Subjects enrolled in each study were required to be free of obvious health problems.

2-dose catch-up vaccination schedule for children 2 to 5 years old

In Study 013, 145 out of 150 subjects (96.7%) in the <6 Mo group of the subjects received three doses of 10-valent pneumococcal conjugate vaccine co-administered with DTPa-IPV/Hib vaccine as 5 subjects were withdrawn before Visit 3. Overall, 147 out of 150 subjects (98.0%) in the 7-11 Mo group and 145 out of 150 subjects (96.7%) in the 12-23 Mo group received two doses of 10-valent pneumococcal conjugate vaccine. In the 7-11 Mo group 3 subjects were withdrawn before Visit 2 and in the 12-23 Mo group 5 subjects

were withdrawn before Visit 2. All subjects in the ≥ 24 Mo group received a single dose of 10-valent pneumococcal conjugate vaccine. The compliance in returning symptom sheets was at least 98.7%. In Study P013, all subjects in the < 6 months and 7-11 months age groups received the booster dose of 10-valent pneumococcal conjugate vaccine. One subject in the < 6 Mo group did not receive the booster dose of DTPa-IPV/Hib vaccine at the time of 10Pn-PD-DiT booster dose as this was administered before the booster vaccination visit. The compliance in returning symptoms sheets was 99.3% in the < 6 Mo group and 100% in the 7-11 Mo group.

In long term Study 046, 62 unprimed children (who had not received any previous pneumococcal vaccine) received 2 single doses of Synflorix after the age of 2 years (mean age of 38 months) and all 62 children completed both doses of the vaccine and completed the study.

Adverse events

All adverse events (irrespective of relationship to study treatment)

Study 002

In Study 002 during the primary vaccination course, 94.8% and 93.5% of injected doses in the 2-dose and 3-dose priming groups respectively, were followed by at least one AE (solicited and/or unsolicited, local and/or general). General AEs were more frequently reported than local AEs. About 95% of injected booster doses in both groups were followed by at least one AE (solicited and/or unsolicited, local and/or general).

Redness was the most frequently reported solicited local AE during primary phase (34.8% in the 2+1 group, 33.8% in the 3+1 group) and booster phase (51.1% in the 2+1 group, 49.1% in the 3+1 group). Swelling > 30 mm was the most frequently reported Grade 3 solicited local symptom following primary vaccination, reported after 7.5% and 3.8% of the doses in the 2-dose and 3-dose priming groups respectively. Redness > 30 mm was the most frequently reported Grade 3 solicited local symptom following booster vaccination, reported after 11.5% to 11.8% of the booster doses in the 2-dose and 3-dose priming groups respectively. Three subjects reported large swelling reactions following the booster dose of DTPa combined vaccine: 2 subjects in the 2-dose priming group and 1 in the 3-dose priming group. Although the collection of reports on large swelling reactions during the primary vaccination course was not initially planned, 4 cases were reported: 3 cases at DTPa combined vaccine injection site and 1 case at Synflorix injection site. All reported large swelling reactions resolved without sequelae within 2-6 days.

Irritability was the most frequently reported solicited general AE in both groups in the primary phase (69.8% in the 2+1 group and 62.2% in the 3+1 group) and the booster phase (64.9% in the 2+1 group and 61.5% in the 3+1 group). Grade 3 fever was only reported during the booster vaccination course (one subject in the 2+1 group).

Comments: Comparison of the incidence of solicited local AEs between the two groups is hampered by the different number of primary doses administered (2 versus 3) and the difference between groups in DTPa combined vaccine co administration (the second dose of DTPa combined vaccine being co administered with the second dose of 10Pn-PD-DiT in the 2-dose priming group and with the third dose of 10Pn-PD-DiT in the 3-dose priming group). However, the observed incidences of solicited local AEs were within the same ranges following the first vaccination in both groups as well as following the second dose of DTPa combined vaccine co administered with the second dose of 10Pn-PD-DiT in the 2-dose priming group and the third dose of 10Pn-PD-DiT in the 3-dose priming group.

Study 046

In the Primed groups during the 31 day post-vaccination period, 92.2% and 89.8% of subjects in the 10Pn-2d and the 10Pn-3d groups, respectively, reported at least one AE.

Incidence of at least one Grade 3 AE was 29.4% and 32.2%, respectively. In the Unprimed group, 85.5% of documented doses were followed by at least one AE and 23.4% of documented doses were followed by at least one Grade 3 AE.

Pain at injection site was the most frequently reported solicited local AE in both the primed and unprimed groups (80.4%, 74.6% and 62.1% in the 2+1, 3+1 and unprimed groups, respectively). Grade 3 solicited local AEs were reported by a maximum of 17.6% of subjects in the 2+1 group and 20.3% of subjects in 3+1 group. The overall/dose incidence of Grade 3 solicited local symptoms ranged from 4.8% to 13.7% in the unprimed group. Large swelling reactions were reported by 1 subject in the 10Pn-3d group and by 1 subject in the unprimed group after the first dose.

The most frequently reported solicited general AEs during the primary phase were irritability and drowsiness (both 39.2%) in the 2+1 group and irritability in the 3+1 group (45.8%). Irritability was the most frequently reported solicited general AE in the unprimed group. None of the subjects reported Grade 3 fever or any other Grade 3 solicited AE following vaccination.

Study 013

High incidences of any AE (solicited and unsolicited, general and local) after each dose were reported in all study groups including the <6 Mo control group (at least 90.3% in the <6 Mo group, 94.6% in the 7-11 Mo group, 86.0% in the 12-23 Mo group and 91.9% in the ≥24 Mo group).

The <6 Mo group received the 10Pn-PD-DiT vaccine co administered with the DTPa-IPV/Hib vaccine. In general, there was no increase in the overall incidence of AEs with successive doses for the groups receiving more than one dose. For the <6 Mo group, the overall/dose incidence of local AEs (solicited and unsolicited) reported during the 31 day post vaccination period was 49.1% at both the 10Pn-PD-DiT vaccine and DTPa-IPV/Hib vaccine injection sites. The incidence of local AEs with Grade 3 intensity (solicited and unsolicited) for the 10Pn-PD-DiT vaccine and DTPa-IPV/Hib vaccines was 3.6% and 3.4%, respectively.

The observed percentage of subjects reporting at least one unsolicited AE was 66.7% for the <6 Mo group, 77.3% for the 7-11 Mo group, 67.3% for the 12-23 Mo group and 36.0% for the ≥24 Mo group. As might be expected in these age groups, the most frequently reported unsolicited AEs were upper respiratory tract infection (26.7%) in the <6 Mo group, upper respiratory tract infection (23.3%) and rhinitis (20.7%) in the 7-11 Mo group, upper respiratory tract infection (14.0%) and otitis media (14.0%) in the 12-23 Mo group and otitis media (6.7%) in the ≥24 Mo group.

Comments: Incidences of unsolicited symptoms cannot be compared between groups given the difference in the duration of follow-up for unsolicited adverse events: 31 days after each vaccine dose, or a total follow-up period for unsolicited adverse events of 1, 2 or 3 months depending on the group.

Safety results after booster vaccination in the <6 Mo and 7-11 Mo groups in Study P013

The overall incidence of AEs (solicited and unsolicited), reported during the 31 day post booster vaccination period is presented in Table 18. Because only the <6 Mo group received DTPa-IPV/Hib vaccine as co administered vaccine, comparison of reactogenicity between groups should be done with caution. After the primary vaccination, high incidences of any AE (solicited and unsolicited, general and local) were reported in both groups. General symptoms were reported more frequently than local symptoms in both groups. The observed incidence of AEs following booster vaccination was higher in the <6 Mo group than in the 7-11 Mo group most likely due to the co administration of DTPa-IPV/Hib in the <6 Mo group.

The observed percentage of subjects reporting at least one unsolicited AE was 62.1% in the <6 Mo group and 43.4% in the 7-11 Mo group. The most frequently reported unsolicited AEs were rhinitis (16.6%) and upper respiratory tract infection (17.2%) in the <6 Mo group and pyrexia (8.3%) and upper respiratory tract infection (8.3%) in the 7-11 Mo group.

Table 18. Study 046: Safety in booster vaccinated cohort.

Incidence and nature of symptoms (solicited and unsolicited) reported during the 31-day (Days 0-30) post-booster vaccination period (Booster Total vaccinated cohort)

Group	Any symptom					General symptoms					Local symptoms				
	N	n	%	95% CI		N	n	%	95% CI		N	n	%	95% CI	
			LL	UL				LL	UL				LL	UL	
<6Mo	144	140	97.2	93.0	99.2	144	135	93.8	88.5	97.1	144	115	79.9	72.4	86.1
7-11Mo	145	128	88.3	81.9	93.0	145	110	75.9	68.1	82.6	145	98	67.6	59.3	75.1

<6Mo = 10Pn-PD-DiT + DTPa-IPV/Hib (3, 4, 5 and 12-15 months)

7-11Mo = 10Pn-PD-DiT (7-11, 8-12 and 12-15 months)

N= number of subjects with the documented dose

n/= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Treatment-related adverse events (adverse drug reactions)

In **Study 002**, 5.7% and 6.7% of primary doses in the 2+1 group and the 3+1 group, respectively, were followed by at least one unsolicited symptom considered causally related to vaccination (Table 19). The corresponding percentages following booster doses were 4.0% and 5.3% (Table 20). The incidence of Grade 3 solicited general AEs considered by the investigator to be causally related to vaccination in both groups ranged from 0.0% to 5.2% during the primary vaccination course and from 0.0% to 3.4% after the booster dose. The different number of primary doses administered and the difference in DTPa combined vaccine co-administration made the comparison between the 2+1 and 3+1 groups difficult. However, the incidences of solicited general AEs were in the same ranges after the first dose in both groups, and no increase was observed after the second/third doses.

Table 19. Study 002

Study 002: Percentage of doses with unsolicited symptoms with causal relationship to vaccination, within the 31-day post-primary vaccination period, classified by MedDRA Primary System Organ Class and Preferred Term (Total vaccinated cohort)

Primary System Organ Class (CODE)	Preferred Term (CODE)	2+1 N = 349				3+1 N = 524			
		n	%	95% CI		n	%	95% CI	
At least one symptom		20	5.7	3.5	8.7	35	6.7	4.7	8.2
Gastrointestinal disorders (10017947)	Abdominal pain (10000081)	0	0.0	0.0	1.1	1	0.2	0.0	1.1
	Diarrhoea (10012735)	7	2.0	0.8	4.1	3	0.6	0.1	1.7
	Vomiting (10047700)	2	0.6	0.1	2.1	6	1.1	0.4	2.5
General disorders and administration site conditions (10018085)	Asthenia (10003549)	0	0.0	0.0	1.1	1	0.2	0.0	1.1
	Injection site bruising (10022052)	0	0.0	0.0	1.1	1	0.2	0.0	1.1
	Injection site discolouration (10051572)	2	0.6	0.1	2.1	1	0.2	0.0	1.1
	Injection site eczema (10066221)	0	0.0	0.0	1.1	1	0.2	0.0	1.1
	Injection site haematoma (10022066)	2	0.6	0.1	2.1	1	0.2	0.0	1.1
	Injection site mass (10022081)	0	0.0	0.0	1.1	3	0.6	0.1	1.7
	Injection site nodule (10057880)	4	1.1	0.3	2.9	10	1.9	0.9	3.5
	Injection site reaction (10022095)	1	0.3	0.0	1.6	0	0.0	0.0	0.7
	Injection site swelling (10053425)	0	0.0	0.0	1.1	1	0.2	0.0	1.1
	Irritability (10022998)	0	0.0	0.0	1.1	1	0.2	0.0	1.1
	Thirst (10043458)	0	0.0	0.0	1.1	1	0.2	0.0	1.1
Infections and infestations (10021881)	Lower respiratory tract infection (10024968)	0	0.0	0.0	1.1	1	0.2	0.0	1.1
	Nasopharyngitis (10028810)	2	0.6	0.1	2.1	2	0.4	0.0	1.4
Metabolism and nutrition disorders (10027433)	Increased appetite (10021854)	0	0.0	0.0	1.1	1	0.2	0.0	1.1
Musculoskeletal and connective tissue disorders (10028395)	Musculoskeletal stiffness (10052904)	0	0.0	0.0	1.1	1	0.2	0.0	1.1
Nervous system disorders (10029205)	Psychomotor hyperactivity (10037211)	1	0.3	0.0	1.6	0	0.0	0.0	0.7
Skin and subcutaneous tissue disorders (10040785)	Urticaria (10046735)	1	0.3	0.0	1.6	1	0.2	0.0	1.1

2+1= Synflorix (2-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)

3+1= Synflorix (2-3-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)

N = number of administered doses; n/% = number/percentage of doses with the symptom

95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 20. Study 002

Study 002: Percentage of subjects reporting the occurrence of unsolicited symptoms with causal relationship to vaccination, within the 31-day post-booster vaccination period, classified by MedDRA Primary System Organ Class and Preferred Term (Total vaccinated cohort)

Primary System Organ Class (CODE)	Preferred Term (CODE)	2+1 N = 174				3+1 N = 171			
		n	%	95% CI		n	%	95% CI	
At least one symptom		7	4.0	1.6	8.1	9	5.3	2.4	9.8
Gastrointestinal disorders (10017947)	Diarrhoea (10012735)	2	1.1	0.1	4.1	1	0.6	0.0	3.2
	Vomiting (10047700)	1	0.6	0.0	3.2	0	0.0	0.0	2.1
General disorders and administration site conditions (10018085)	Injection site eczema (10066221)	0	0.0	0.0	2.1	1	0.6	0.0	3.2
	Injection site haematoma (10022066)	0	0.0	0.0	2.1	1	0.6	0.0	3.2
	Injection site nodule (10057880)	4	2.3	0.6	5.8	2	1.2	0.1	4.2
	Injection site papule (10066044)	0	0.0	0.0	2.1	1	0.6	0.0	3.2
Infections and infestations (10021881)	Injection site pruritus (10022093)	0	0.0	0.0	2.1	1	0.6	0.0	3.2
	Otitis media (10033078)	0	0.0	0.0	2.1	1	0.6	0.0	3.2
Nervous system disorders (10029205)	Febrile convulsion (10016284)	1	0.6	0.0	3.2	0	0.0	0.0	2.1
Skin and subcutaneous tissue disorders (10040785)	Erythema (10015150)	1	0.6	0.0	3.2	0	0.0	0.0	2.1
	Rash generalised (10037858)	0	0.0	0.0	2.1	1	0.6	0.0	3.2

2+1= Synflorix (2-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)

3+1= Synflorix (2-3-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months)

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)

N = number of subjects with at least one administered dose

n/% = number/percentage of subjects reporting at least once the symptom

95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

In **Study 046**, 92.2% of subjects in the 10Pn-2d group and 88.1% of subjects in the 10Pn-3d group reported at least one AE assessed by the study investigator to be causally related to the vaccine administration; 13.7% of subjects in the 10Pn-2d group and 11.9% of subjects in the 10Pn-3d group reported at least one AE requiring a medical consultation.

The overall/dose incidence of at least one unsolicited AE was 40.3%, and 8.1% of the doses were followed by at least one unsolicited event that was considered to be causally related to vaccination. The most common unsolicited AEs considered to be causally related to vaccination were nausea, vomiting, injection site hematoma, pyrexia and rhinitis (all reported after 1.6% of the doses). Overall, 5.9% and 8.5% of the subjects in the 2+1 and the 3+1 groups, respectively, reported at least one unsolicited AE causally related to vaccination. In the unprimed group, 8.1% of the doses were followed by at least one unsolicited AE causally related to vaccination. None of the Grade 3 unsolicited symptoms were assessed by the investigator as being causally related to Synflorix.

In **Study 013**, pain (any and Grade 3) was the most commonly reported solicited local symptom at the 10Pn-PD-DiT injection site in the 12- 23 months of age and ≥ 24 months of age groups, whereas redness was more common in the 7-11 months of age group. High incidences of pain in the 12-23 months and ≥ 24 months of age groups have been previously documented for the licensed Prevenar vaccine²⁹.

Large swelling reactions were reported by four out of 300 subjects at the 10Pn-PD-DiT injection site: one subject was in 12-23 months group and three subjects in ≥ 24 months group. All were local reactions around the injection site, not involving adjacent joints. Two were associated with functional impairment that prevented normal activities and all resolved within 2 days.

Regardless the number of vaccine doses and the age of the subjects, the most frequently reported solicited general AE after each dose was irritability in all groups. The low incidence of fever observed in the ≥ 24 Mo group is in line with the incidence reported by de Aristegui et al²⁹ in children 24-36 months of age who received a single dose of Prevenar. No cases of Grade 3 fever (rectal temperature $> 40^{\circ}\text{C}$) were reported in any of the groups.

Low incidences of Grade 3 solicited general AEs were reported in all groups after each dose with a maximum of 3.4%, except in the < 6 Mo group where irritability was reported with an incidence of 8.1% post dose 1, although the overall/dose incidence for the full three dose primary vaccination course in this group was 3.9%. Most of the reported Grade 3 solicited general AEs were considered by the investigator to be causally related to vaccination.

The observed percentage of subjects reporting at least one unsolicited AE, assessed by the study investigator to be causally related to vaccination was 21.3% in the < 6 Mo group, 24.0% in the 7-11 Mo group, 19.3% in the 12-23 Mo group and 11.3% in the ≥ 24 Mo group. Injection site induration was the more frequently reported unsolicited adverse event assessed by the investigator to be causally related to vaccination in all groups except in the ≥ 24 Mo group in which few of these unsolicited adverse events were reported.

The observed percentage of subjects reporting at least one Grade 3 unsolicited AE was 7.3% in the < 6 Mo group, 12.0% in the 7-11 Mo group, 15.3% in the 12-23 Mo group and 1.3% in the ≥ 24 Mo group. The overall/dose incidence of at least one unsolicited AE was 56.6% in the 7-11 months of age group (two doses), 43.4% in the 7-11 months of age group (third dose), 47.8% in the 12-23 months of age group and 36.0% in the > 24 months of age group. The most common unsolicited AE considered to be causally related to vaccination was injection site induration in the two groups receiving two 10Pn-PDDiT doses. In the > 24 months of age group, the most common related AE was headache (2.0%).

Comments: it is important to note that the subjects in the < 6 Mo group received DTPa-IPV/Hib vaccine coadministered with the 10-valent pneumococcal conjugate vaccine.

²⁹ Aristegui J, Cos Arregui B. Evaluation of the safety and immunogenicity of pneumococcal seven-valent conjugate vaccine (Prevenar®) administered in previously unvaccinated Spanish children aged 24 to 36 months. *Vaccine*. 2005; 23:1917-1922.

Higher incidences of fever have been reported in several clinical studies after co administration of DTPa combined vaccines with a 7-valent pneumococcal conjugate vaccine compared to administration of the DTPa combined vaccines alone^{30, 31, 32}.

Although comparison of reactogenicity between the different catch-up groups needs to be done with caution given the difference in age and number of vaccine doses, fever >38°C was less commonly reported in the ≥24 months of age group compared to both the 7-11 months of age and 12-23 months of age groups. In all groups, general symptoms of Grade 3 intensity were infrequently reported and following no more than 2.4% of doses. There were no cases of fever > 40.0°C in any of the catch-up groups

Prevalence of concomitant medications, mainly antipyretics, during the 4 day post vaccination period following each dose, overall/dose and overall/subject: Overall, prevalence of concomitant antipyretics was highest in the < 6 months group and lowest in the ≥24 months group (64%, 45%, 37% and 21% of subjects in the <6 Mo, 7-11 Mo, 12-23 Mo and ≥24 Mo groups, respectively).

Safety results after booster vaccination in the <6 Mo and 7-11 Mo groups in study P013

For the <6 Mo group, a high incidence of local AEs (solicited and unsolicited) was reported during the 31 day post vaccination period at both the 10Pn-PD-DiT vaccine (72.2%) and the DTPa-IPV/Hib vaccine (72.7%) injection sites. The incidence of local AEs with Grade 3 intensity (solicited and unsolicited) for the 10Pn-PD-DiT vaccine and DTPa-IPV/Hib vaccine was 12.5% and 11.9%, respectively. The most frequently reported solicited local AEs was pain in the <6 Mo group (63.2%) and redness in the 7-11 Mo group (50.3%). The incidence of pain reported in the <6 Mo group was higher than that reported in the 7-11 Mo group (44.1%). Grade 3 solicited local AEs were reported with a maximum incidence of 7.6% in the <6 Mo group and 4.8% in the 7-11 Mo group.

Large swelling reactions were reported by two subjects in the <6 Mo group and one subject on the 7-11 Mo group. These swelling reactions developed within two days after booster vaccination and resolved within 1 or 2 days.

The most frequently reported solicited general AE in both groups was irritability. Higher incidences of solicited general AEs seemed to be reported in the <6 Mo group compared to the 7-11 Mo group. Nevertheless, the incidence of Grade 3 solicited general AEs considered by the investigator to be causally related to vaccination was low (maximum 3.5%) and within the same range in both groups. Only one case of Grade 3 fever was reported during the 4 day follow-up period (<6 Mo group).

The observed percentage of subjects reporting at least one unsolicited AE assessed by the investigator to be causally related to vaccination was 21.4% in the <6 Mo group and 7.6% in the 7-11 Mo group. The observed percentage of subjects reporting at least one Grade 3 unsolicited AE was 2.8% in the <6 Mo group and 5.5% in the 7-11 Mo group. During the 4 day follow-up period, concomitant antipyretic medication was administered in 39.3% and 22.1% of subjects in the <6 Mo and 7-11 Mo groups, respectively.

³⁰ Knuf M, Habermehl P, Cimino C, *et al.* Immunogenicity, reactogenicity and safety of a 7-valent pneumococcal conjugate vaccine (PCV7) concurrently administered with a DTPa-HBV-IPV/Hib combination vaccine in healthy infants. *Vaccine*. 2006a; 24(22):4727-36.

³¹ Tichmann-Schumann I, Soemantri P, Behre U *et al.* Immunogenicity and reactogenicity of four doses of diphtheria-tetanus-three-component acellular pertussis-hepatitis b-inactivated polio virus-Haemophilus influenzae type b vaccine coadministered with 7-valent pneumococcal conjugate vaccine. *Pediatr Infect Dis J*. 2005; 24(1):70-77.

³² Immunogenicity and safety of a combination diphtheria, tetanus toxoid, acellular pertussis, hepatitis b, and inactivated poliovirus vaccine coadministered with a 7-valent pneumococcal conjugate vaccine and a haemophilus influenzae type b conjugate vaccine
Pichichero M E; Bernstein H; Blatter M M; Schuerman L; Chevart B; Holmes S J; Study I
Source : J Pediatr . 2007 ; 151 (1) : 43-49 .

Study 046: Pain at injection site was the most frequently reported solicited local AE (62.1%, overall/dose). The overall/dose incidence of Grade 3 solicited local symptoms ranged from 4.8% to 13.7% in the unprimed group. Large swelling reaction (> 50 mm) following vaccination was reported by 1 subject after the first dose. The lesion had a diameter of 60 mm and had resolved after 1 day. Irritability was the most frequently reported solicited general adverse event. None of the subjects reported fever >40°C or any other Grade 3 solicited general AEs. There was no increase in incidence of events with consecutive doses.

Deaths and other serious adverse events

There were no deaths reported among subjects during the Studies 002, 046 and 013.

In **Study 002**, a total of 12 SAEs were recorded after the primary vaccination: 5 subjects in the 2+1 group and 7 subjects in the 3+1 group. All 12 events resolved. Following the booster dose, 3 subjects reported SAEs (2 subjects in the 2+1 group and 1 subject in the 3+1 group). Two SAEs were considered by the study investigator as being causally related to vaccination. One subject in the 3+1 group developed lower respiratory tract infection 1 day after dose 1 and was given a diagnosis of "Unspecified acute infection in the lower respiratory tract". The event was reported to be resolved after 7 days but the SAE led to the subject discontinued. Another subject in the 2+1 group experienced febrile convulsions on the same day as the booster vaccination. The event was reported to be resolved after 1 day.

In **Study 046**, 3 subjects (one in each treatment group) reported each one SAE. None of these was considered by the study investigator to be causally related to vaccination and all subjects recovered. In Study 046, one subject in the unprimed group reported an SAE (bronchitis) during the course of the study. This SAE was not considered by the investigator to be causally related to vaccination and the subject recovered uneventfully.

In **Study 013**, 6 subjects in the 7-11 months of age group, 2 subjects in the 12-23 months of age group and none in the >24 months of age group reported at least one SAE (the data lock point was 15 June 2008). None of the subjects reported a causally related SAE or an SAE with a fatal outcome.

Discontinuation due to adverse events

In **Study 002**, in addition to the SAE in a subject in 3+1 group (respiratory infection), two subjects discontinued the study due to AEs: One more subject in the 3+1 group experienced 24 days after dose 1 swelling of the left thigh at the DTPa-HBV-IPV/Hib injection site, Graded 3 in intensity. The event was reported to be resolved after 19 days and was considered by the study investigator to be causally related to vaccination. The subject was withdrawn from the study following parents' decision. Another subject in the 2+1 group did not conduct the last study visit due to suspected virus infection. The subject was discontinued from the study following the parents' decision and recovered without sequelae. This AE is not reported in the database as it occurred more than 30 days after receiving the booster dose. No subjects discontinued from Study 046 due to an adverse event.

In **Study 013**, none of the reported SAEs led to withdrawal. Five subjects were withdrawn due to an AE:

Three subjects in the <6 Mo group

- Motor neuron dysfunction with intensity graded as 2 on Day 28 after vaccine dose 1 which was still ongoing at the time of withdrawal from study and judged as causally related to vaccination;

- Erythema and fatigue with intensity graded as 2 on the day of vaccine dose 1 and this AE resolved without sequelae and was assessed by the study investigator to be causally related to vaccination;
- Otitis media with intensity graded as 3, on Day 35 after vaccine dose 1 and this AE resolved without sequelae.

The subjects also developed varicella with an intensity graded as 2 on Day 45 after vaccine dose 1 which also Both AEs were assessed by the investigator not to be causally related to vaccination.

In the 7-11 Mo group, 1 subject developed an upper respiratory tract infection with intensity graded as 1 on the day of vaccine dose 1 and flatulence and regurgitation, both with intensity graded as 1, one day after vaccine dose 1. All AEs resolved without sequelae and were assessed by the investigator not to be causally related to vaccination.

In the 12-23 Mo group, 1 subject started limping with an intensity graded as 2 on the day of vaccine dose 1 and developed pain in the foot with intensity graded as 2 on Day 29 after vaccine dose 1. Both AEs resolved without sequelae. The limping was assessed by the study investigator to be causally related to vaccination.

None of the subjects receiving booster vaccination (<6 Mo and 7-11 Mo group) reported AEs which led to discontinuation from study.

Laboratory tests

Not applicable.

Post marketing experience

Not relevant to current application.

There were 41 spontaneous reports when Synflorix was used in subjects older than 2 years of age. Out of the 41 reports, there were 21 cases concerning children between 2 and 6 years of age. The sponsor is closely monitoring off-label use in PSURs and so far did not observe any particular safety signal linked to the use of Synflorix in subjects older than 2 years.

Safety issues with the potential for major regulatory impact

Liver toxicity

Not applicable.

Haematological toxicity

Not applicable

Serious skin reactions

The incidence of serious skin reactions such as redness, pain local swelling was low and resolved without any sequelae.

Cardiovascular safety

Not applicable.

Unwanted immunological events

None.

Other safety issues and Safety in special populations, related to drug-drug interactions or other interactions

Not studied.

Evaluator's overall conclusions on clinical safety***Safety of the 2+1 vaccination schedule:***

Study 002: During the primary vaccination course, 94.8% and 93.5% of injected doses in the 2-dose and 3-dose priming groups respectively were followed by at least one adverse event (solicited and/or unsolicited, local and/or general). General adverse events were more frequently reported than local adverse events. About 95% of injected booster doses in both groups were followed by at least one adverse event (solicited and/or unsolicited, local and/or general).

No clinically relevant differences in the solicited reactogenicity profile were observed between the 2+1 and 3+1 dosing schedules. During the primary vaccination course, 27.8% and 35.7% of doses in the 2-dose and 3-dose priming groups, respectively, were followed by at least one unsolicited AEs. The corresponding percentages following booster doses were 36.2% and 42.1%. A total of 15 subjects (7 subjects in the 2-dose priming group and 8 subjects in the 3-dose priming group) reported non fatal SAEs. Of these, 2 subjects (one in each group) reported SAEs that were considered by the study investigator to be causally related to vaccination (that is, lower respiratory tract infection and febrile convulsions). All SAEs resolved without sequelae.

The observed incidences of solicited and/or unsolicited AEs reported during the 31 day post-primary vaccination period was 94.8% in the 2-dose priming group and 93.5% in the 3-dose priming group. About 95% of injected booster doses in both groups were followed by at least one AE (solicited and/or unsolicited, local and/or general). The most frequently reported solicited local and general AEs were redness and irritability, respectively in both groups during both phases (primary and booster). Globally, no clinically relevant differences in the solicited reactogenicity profile were observed between the two study groups.

Study 046: One challenge dose of Synflorix was administered to all subjects at approximately 36 to 42 months of age. Pain at injection site was the most frequently reported solicited local AE in the primed groups for both schedules (80.4% and 74.6% of subjects in the 2+1 and 3+1 groups, respectively). Grade 3 solicited local AEs were reported by a maximum of 17.6% and 20.3% of subjects in the 2+1 and 3+1 groups respectively. The most frequently reported solicited general AEs were irritability and drowsiness (both 39.2%) in the 2+1 group and irritability in the 3+1 group (45.8%). No Grade 3 solicited adverse events were reported. In the 2+1 and 3+1 groups, 47.1% and 40.7% of subjects respectively, reported at least one unsolicited adverse event within the 31-day post-vaccination period. Grade 3 unsolicited AEs were reported in 3.9% and 5.1% of the subjects in the 2+1 and 3+1 groups respectively and none of them were assessed by the investigator to be causally related to vaccination. Three subjects (one in each treatment group) each reported one SAE. None of them were considered to be causally related to vaccination and all subjects recovered.

Study 013 Primary vaccination course: High incidences of any AEs (solicited and unsolicited, local and general) after each dose were reported in all groups. The most frequently reported solicited local AEs were redness and pain. High incidences of pain and Grade 3 pain were reported in the 12-23 Mo and the ≥ 24 Mo groups. Large swelling reactions were reported by one subject in the < 6 Mo group, two subjects in the 7-11 Mo group, one subject in the 12-23 Mo group and three subjects in the ≥ 24 Mo group. The most frequently reported solicited general AE was irritability in all groups. A low incidence of fever was observed in the ≥ 24 Mo groups. No cases of Grade 3 fever (rectal

temperature > 40°C) were reported in any of the groups. Generally, low incidences of Grade 3 general AEs, assessed by the study investigator to be causally related to vaccination, were reported in all groups.

The observed percentage of subjects reporting at least one unsolicited AE within 31 days after vaccination was 66.7% for the < 6Mo group, 77.3% for the 7-11 Mo group, 67.3% for the 12-23 Mo group and 36.0% for the ≥24 Mo group. The percentage of subjects reporting at least one unsolicited AE considered by the study investigator to be causally related to vaccination was 21.3% in the < 6Mo group, 24.0% in the 7-11 Mo group, 19.3% in the 12-23 Mo group and 11.3% in the ≥24 Mo group. Eight (8) subjects reported at least one SAE after primary vaccination: 4 subjects in the <6 Mo group, 2 subjects in the 7-11 Mo group and 2 subjects in the 12-23 Mo group. No fatal SAEs were reported. None of the reported SAEs was assessed by the study investigator to be causally related to vaccination. All SAEs resolved without sequelae except one (psychomotor retardation) which was not resolved at the time of finalisation of this study report.

Booster vaccination (<6 Mo and 7-11 Mo group): High incidences of any AEs (solicited and unsolicited, local and general) were reported in both groups. The observed incidence of AEs was higher in the <6 Mo group compared to the 7-11 Mo group probably due to the co administration of DTPa-IPV/Hib vaccine in the <6 Mo group. The most frequently reported solicited local AEs were pain in the <6 Mo group and redness in the 7-11 Mo group. The most frequently reported solicited general AE was irritability in both groups. Higher incidences of solicited general AEs seemed to be reported in the <6 Mo group compared to the 7-11 Mo group. Low incidences of Grade 3 general AEs assessed by the study investigator to be causally related to vaccination were reported in both groups. Only one case of Grade 3 fever (rectal temperature >40°C) was reported (<6 Mo group). The observed percentage of subjects reporting at least one unsolicited AE within 31 days after vaccination was 62.1% for the < 6Mo group and 43.4% for the 7-11 Mo group. The percentage of subjects reporting at least one unsolicited AE considered by the study investigator to be causally related to vaccination was 21.4% in the < 6Mo group and 7.6% in the 7-11 Mo group. In the time period between the primary vaccination course and the booster vaccination 16 subjects reported at least one SAE: 13 subjects in the 6 month period between primary and booster vaccination in the <6 Mo group and 3 subjects in the 3 month period between primary and booster vaccination in the 7-11 Mo group. None of the reported SAEs was assessed by the study investigator to be causally related to vaccination. All SAEs resolved without sequelae except one (acute pyelonephritis). Two (2) subjects reported at least one SAE after the booster vaccination (one in each group). None of the reported SAEs was assessed by the investigator to be causally related to vaccination. All SAEs resolved without sequelae.

Overall, safety following the new proposed 2+1 vaccination schedule was similar to that observed of the approved 3+1 schedule.

2-dose catch-up vaccination schedule for children 2 to 5 years old

Study 013: The most frequently reported solicited local AEs were redness and pain in the ≥24 Mo group with high incidences of pain and Grade 3 pain. The most frequently reported solicited general AE was irritability. A low incidence of fever was observed in the ≥24 Mo groups. No cases of Grade 3 fever (rectal temperature > 40°C) were reported. The observed percentage of subjects reporting at least one unsolicited AE within 31 days after vaccination was 36.0% for the ≥24 Mo group and the percentage of subjects reporting at least one unsolicited AE considered by the study investigator to be causally related to vaccination was 11.3%. No SAEs were reported in the ≥24 Mo group.

Study 046: In the unprimed group, overall 85.5% of documented doses were followed by at least one AE. Pain was the most frequently reported solicited local AE and irritability was the most frequently reported solicited general AE. Large swelling reaction was

reported by 1 subject. None of the subjects reported fever > 40°C or any other Grade 3 solicited general AEs. There was no increase in the incidence of solicited symptoms with consecutive doses. The observed percentage of administered doses followed by at least one unsolicited AE within 31 days after vaccination was 40.3%. Three subjects (one in each treatment group) reported each one SAE during the course of the study. None of these was considered to be causally related to vaccination and all subjects recovered uneventfully.

Overall there did not appear to be any serious safety concerns following 2-dose catch-up vaccination with Synflorix in children aged 2-5 years.

Clinical summary and conclusions

First round benefit-risk assessment

Benefits

The comparison of 2+1 and 3+1 schedules in Study 002 indicated that the immune response following a 2 primary dose was generally lower to that observed after 3 primary doses²⁰. These findings are consistent with those from studies conducted with Prevenar²¹. The immune responses measured after two vaccine doses in the head to head comparison with Prevenar in Study 011 were overall comparable with notably higher results observed for serotype 6B with Synflorix²², although interpretation of these results was limited by the post hoc nature of the analysis. Similar results were observed in a head to head comparison between Prevenar 13 and Prevenar²⁴.

Recent clinical data from Study 046 demonstrated the persistence of antibodies with no observation of accelerated waning of immune response following 2+1 schedule vs 3+1 schedule. A rapid and robust anamnestic response was observed following booster dose with both schedules, suggesting similar induction of immunological memory regardless of the primary vaccination schedule. A previously published analysis of the long term immunogenicity and efficacy of a 9-valent conjugate pneumococcal vaccine in human immunodeficiency virus (HIV)-infected and HIV uninfected children suggested that an anamnestic response observed several years after primary immunisation rather than persistence of antibodies may be a major determinant of long term protection^{33, 34}.

Co administration of Synflorix with the DTPa-HBV-IPV/HiB did not affect the immune responses to the DTP vaccine.

In Study 046, a single dose of Synflorix administered during the fourth year of life as a challenge dose elicited higher ELISA GMCs 7-10 days following vaccination in 2-dose primed subjects (ranging from 4.00 to 20.28 µg/ml) and 3-dose primed subjects (ranging from 4.72 to 30.55 µg/ml) compared to unprimed subjects (ranging from 0.10 to 2.37 µg/ml). The 2-8 fold increase in ELISA GMCs pre to post vaccination was similar in the 2-dose and 3-dose primed subjects. The percentage of subjects with antibody concentrations > 0.2 µg/mL after the additional vaccination was 100% for all serotypes in the 2+1 and the 3+1 groups except for serotypes 6B and 23F (98.0%) in the 2+1 group.

³³ Madhi SA, Adrian P et al. Long-term immunogenicity and efficacy of a 9-valent conjugate pneumococcal vaccine in human immunodeficient virus infected and non-infected children in the absence of a booster dose of vaccine. *Vaccine*. 2007; 25:2451-2457.

³⁴ Madhi SA, Klugman KP, Kuwanda L, Cutland C, Käyhty H, Adrian P. Quantitative and qualitative anamnestic immune responses to pneumococcal conjugate vaccine in HIV-infected and HIV-uninfected children 5 years after vaccination. *J Infect Dis*. 2009; 199(8):1168-76.

In the unprimed group, the percentage of subjects above the threshold of 0.2 >g/ml after the first dose was generally lower than primed subjects and ranged from 26.7% to 100%. Higher OPA GMTs were observed after the additional vaccine dose in primed subjects as compared to the unprimed age-matched control group. The percentage of subjects with an OPA activity titre >8, 7-10 days after the additional vaccination in the primed groups was 100% for all serotypes except for serotype 6B (94.4% in the 3+1 group and 95.7% in 2+1 group) and serotype 19F (97.9% in the 2+1 group). In the unprimed group after the first dose, the percentage of subjects with an OPA activity titre > 8 was at least 94.7% for all serotypes except for 6B (77.8%) and 19F (89.5%).

In Study 013, a single dose of the 10-valent pneumococcal conjugate vaccine at ≥ 24 months of age did not seem to induce an acceptable immune response for some of the pneumococcal vaccine serotypes. Therefore, an additional dose could be beneficial beyond the second year of life and this was demonstrated in Study 046.

In Study 046, 10Pn-PD-DiT vaccine given as a 2-dose catch-up vaccination in children during their fourth year of life elicited high levels of antibodies against vaccine pneumococcal serotypes and Protein D. A 2-dose catch-up vaccination course with the 10Pn-PD-DiT vaccine administered to children in their fourth year of life previously not vaccinated with any pneumococcal vaccine was safe and well tolerated. The immune responses after 2 doses in Study 046 were clearly higher than those observed after one dose in this age group in Study 013 for each of the pneumococcal serotypes and for Protein D.

There were no new safety concerns following 2-dose catch-up vaccination with Synflorix in children aged 2 to 5 years not previously vaccinated with any pneumococcal vaccine.

Risks

Studies on IPD effectiveness of Prevenar indicated that the lower immune response observed with the 2+1 schedule had no major impact on vaccine effectiveness^{4,3,5}. Modelling of the direct impact of 2+1 schedule on IPD indicated that two doses of Synflorix is expected to prevent at least as much and usually more IPD than two doses of Prevenar¹⁷. Furthermore, the effects of lower percentage of patients with OPA titres >8 in 2-dose primed compared to 3-dose primed subjects for serotypes 6B, 18C and 23F on efficacy of vaccines and incidence of IPD was not evaluated and would need to be monitored in postmarketing studies as these serotypes are generally associated with more severe IPD²³.

There was no significant difference in the AE profile between the 2+1 and 3+1 dosing schedules. The most frequently reported solicited local and general AEs were redness and irritability, respectively. Incidence of SAEs was low and similar with both dosing schedules and all SAEs resolved without sequelae.

Safety of Synflorix was also assessed in about 200 children aged 2 to 5 years. Pain and redness were more commonly reported when Synflorix was administered to children aged ≥ 24 months. However, incidence of fever was low in the ≥ 24 month group and no cases of Grade 3 fever were reported. No SAEs were reported in the age group >24 months.

Benefit-risk balance

The currently approved vaccination schedule in the Synflorix PI consists of 3 primary doses with an interval of at least 1 month between doses. A booster dose is recommended at least 6 months after the last priming dose. The purpose of the current submission was to present data from three clinical trials in order to support the use of a 2-dose primary course followed by a booster dose in the context of routine infant immunisation programs. Two clinical trials were already presented in the registration file: the 2-dose primary vaccination Study 002 and the Prevenar head to head comparison Study 011. The more recent Study 46 is the 2-3 years follow-up of Study 002 and demonstrates long term protection following vaccination with the 2+1 schedule.

The data presented in this document provide evidence that Synflorix is well tolerated and elicits immune responses to all serotypes after a 2-dose primary vaccination course in infants. It should be noted that vaccination with Synflorix, like Prevenar seemed less immunogenic for several serotypes prior to the booster vaccination in subjects receiving 2 primary doses compared to a 3 dose primary schedule. However, the immunogenicity of the 2-dose primary schedule was assessed in another study comparing Synflorix to Prevenar directly (Study 011) which showed similar immune responses after the second dose for both vaccines in terms of ELISA antibody concentrations and functional antibody (OPA) titres, although interpretation was limited due to post hoc nature of the analysis.

These head-to-head immunogenicity data, combined with the effectiveness data for Prevenar when administered according to a 2+1 schedule were used to develop an algorithm to predict the direct impact of Synflorix against IPD. This algorithm predicts that Synflorix can provide substantial protection in countries using 2+1 schedule in the context of routine immunisation programs similar to that predicted for Prevenar given along the same schedule. It is also reassuring to note that following two primary doses, the immunogenicity profile of Synflorix (containing pneumococcal serotypes 1, 5, 6B, 7F, 9V, 14, 23F, 4, 18C and 19F) for the seven serotypes present in Prevenar (4, 6B, 9V, 14, 18C, 19F and 23F) appears similar to that of the recently licensed Prevenar 13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F).

The persistence of antibodies 24-34 months after the booster dose was demonstrated for Synflorix under both schedules. A challenge dose of Synflorix administered to children in their fourth year of life, primed according to either a 2+1 or 3+1 schedule was shown to be well tolerated. This dose elicited a robust immune response, higher than that measured in unprimed subjects, indicating immunological memory in primed subjects regardless of the primary vaccination schedule.

Overall, the clinical data support the sponsor's proposed changes to the PI. The 3+1 schedule remains the recommended vaccination schedule in children less than 12 months of age since the prevention of disease using a 3+1 schedule may be higher than that afforded by a 2+1 schedule based on the immune responses observed in Study 002. As a consequence, the sponsor has proposed wording in draft PI *Dosage and Administration* section to recommend the 3+1 schedule to ensure optimal protection. Nevertheless, based on the data presented the use of the 2+1 schedule for Synflorix within routine infant immunisation programs and according to official recommendations is expected to provide protection to the vaccine serotypes causing IPD in children less than two years of age and to offer long lasting protection for several years after primary vaccination. Given the increasing use of 2+1 schedule in routine infant immunisation programs, including the use of Synflorix within this context, the evaluators agreed with the sponsor's belief that it is important to extend the posology of Synflorix to include a 2+1 schedule in the context of routine infant immunisation programs.

In Study 013, a single dose of the 10-valent pneumococcal conjugate vaccine at ≥ 24 months of age did not seem to induce an acceptable immune response for some of the pneumococcal vaccine serotypes. Therefore, an additional dose could be beneficial beyond the second year of life and this was demonstrated in Study 046. In Study 046, 10Pn-PD-DiT vaccine given as a 2-dose catch-up vaccination in children during their fourth year of life elicited high levels of antibodies against vaccine pneumococcal serotypes and Protein D. A 2-dose catch-up vaccination course with the 10Pn-PD-DiT vaccine administered to children in their fourth year of life previously not vaccinated with any pneumococcal vaccine was safe and well tolerated. The immune responses after 2 doses in Study 046 were clearly higher than those observed after one dose in this age group in Study 013 for each of the pneumococcal serotypes and for Protein D.

In Study 046, no direct control group of infants below 6 months receiving 3 primary doses of Synflorix was present. Therefore, the comparison of the 2-dose catch-up was made to

the infant group that received the 3-dose primary vaccination in the preceding Study 002. Without an immunological correlate for individual protection, the comparison of the immune response after catch-up vaccination in older children to those after a 3-dose primary schedule in infants below 6 months of age was justified because the catch-up vaccination can actually be seen as primary vaccination in older children. In Study 046, two doses resulted in higher GMCs and GMTs compared to a 3-dose primary vaccination course for each of the pneumococcal serotypes and a similar response to Protein D. Although acknowledging the limitations when comparing results between different studies (such as control groups with different schedules, different age at first dose, different countries, 2 year interval between studies), the immune responses after 2 doses in Study 046 in unprimed subjects were clearly higher than those following only single dose catch-up vaccination in Study 013 not only for the pneumococcal serotypes but also for Protein D.

Most of the invasive pneumococcal disease as well as acute otitis media (AOM) and pneumonia occur in children below 5 years of age¹⁷, while currently approved indication for Synflorix is only for children below 2 years of age. The two other licensed pneumococcal conjugate vaccines (PCV7 and PCV13) are registered up to 5 years of age, recommending one dose between 2 and 5 years of age. The current submission provided adequate evidence to demonstrate similar immune response and safety when Synflorix is administered as a 2-dose catch-up vaccination for children aged 2-5 years not previously immunised with pneumococcal vaccine.

Overall, the benefit risk profile of Synflorix is favourable for the Active immunisation of infants and children from the age of *6 weeks up to 5 years* against disease caused by *Streptococcus pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (including invasive disease, pneumonia and acute otitis media). The benefit risk profile is also favourable for the inclusion of an option of 2-dose primary vaccination schedule in addition to the already approved 3-dose primary schedule in the Synflorix PI.

First round recommendation regarding authorisation

It was recommended that Synflorix be approved for the indication of:

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

The evaluator also recommended amendments to the draft PI to the Delegate, the details of which are beyond the scope of the AusPAR.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing safety Concerns which are shown at Table 21.

Table 21. Ongoing Safety Concerns.

Important identified risks	None
Important potential risks	Febrile convulsions
	Possible serotype replacement of disease isolates
	Apnoea in full term and premature infants
	Possible breakthrough infections/vaccine failure
	Unforeseen safety signals arising in the post-authorisation period
Important identified interaction	Paracetamol (prophylactic setting)
	Inactivates poliovirus type 2
Important missing information	Clinical data on immune-compromised /immune-deficient subjects including HIV-positive subjects

OPR reviewer comment

The section *Detailed action plan for specific safety concerns* of the RMP contains tables for several safety issues that are not included in the above summary table of safety concerns. All of these have associated additional pharmacovigilance activities, and are:

1. Potential hyporesponsiveness following a dose of 23-valent pneumococcal polysaccharide vaccine – Identified interaction,
2. Clinical data on preterm/low birth weight infants – Missing information, and
3. Data in children with sickle cell disease, asplenia and nephritic syndrome – Missing information.

The sponsor was requested to justify the exclusion of these safety issues from the summary table or commit to provide an updated table in the RMP.

Pending the nonclinical and clinical evaluation, and the above comments, the above summary of the Ongoing Safety Concerns was considered acceptable.

Pharmacovigilance plan

In addition to routine pharmacovigilance activities, several additional activities including data collection from ongoing clinical trials and the feasibility of a post market surveillance study to monitor IPD (EU states) was being investigated.

OPR reviewer's comments in regard to the pharmacovigilance plan

The protocols for the ongoing studies have not been evaluated as the studies have all started and are not being conducted in Australia.

Regarding the potential risks of febrile convulsions and unforeseen safety signals, additional information will be provided by the combination of routine pharmacovigilance (PV) and ongoing studies due to report in the next 2 years. This was accepted by OPR.

While the RMP section describing the risk of apnoea in preterm/low birth weight infants has been reviewed, the data from the specific studies assigned to this concern (10PN-PD-DIT-015 and 10PN-PD-DIT-016 BST: 015) has not been evaluated. Given that these 2 studies are complete and apparently reported on, the sponsor was requested to provide further discussion about the current plan moving forward regarding PV activities for this

potential risk and the relevant Missing information concern, drawing on the findings from these 2 studies.

The plan for post market surveillance study(s) to monitor serotype replacement and vaccine failure appear reasonable. The sponsor was requested to provide milestones on when they will update the TGA regarding progress of this action, including the submission of interim and final reports. The final study report for Study number 043 will be expected in early 2013 along with a discussion regarding the implications of the findings.

The results of Study 10PN-PD-DIT-014 BST:010, which evaluated the prophylactic use of antipyretic treatment have not been evaluated as part of this report but apparently has been submitted to the Committee for Medicinal Products for Human Use (CHMP) for review. The description in the RMP of this potential risk indicates that the prophylactic use of antipyretics leads to a reduction in febrile reactions post vaccination in recipients and may also lead to a reduced immunological response to the vaccines. The clinical relevance is unknown at this time, including the relevance of any difference in effect between the primary series and booster doses. Study 10PN-PD-DIT-050 will further explore this issue and the sponsor will provide the final report to the European Medicines Agency (EMA) on completion. As part of implementation of the RMP, the TGA will also expect to receive these study results by mid-2013, along with a discussion of the implications of the findings and the evaluation by the EMA.

The risk of hyporesponsiveness following a booster dose of Synflorix after vaccination with Pneumovax 23 is very small in the Australian context, and therefore the implications of this interaction are minimal here at this time. The common routine use of Synflorix in Australia is directed by the National Immunisation Program (NIP), which recommends primary pneumococcal vaccination (7, 10, or 13 valent) at 2, 4, and 6 months of age for all children. There is no routine booster dose and no routine Pneumovax 23 dose for children. At risk groups can receive additional doses, specifically Aboriginal and Torres Strait Islander children at age 18-24 months (Pneumovax 23) and children with at risk underlying medical conditions at 4-5 years (pneumococcal 7, 10, or 13 valent). Nevertheless, the final study report will be expected by the TGA.

Regarding the two areas of Missing information, Immunocompromised/Immunodeficient subjects and children with sickle cell disease, asplenia and nephritic syndrome (children at high risk for severe IPD), a study report and a discussion of the implications for the current PV and risk minimisation activities (including the draft PI) will be expected according to timelines outlined in the RMP.

Risk minimisation activities

Routine activities were proposed as adequate for all safety concerns.

OPR reviewer comment:

This was considered acceptable.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application and the implementation of a RMP satisfactory to the TGA will be imposed as a condition of registration. These recommendations remain dependent on the clinical evaluation report.

Ongoing safety concerns

- The section *Detailed action plan for specific safety concerns* of the RMP contains tables for the following safety issues that are not included in the summary table of safety concerns:

- Potential hyporesponsiveness following a dose of 23-valent pneumococcal polysaccharide vaccine : Identified interaction,
- Clinical data on preterm/low birth weight infants: Missing information, and
- Data in children with sickle cell disease, asplenia and nephritic syndrome: Missing information.

These should be included in an updated summary table of Ongoing Safety Concerns in the RMP, unless the sponsor justifies the exclusion of these safety issues from the summary table.

Pharmacovigilance activities

- The 2 studies assigned to the risk of apnoea in preterm/low birth weight infants (10PN-PD-DIT-015 and 10PN-PD-DIT-016 BST: 015) are apparently complete and reported on. Therefore an update on the current plan for monitoring this safety concern is required, which should include how the findings from the above studies informed this plan (a discussion of the implications of the studies and how these have been addressed in the current plan).
- Milestones are required for when the TGA will be updated on the progress of the plan for post market surveillance study(s) to monitor serotype replacement and vaccine failure. This should include timelines for the submission of protocols, interim and final reports.
- As part of monitoring the implementation of the RMP, the TGA will specifically expect the following to be submitted according to timelines outlined in the RMP:
 - The final study report for Study 10PN-PD-DIT-043, with a discussion regarding the implications of the findings,
 - The study report for Study 10PN-PD-DIT-050 (prophylactic anti-pyretic effect), with a discussion of the implications of the findings and the evaluation by the EMA,
 - The study report and a discussion of the implications for the current PV and risk minimisation activities (including the PI), for the two areas of missing information, immunocompromised/ immunodeficient subjects and children with sickles cell disease, asplenia and nephritic syndrome (children at high risk for severe IPD).

Potential for medication errors

- While medication errors do not seem to be a concern at this stage, it was considered useful if the sponsor provided a brief summary of overall post authorisation medication errors.

VI. Overall conclusion and risk/benefit assessment

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

The submission was supported by clinical data and risk management plan. The clinical evaluation report (CER) is a comprehensive review of data and recommends approval of all proposed changes. Some results are summarised in this Overview. The CER should be consulted for details.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Overview of Data

Alternative 2+1 schedule for routine immunisation in infants

Two clinical studies (002 & 011) were included. These have also been previously evaluated by the TGA. The studies included co administration with other childhood vaccines (DTPa, HBV/IPV/HiB, MenC, Hib/MenC) according to the national guidelines.

Study 002 investigated 3+1 schedule at 2, 3, 4 and 11 months of age against 2+1 schedule at 2, 4 and 11 months of age with Synflorix in both groups. The study population was full-term born infants at 8 to 16 weeks of age at the time of first vaccination. About 175 infants in each of the 2 groups took part. The observed mean ages for 2+1 vaccination were 12 weeks, 20.8 weeks and 11.1 months at the respective timepoints. The observed mean ages for 3+1 vaccination were 12.2 weeks, 16.7 weeks, 21.4 weeks and 11.2 months at the respective timepoints.

One month post priming (completion of 2 and 3 dose series in the respective groups), at least 92.8% subjects in the 2-dose priming group and 96.1% subjects in the 3-dose priming group had antibody concentrations $\geq 0.2\mu\text{g/mL}$ (seroprotection) for each vaccine pneumococcal serotype with the exception of serotypes 6B (55.7% versus 63.1% for 2 and 3 dose groups respectively) and 23F (69.3% versus 77.6% for 2 and 3 dose groups respectively).

At the pre booster timepoint, at least 86.4% subjects in the 2-dose group and 94.6% subjects in the 3-dose priming group had antibody concentrations $\geq 0.05\mu\text{g/mL}$ (seropositive) for each vaccine pneumococcal serotype.

One month after the booster dose, the percentages of subjects with antibody concentrations $\geq 0.2\mu\text{g/mL}$ (seroprotection) for all serotypes except serotype 6B (88.5% versus 96.6% in 2 and 3 dose group, respectively) were similar in the two groups ($\approx 95\text{-}100\%$).

At one month post priming (completion of 2 and 3 dose series in the respective groups) at least 82.6% subjects in the 2-dose priming group and 90.8% of subjects in the 3-dose priming group had functional opsonophagocytic activity (OPA) titer ≥ 8 against each vaccine pneumococcal serotype except for serotypes 1 (60.8% versus 62.9% for 2 and 3 dose group respectively) and 6B (74.4% versus 88.8% for 2 and 3 dose groups respectively).

One month after the booster dose, the observed percentages of subjects with OPA ≥ 8 against each vaccine pneumococcal serotypes were similar in both groups ranging from 78% to 100% with the exception of serotypes 5 (87.2% versus 97.5% in 2 and 3 dose groups respectively) and 6B (81.1% versus 90.3% in 2 and 3 dose groups respectively).

Study 011 investigated 3+1 schedule at 2, 4 and 6 months of age comparing Synflorix and Prevenar (7v) in the two groups. This report includes a post hoc analysis of incidental immunogenicity data at 2 months after the 2 primary doses obtained in this study.

The percentage of subjects with antibody concentration $\geq 0.20\mu\text{g/mL}$ (seroprotection) two months after the second dose was in the same range ($\sim 75\%$ to 99%) for both vaccines recipients with the exception of serotypes not included in Prevenar (7v) and serotypes 6B (64% versus 31% for Synflorix and Prevenar respectively), and 18C (87% versus 98% for Synflorix & Prevenar respectively).

Two months post dose 2 for each of the serotypes common to both vaccines the OPA GMTs and the percentage of subjects reaching OPA titres ≥ 8 was similar in both vaccine recipients with the exception of serotypes 6B (62.8% versus 34.9% for Synflorix versus Prevenar), 19F (84.1% versus 67.9% for Synflorix versus Prevenar) and 23F (96.6% versus 88.7% for Synflorix versus Prevenar).

Catch-up vaccination between 2-5 years of age

Study 013 investigated 'catch up' vaccination in previously unvaccinated children. The study also included co administration of other childhood vaccines (DTPa combined) according to national guidelines. The following age strata formed the 4 treatment groups with different vaccination schedule in each:

1. *Control group (infants < 6 months age):*

Three primary doses one month apart with booster at 12-15 months of age

2. *7 to 11 months age:*

Two primary doses with at least 4 weeks interval with booster at least 3 months after last primary dose

3. *12 to 23 months age group:*

Two doses with at least 2 months in between the doses

4. *24 months to 5 years age group:*

One dose only

There were about 150 subjects in each group.

At the time of the first vaccine dose the observed mean ages were 10.9 weeks, 8.3 months, 17.9 months and 36.4 months in the above 4 groups respectively.

At the time of the booster dose the observed mean ages were 12.2 and 13.4 months for the <6 months and 7-11 months groups respectively.

One month post dose 3 (completion of primary series) in the control group at least 93.8% subjects had antibody concentrations $\geq 0.2\mu\text{g/mL}$ for each of the vaccine pneumococcal serotypes except for serotypes 6B (72.5%) and 23F (87.0%).

2. 7 to 11 months age group

One month after completion of primary series (2 doses), the antibody concentrations $\geq 0.2\mu\text{g/mL}$ (seroprotection) were reached in at least 95.6% subjects for each of the vaccine pneumococcal serotypes except for serotypes 6B (51.1%) and 23F (70.4%). The ELISA antibody GMCs were lower for serotypes 6B, 9V and 23F and higher for serotypes 4, 18C and 19F compared with the control group.

At least 84.4% subjects had OPA ≥ 8 for each of the vaccine pneumococcal serotypes except for serotypes 1 (45.8%), 5 (76.1%) and 6B (33.3%). The OPA GMTs were lower for serotype 6B and were higher for serotype 18C compared to those observed in the control group.

Prior to booster dose that is, 3-4 months after the completion of the primary series at least 95.6% of subjects had antibody concentrations $\geq 0.05\mu\text{g/mL}$ (seropositive) for each of the vaccine pneumococcal serotypes and at least 71% subjects had OPA ≥ 8 for each of the vaccine pneumococcal serotypes except for serotype 1 (28.9%).

One month post-booster the ELISA antibody GMCs were lower for serotypes 9V and 23F and were higher for serotypes 14, 18C and 19F compared to those observed for the same serotypes following booster vaccination in the control group.

The percentage of subjects with ELISA antibody concentrations $\geq 0.2 \mu\text{g/mL}$ was in the same range ($\sim 96\text{-}100\%$) compared to that observed following booster vaccination in the control group for all serotypes.

One month post booster vaccination, for each of the vaccine pneumococcal serotypes, at least 90% of subjects had OPA ≥ 8 in the 7-11 months age group and this was comparable with the control group. For all serotypes the post booster OPA GMTs were higher compared to those observed one month post booster in the control group.

3. 12 to 23 months age group

One month post dose 2 that is, full 'catch-up' vaccination, the antibody concentrations $\geq 0.2 \mu\text{g/mL}$ were achieved by at least 97.7% subjects for each of the vaccine pneumococcal serotypes except for serotypes 6B (81.2%) and 23F (91.7%). The percentage of subjects with ELISA antibody concentrations $\geq 0.2 \mu\text{g/mL}$ was lower for serotypes 6B and 23F compared to one month post booster levels in the control group (81.2% versus 96.4% and 91.7% versus 99.3% respectively).

One month post dose 2, at least 84% subjects in this age group had OPA activity ≥ 8 for each of the vaccine pneumococcal serotypes except for serotypes 1 (45.1%) and 6B (75.5%). The respective percentages for serotypes 1 and 6B were 83.3% and 84.4% in the control group. The OPA GMTs observed post dose 2 were higher for serotypes 9V and 18C and lower for serotypes 1, 4, 5 and 23F compared to control group.

4. 24 months to 5 years age group

One month post dose 1 that is, full 'catch-up' vaccination, antibody concentrations $\geq 0.2 \mu\text{g/mL}$ were measured in at least 91.4% of the subjects for all pneumococcal serotypes except 6B (68.6%) and 23F (66.9%). The percentage of subjects with ELISA antibody concentrations $\geq 0.2 \mu\text{g/mL}$ was lower for serotypes 6B, 14 and 23F compared to the one month post booster time point in the control group (68.6% versus 96.4%, 91.4% versus 100% and 66.9% versus 99.3% respectively).

At one month post dose 1, at least 90.2% subjects had OPA ≥ 8 for each of the vaccine pneumococcal serotypes, except for serotypes 1 (46.3%), 5 (56.4%) and 6B (64.7%).

Long term antibody persistence data

Study 046 provided long-term antibodies persistence data, that is, 2-3 years following completion of vaccination (2+1 or 3+1 schedule) in Study 002. The study also investigated administration of an additional ('challenge') dose in the fourth year (36-46 months of age) of life in the 2+1 or 3+1 vaccinated groups and administration of 2 doses ('catch up') in an age-matched unvaccinated group at 36-46 and 38-48 months of age. This latter data in unvaccinated children with 2 dose 'catch-up' complements the data in Study 013 in which suboptimal response was found with a single dose 'catch-up' vaccination in the unvaccinated group aged 24 months to 5 years.

The follow-up data in Study 046 showed trend towards lower antibody levels for most serotypes at 24-36 months in the 2+1 primed children compared to 3+1 primed children. However, waning of immunity occurred at similar pace in both groups. A single additional dose of vaccine in the current study during fourth year of life in subjects having been primed according to a 2+1 schedule or a 3+1 schedule elicited robust anamnestic immune response measured 7-10 days after vaccination with nearly all recipients ($\sim 100\%$) achieving protective antibody levels ($\geq 0.2 \mu\text{g/mL}$) for all vaccine serotypes. The response was similarly robust in previously unvaccinated children who achieved similarly protective levels at one month after completion of 2 dose vaccination. The results for OPA titers ≥ 8 were similar.

Co administration with the other routine childhood vaccines did not appear to affect the immune response in any study.

The safety data are provided in CER. No significant difference in adverse effects profile was found with 2+1 or 3+1 schedules. No unexpected adverse effects were reported in the 'catch-up' vaccination in unvaccinated children.

Risk management plan

It was requested that the sponsor submit an updated RMP with their Pre-Advisory Committee on Prescription Medicines (ACPM) response.

Risk-benefit analysis

Delegate considerations

Synflorix (10v) has 3 additional serotypes (1, 5 and 7F) to those in Prevenar (7v), whereas Prevenar 13 (13v) has 3 additional serotypes (3, 6A and 19A) not included in Synflorix (10v).

Prevenar 13 (13v) has replaced Prevenar (7v) or Synflorix (Northern Territory) on the NIP as 3 dose primary series at 2, 4 and 6 months of age. The NIP does not include routine administration of booster.

The studies in the current submission assessed immune response measuring anti-capsular pneumococcal immunoglobulin subtype G (IgG) antibodies using modified ELISA assay developed by the sponsor with respect to proportion of subjects reaching antibody concentration of > 0.2 µg/mL and the GMC. Functional antibodies were also assessed.

These modified ELISA (22F inhibition assay) is identical to that used in studies at the time of registration of Synflorix and the seroprotective cut-off threshold of > 0.2 µg/mL has been accepted for Synflorix against the WHO established cut-off of 0.35 µg/mL derived from Prevenar efficacy trials data.

With respect to the 2 changes sought in the current submission:

1. Studies 002 and 011 provide evidence of comparability of 3+1 and 2+1 primary vaccination schedules with somewhat lower immune response with 2 priming doses compared to 3 priming doses for some serotypes. It would appear that completion of vaccination with booster dose in a 2+1 schedule will be important. As noted above the Australian NIP does not stipulate booster dose with a 3-dose priming series at 2, 4 and 6 months of age. Although the proposed text in the Dosage and Administration section of the draft PI includes a comment that 3+1 schedule is optimal and that 2+1 is an alternative, the Delegate was of the view that a recommendation of 2+1 schedule should include a guidance that when this schedule is used, care should be taken not to omit the booster dose. The Committee's advice was requested.

Please note that Prevenar 13 is not approved with 2+1 schedule and a direct comparison of Synflorix (2+1) and Prevenar 13 (2+1) is not available.

2. The anamnestic immune response in fourth year of life to children vaccinated with 2+1 or 3+1 Synflorix was satisfactory based on Study 046.

The data in Study 013 provides acceptable supporting evidence for the proposed recommendations in unvaccinated children from 7 months to 5 years of age. However, in this study in age group 24 months to 5 years, the use of a single dose as full 'catch-up' vaccination was found to be suboptimal. Based on Study 046 in which an age-matched unvaccinated group was vaccinated with 2 doses, the sponsor has proposed 2 doses at interval of 2 months with no booster. The evidence was considered acceptable for this recommendation. The Committee advice was requested.

Please note that similar dosing recommendations have been approved for Prevenar 13 in unvaccinated children except in age group 7 months to 5 years where only 1 dose is required.

Delegate's proposed action

Pending advice from the ACPM, the Delegate proposed to approve the requested changes for addition of an alternative 2+1 vaccination schedule for routine infant immunisation against pneumococcal disease using Synflorix and extension of population to 5 years with recommendations for unvaccinated children from 7 months to 5 years.

The sponsor was requested to provide annotated and clean copies of the proposed PI in its Pre-ACPM response. It was expected that further changes will need to be negotiated following consideration by the ACPM and prior to finalisation of the submission.

Advice from the ACPM was requested.

Sponsor response

Summary

This submission contains clinical studies to support the following changes to the registered details:

- Addition of an alternative 2+1 vaccination schedule as part of routine immunisation program,
- Extension of the age population from "6 weeks up to 2 years" to "6 weeks up to 5 years" and
- Extension of the population to include previously unvaccinated children from 7 months to 5 years.

Clinical Studies 002 and 011 support the adequacy of short term immune response with the 2+1 schedule and Study 046 supports the claim of long lasting protection and immunological memory following the 2+1 schedule. Additionally clinical Studies 013 and 046 support the extension of the population to include previously unvaccinated children between 7 months and 5 years of age.

The clinical evaluator concluded that the overall risk benefit of Synflorix is favourable for active immunisation of children from the age of 6 weeks to 5 years and for inclusion of an option for a 2-dose primary vaccination schedule in addition to the already approved 3-dose primary schedule. The Delegate has also recommended approval of the proposed changes with specific advice requested from the ACPM.

The sponsor agreed with the Delegate's assertion that the booster dose should be an important part of the 2-dose vaccination schedule. However, the sponsor contended that the immunogenicity data of Synflorix indicate that a booster dose is required to provide optimal protection in children irrespective of the primary schedule. As such it would not be appropriate to use wording in the PI that would suggest that a booster dose for the 2-dose schedule was more important than for the 3-dose schedule. Additionally, although the available data suggests that the 2-dose primary schedule is less immunogenic than the 3-dose primary schedule, the studies were not designed nor powered to make this assessment, rather to confirm the adequacy of the immunogenic response of each schedule.

The sponsor also agreed with the Delegate's conclusion that the 2 dose catch up in unvaccinated children between the age of 7 months and 5 years is supported by Studies 013 and 046. It is important to note that the 1 dose catch up with Synflorix in children over 2 years of age was immunogenic but elicited lower immune responses for some

serotypes as compared to 3-dose primary vaccination in infants. However, the immune responses after 2-dose catch up in this same age group with Synflorix was higher than after one dose in Study 013 for each serotype and thus was selected as the optimal dose based on data from Study 046.

Response to the Delegate's Pre-ACPM Questions

- 1. Studies 002 and 011 provide evidence of comparability of 3+1 and 2+1 primary vaccination schedules with somewhat lower immune response with 2 priming doses compared to 3 priming doses for some serotypes. It would appear that completion of vaccination with booster dose in a 2+1 schedule will be important. As noted above the Australian NIP does not stipulate booster dose with a 3-dose priming series at 2, 4 and 6 months of age. Although the proposed text in the Dosage and Administration section PI includes comment that 3+1 schedule is optimal and that 2+1 is an alternative, the Delegate was of the view that a recommendation of 2+1 schedule should include a guidance that when this schedule is used, care should be taken not to omit the booster dose. The Committee's advice was requested.*

The sponsor agreed with the Delegates recommendation that the PI should include guidance on the need for a booster dose in the 2+1 schedule and acknowledged that this booster dose should be given with a 2-dose primary series.

The immunogenicity data of Synflorix indicate that a booster dose was required to provide optimal protection in children irrespective of the primary schedule. The sponsor believes that the booster dose is an important part of both the 3+1 and 2+1 schedules and as such the draft PI includes recommendation for a booster dose for both primary schedules.

The sponsor also acknowledges that the immunogenic response was lower for several serotypes in subjects receiving a 2-dose primary vaccination schedule compared to a 3-dose primary schedule. However, it should be taken into consideration that the studies undertaken were not designed nor powered to compare the 2+1 and 3+1 schedules, rather the main objective was to confirm the adequacy of the immunogenic response with the 2+1 and 3+1 schedules.

The sponsor contended that appropriate information had been included in draft the PI to emphasise the importance of the booster dose for both the 3+1 and 2+1 schedules and to clarify the difference in immunogenic response between the 2 schedules.

In conclusion, the sponsor believed that a booster dose is important in either vaccination schedule to achieve maximum protection and that there should be no differentiation in the emphasis on this requirement between the schedules. The draft PI clearly states that the 2-dose primary series is less immunogenic than the 3-dose primary series with respect to some serotypes.

- 2. The data in Study 013 provides acceptable supporting evidence for the proposed recommendations in unvaccinated children from 7 months to 5 years of age. However, in this study in age group 24 months to 5 years, the use of a single dose as full 'catch-up' vaccination was found to be suboptimal. Based on Study 046 in which an age-matched unvaccinated group was vaccinated with 2 doses, the sponsor has proposed 2 doses at interval of 2 months with no booster. The evidence was considered acceptable for this recommendation. The Committee advice was requested.*

The sponsor conducted 2 clinical studies to evaluate the appropriate dosing schedule in children ≥ 2 years of age. Study 013 evaluated different catch-up vaccination schedules for three age groups, that is 7-11 months of age, 12-23 months of age and ≥ 24 months of age and Study 046 evaluated two doses in the fourth year of life.

In the oldest age group in Study 013 (≥ 24 Mo group), at least 91.4% of the subjects had antibody concentrations ≥ 0.2 $\mu\text{g/mL}$ post dose 1 for each pneumococcal serotypes except

for serotypes 6B (68.6%) and 23F (66.9%). The antibody GMCs were lower for serotypes 1, 5, 14 and 23F and higher for serotypes 4, 18C and 19F compared to those observed for the same serotypes in the <6 Mo group after a 3-dose primary series. At least 90.2% of the subjects had an OPA titre ≥ 8 for each of the serotypes except for serotypes 1 (46.3%), 5 (56.4%) and 6B (64.7%). The GMTs were lower for serotype 5 and higher for serotypes 4, 18C and 19F compared to those observed in the <6 Mo group after a 3-dose primary series. The anti-PD GMC and the proportion of subjects (76.3%) with measurable anti-PD antibody concentrations (≥ 100 EL.U/ml) after one dose in the ≥ 24 Mo group were lower compared to the responses after a 3-dose primary vaccination schedule (for example, 100% of subjects with measurable anti-PD antibody concentrations).

The data from Study 013 demonstrated that one Synflorix dose in children 2-5 years of age was immunogenic. The response was less immunogenic for several serotypes compared to a 3-dose primary schedule. As would be expected, the data from Study 046 indicated that two catch-up doses in unvaccinated children in their fourth year of life provided higher immune responses for each serotype than after one dose in Study 013. These studies were independent and descriptive in nature and as such any comparison of dosing schedules should be interpreted with caution.

It is important to point out that the available data is not suggesting 1 catch up dose of Synflorix will not be clinically effective. Based on the available evidence it was concluded that unvaccinated children between 24 months and 5 years of age should be given 2 doses of pneumococcal conjugate vaccine consistent with the text in the Dosage and Administration section of the PI.

Conclusion

In conclusion the sponsor noted the Delegates recommendation to approve the proposed changes to the indication and dosage for Synflorix.

The sponsor proposed to retain the current wording in relation to the recommendation for a booster dose for both the 3+1 and 2+1 dose without differentiating the wording and therefore implied importance of the booster dose for the 2-dose primary schedule compared with the 3-dose primary schedule. Appropriate text has been included in the draft PI to inform the health care provider of the lower immunogenic response with the 2-dose primary schedule.

The 2-dose catch up in non vaccinated children was considered the optimal dose for use based on the available data.

Proposed Indication Statement:

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

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of pharmaceutical efficacy, safety and quality agreed with the delegate and considered this product has a positive benefit-risk profile for the indication;

For active immunisation of infants and children from the age of 6 weeks up to 5 years against disease caused by Streptococcus pneumoniae serotypes 1, 4, 5, 6b, 7F, 9V, 14, 18C, 19F and 23F (including invasive disease, pneumonia, and acute otitis media).

The ACPM advised that although the proposed dose schedule has a lower immune response compared to the currently approved 3+1 regime; the data provided support the addition of an alternative 2+1 vaccination schedule for routine infant immunisation against pneumococcal disease.

The ACPM also agreed that the data provided support the extension of the population to include children between 2 and 5 years of age with the recommendations for unvaccinated children from 7 months to 5 years as proposed by the delegate.

The ACPM supported the amendments proposed by the delegate to the Product Information (PI) and Consumer Medicines Information (CMI), including;

- a statement in the *Dosage and Administration* section instruction that a booster dose should always be administered when the 2+1 schedule is used.
- a clear explanation of the rationale for the proposed dose schedule.

The ACPM advised that as a condition of registration the full implementation of the Risk Management should be required.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Synflorix pneumococcal polysaccharide conjugate vaccine, 10-valent adsorbed suspension for injection vial and Synflorix pneumococcal polysaccharide conjugate vaccine, 10-valent adsorbed suspension for injection pre-filled syringe for the new indication:

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

Specific conditions applying to these therapeutic goods

1. The implementation in Australia of the Synflorix pneumococcal polysaccharide conjugate vaccine Risk Management Plan version 5, August 2010 included with this submission and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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Reference/Publication #