23 June 2011
EMA/736592/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Synflorix

pneumococcal polysaccharide conjugate vaccine (adsorbed)
Procedure No.: EMEA/H/C/000973/II/0020

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Scientific discussion

1.1. Introduction

Streptococcus pneumoniae is the leading cause of invasive pneumococcal disease (IPD) (including septicaemia, meningitis, and bacteraemic pneumonia) and non invasive pneumococcal diseases (such as acute otitis media (AOM), non-bacteraemic pneumonia, sinusitis, and bronchitis) in young children. WHO estimates that about 16 million people, including up to 1 million children under 5 years old, die every year of pneumococcal disease. The highest incidence of IPD is found at the extremes of age - in young children <2 years of age and in elderly adults. The highest morbidity and mortality rates have been reported in developing countries, but the disease burden is considerable also in industrialised countries. Extrapolation of data on hospitalizations due to IPD from England and Wales (prior to introduction of Prevenar) to the European Union (EU) paediatric population <5 years of age indicate that there would be 6500 IPD cases and 61,000 pneumonia cases annually. Acute otitis media (AOM) is most prevalent in early childhood and it has been estimated that each year in the EU 2.1 million AOM cases occur in children <5 years of age.
Bacteria are isolated in ~70% of children with otitis media, with *S. pneumoniae* and *H. influenzae* being the most commonly identified pathogens.
Despite the availability of antibiotic therapies the mortality of pneumococcal disease remains high. The continuing emergence of penicillin-resistant and multidrug-resistant pneumococcal strains is an increasing global threat posing serious therapeutic challenges. Although the resistance patterns vary between countries, the predominance of certain serotypes (i.e. 6A, 6B, 9V, 14, 19A, 19F, and 23F) among the resistant organisms is shared.

Synflorix is a second generation vaccine being developed and contains other carrier proteins (protein D, diphtheria toxoid [DT] and tetanus toxoid [TT]) and three more pneumococcal serotypes (1, 5 and 7F) in addition to the seven shared with Prevenar. The three additional serotypes are among the major IPD causing serotypes worldwide and represent in Europe a combined average of 13% of all IPD in children <5 years of age. Protein D was selected as a carrier protein, due to its potential to provide protection against *H. influenzae* infections.
The Company proposes to update the indication section of the Synflorix Summary of Product Characteristics (SmPC) by increasing the upper age limit of infants and children from 2 years to 5 years. Accordingly the sections posology, adverse events and pharmacodynamics have been amended.

The proposed changes are supported by two clinical studies, 10PN-PD-DIT-013 and -046. During the assessment, new reactogenicity results became available from study 10PN-PD-DIT-070 in Kenya (600 children of 12-59 months of age exposed to one or two doses of Synflorix). The reactogenicity profile of Synflorix across age groups in study 070 is described below and supports the claim according to which two doses of Synflorix are safe and well tolerated in children 2-5 years of age.

Additional supporting safety data in children above 4 years of age have also been provided during the assessment.

Variation requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of Summary of Product Characteristics, Annex II and Package Leaflet

The scope of the variation includes updating the indication Section 4.1 to increase the upper age limit of infants and children from 2 years to 5 years and updating all relevant sections of the Summary of Product Characteristics (SmPC), i.e. 4.1, 4.2, 4.8 and 5.1 and Package Leaflet.

Amend the version number of the RMP mentioned in Annex II in order to reflect the latest approved RMP version 5.0.

The proposed changes are supported by two main clinical studies 10PN-PD-DIT-013 and -046 and one supportive study 10PN-PD-DIT-070.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included an EMA decision (P/104/2010) for the following condition(s):

- Diseases caused by Streptococcus pneumoniae
- Acute otitis media caused by Haemophilus influenzae

On the agreement of a paediatric investigation plan (PIP).

The PIP is not yet completed.

1.2. Clinical aspects

Three clinical studies were submitted to support the proposed change of indication, 10PN-PD-DIT-013, 10PN-PD-DIT-046 and study 10PN-PD-DIT-070. Study 10PN-PD-DIT-013 was submitted at the time of the initial MAA, and assessed during the approval procedure. The study 10PN-PD-DIT-013 results are summarised in this assessment report (AR). Study 10PN-PD-DIT-046 was submitted during the type II variation EMEA/H/C/973/II/14, with the purpose of adding the 2+1 primary vaccination schedule, in addition to the 3+1 primary schedule. The EC decision for variation II/14 was issued on 24 January 2011. Study 10PN-PD-DIT-070 was submitted as additional supporting data that became available in support of the current variation.

Clinical efficacy

Methods

Study 10PN-PD-DIT-013 is an open, controlled study with 4 parallel groups stratified according to age and with different vaccination schedules and blood sampling time points according to the age group, which are detailed in Table 1.

Primary objective was to evaluate the immunogenicity of the 10-valent pneumococcal conjugate vaccine (10Pn-PD-DiT), when given as a catch-up immunization in children older than 7 months of age (three age-groups with different schedules).

Secondary objectives included the evaluation of safety and reactogenicity of 10Pn-PD-DiT as well as the immunogenicity, safety and reactogenicity of DTPa-IPV/Hib vaccine when co-administered in the group starting vaccination before 6 months of age.

Table 1. Study 10PN-PD-DIT-013: groups with vaccination schedules and blood samples

Group	Age at first vaccination	Vaccination schedule	Vaccine	Blood sampling timepoint
< 6 months of age (<6 Mo)	9-12 weeks	3 primary doses at 3-4-5 and a booster at 12 to 15 months of age	10Pn-PD-DiT DTPa-IPV/Hib	One month post dose III, pre and post booster dose
7-11 months of age (7-11Mo)	7-11 months	2 doses with at least 4 weeks interval and a booster dose at least 3 months after the last primary dose	10Pn-PD-DiT	One month post dose II, pre and post booster dose
12-23 months of age (12-23 Mo)	12-23 months	2 doses with at least 2 months interval	10Pn-PD-DiT	Pre dose I and one month post dose II
≥24 months of age (≥24 Mo)	24 months-5 years	1 dose	10Pn-PD-DiT	Pre and one month post dose I

Study participants

The Table below shows the total number of subjects vaccinated, completed and withdrawn from study 013 which corresponds to the Primary Total Vaccinated Cohort

	<6Mo	7-11Mo	12-23Mo	>=24Mo	Total
Number of subjects vaccinated	150	150	150	150	600
Number of subjects completed	145	146	142	148	581
Number of subjects withdrawn	5	4	8	2	19
Reasons for withdrawal :					
Serious Adverse Event	0	0	0	0	0
Non-serious adverse event	3	1	1	0	5
Protocol violation	0	0	0	0	0
Consent withdrawal (not due to an adverse event)	1	2	4	0	7
Migrated/moved from study area	0	0	0	0	0
Lost to follow-up (subjects with incomplete vaccination course)	1	0	0	0	1
Lost to follow-up (subjects with complete vaccination course)	0	0	2	2	4
Others	0	1	1	0	2

<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)

Vaccinated = number of subjects who were vaccinated into the study
Completed = number of subjects who completed primary course - visit 4 for < 6 Mo group
visit 3 for 7-11 Mo group
visit 3 for 12-23 Mo group
visit 2 for >= 24 Mo group
Withdrawn = number of subjects who did not come for the last visit of primary course

Statistical methods and endpoints

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).

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

Serological Methods

All serological assays used to evaluate the anti-pneumococcal antibody and OPA responses were performed in the MAH's laboratory in Rixensart, Belgium 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 study 10PN-PD-DIT-013. The analysis of the immunogenicity was performed on the according to protocol (ATP) cohort for immunogenicity.

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 0.2μg/ml after catch-up vaccination and after a 3-dose primary schedule in infants below 6 months of age.
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 is justified because the catch-up vaccination can actually be seen as primary vaccination in older children. The immune response after full catch-up vaccination should therefore be at least as good as after 3 doses in infants below 6 months of age.

Study 10PN-PD-DIT-046 is an open, controlled, long-term follow-up study with three parallel groups and is an extension study of the primary and booster vaccination study 10PN-PD-DIT-002. The study design is detailed further in Table 2 and Figure 1.
The number of subjects included in the study is shown below.

Number of subjects	Total	10Pn-2d	10Pn-3d	unprimed
Number of subjects planned	210	70	70	70
Number of subjects enrolled	172	51	59	62
Number of subjects completed	171	51	58	62
Total vaccinated cohort	172	51	59	62
According to Protocol (ATP) for safety/persistence	172	51	59	62
According to Protocol (ATP) for immunogenicity	167	51	57	60

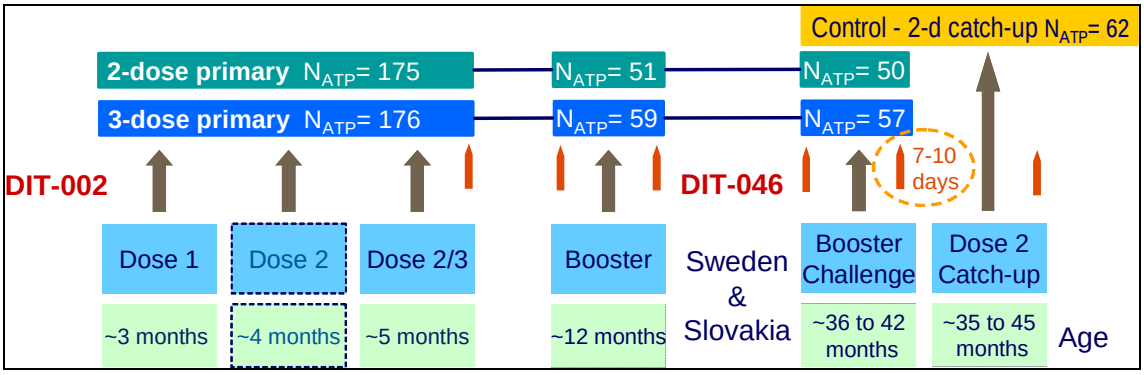
Primary objective was to assess the immune responses following vaccination with a booster dose of the 10Pn-PD-DiT vaccine administered at 36-46 months of age in children previously vaccinated with the 10Pn-PD-DiT vaccine in study 10PN-PD-DIT-002 according to either a 3-dose or 2-dose primary vaccination within the first 6 months of age and booster vaccination at 11 months of age and to assess

the immune responses following vaccination with a single dose of the 10Pn-PD-DiT vaccine in age-matched unprimed children.
Secondary objectives included the assessment of safety, reactogenicity and immunogenicity of the 10Pn-PD-DiT vaccine when given as a 2-dose vaccination course to unprimed children in their fourth year of life.

Table 2. Study 10PN-PD-DIT-046: groups with vaccination schedules and blood samples

Group	Vaccination schedule in 002	Vaccination schedule in 046	Blood sampling timepoint
10Pn-2d	2+1 at 2-4 and 11months of age	1 dose at 36-46 months of age	Pre and 7-10 days post dose 1
10Pn-3d	3+1 at 2-3-4 and 11months of age	1 dose at 36-46 months of age	Pre and 7-10 days post dose 1
Unprimed	-	2 doses at 36-46 and 38-48 months of age	Pre and 7-10 days post dose 1 One month post dose 2

Figure 1. Study design 10PN-PD-DIT-002 and -046



For the evaluation of immunogenicity of an appropriate schedule for catch-up vaccination, the following parameters were measured prior to, 7-10 days post-dose 1 (all groups), 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).

Statistical methods and endpoints
Where appropriate, for each treatment group, at each time-point for which a blood-analysis result was available and for each pneumococcal serotype and for protein D:

- Antibody GMCs/GMTs with 95% CIs was tabulated.
- Seropositivity rates with exact 95% CIs were calculated.
- Percentage of subjects with pneumococcal antibody concentrations ≥0.2μg/ml with exact 95% CIs was calculated for each pneumococcal serotype.
- The distribution of antibody concentrations/titres was displayed using table and/or reverse cumulative distribution curve.

- For each pneumococcal serotype, at each time point for which a blood analysis result was available, geometric mean of ratios of opsonophagocytic titres/ELISA concentrations were tabulated with their 95% CIs.

Without an immunological correlate for individual protection, the comparison of the immune response after full catch-up vaccination in older children to those after a 3-dose primary schedule in infants below 6 months of age is 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. Although in study 046 no direct control group of infants receiving a 3-dose primary schedule was available, in the preceding study 002 this group was present and can be compared with. 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, 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.

Results of main studies

Immunogenicity results for study 10PN-PD-DIT-013 and study 10PN-PD-DIT-046 are presented in Table 3 and Table 4. In addition to the results for the unprimed group in study 10PN-PD-DIT-046 the immune responses for the 3-dose primary schedule in infants vaccinated in the preceding study 10PN-PD-DIT-002 are shown.

Table 3. Immune responses in studies 10PN-PD-DIT-013, -002 and -046

		ELISA								OPA							
			≥ 0.2µg/ml				GMC				≥ 8				GMT		
Study	Group	N	n	%	95%CI		Value	95%CI		N	n	%	95%CI		Value	95%CI	
Serotype 4																	
013	< 6 Mo pd3	131	128	**97.7**	93.5	99.5	**1.84**	1.57	2.15	41	40	**97.6**	87.1	99.9	**675.6**	475.4	960.0
	7-11Mo	114	114	**100**	96.8	100	**3.79**	3.27	4.40	38	38	**100**	90.7	100	**978.3**	720.6	1328.1
	12-23Mo	133	133	**100**	97.3	100	**4.21**	3.77	4.69	50	48	**96.0**	86.3	99.5	**912.1**	617.8	1346.8
	≥24Mo	140	140	**100**	97.4	100	**5.72**	5.00	6.54	36	36	**100**	90.3	100	**2227.6**	1694.0	2929.3
002	10Pn_3d	153	152	**99.3**	96.4	100	**1.71**	1.47	1.99	132	131	**99.2**	95.9	100	**758.9**	647.8	888.9
046	Unprim	60	60	**100**	94.0	100	**8.44**	7.16	9.94	56	56	**100**	93.6	100	**2687.5**	2165.0	3336.1
Serotype 6B																	
013	< 6 Mo pd3	131	95	**72.5**	64.0	80.0	**0.37**	0.29	0.48	38	29	**76.3**	59.8	88.6	**296.0**	130.3	672.2
	7-11Mo	114	110	**96.5**	91.3	99.0	**1.39**	1.14	1.69	40	37	**92.5**	79.6	98.4	**620.3**	356.5	1079.4
	12-23Mo	133	108	**81.2**	73.5	87.5	**0.53**	0.43	0.65	49	37	**75.5**	61.1	86.7	**304.3**	143.8	644.2
	≥24Mo	140	96	**68.6**	60.2	76.1	**0.38**	0.30	0.47	34	22	**64.7**	46.5	80.3	**331.7**	99.1	1109.8
002	10Pn_3d	149	94	**63.1**	54.8	70.8	**0.31**	0.25	0.38	126	112	**88.9**	82.1	93.8	**379.6**	272.4	529.1
046	Unprim	60	56	**93.3**	83.8	98.2	**1.11**	0.84	1.46	57	53	**93.0**	83.0	98.1	**1040.9**	652.8	1659.5
Serotype 9V																	
013	< 6 Mo pd3	131	128	**97.7**	93.5	99.5	**1.33**	1.14	1.55	41	41	**100**	91.4	100	**1281.1**	895.0	1833.7
	7-11Mo	114	114	**100**	96.8	100	**2.13**	1.82	2.50	38	38	**100**	90.7	100	**2241.2**	1758.7	2856.0
	12-23Mo	133	130	**97.7**	93.5	99.5	**1.50**	1.30	1.73	50	50	**100**	92.9	100	**3525.8**	2675.4	4646.4
	≥24Mo	140	132	**94.3**	89.1	97.5	**1.01**	0.84	1.22	37	37	**100**	90.5	100	**4526.0**	3581.7	5719.3
002	10Pn_3d	153	152	**99.3**	96.4	100	**1.47**	1.29	1.68	132	132	**100**	97.2	100	**1343.4**	1130.8	1596.0
046	Unprim	60	60	**100**	94.0	100	**2.22**	1.74	2.82	55	55	**100**	93.5	100	**6085.2**	4718.5	7847.9
Serotype 14																	
013	< 6 Mo pd3	131	130	**99.2**	95.8	100	**3.00**	2.61	3.46	42	41	**97.6**	87.4	99.9	**1523.3**	1028.7	2255.6
	7-11Mo	114	114	**100**	96.8	100	**5.41**	4.71	6.22	40	40	**100**	91.2	100	**1859.4**	1452.1	2380.9
	12-23Mo	133	132	**99.2**	95.9	100	**4.24**	3.64	4.95	51	51	**100**	93.0	100	**2277.2**	1804.9	2873.0
	≥24Mo	139	127	**91.4**	85.4	95.5	**1.36**	1.06	1.74	40	40	**100**	91.2	100	**1957.4**	1516.6	2526.3
002	10Pn_3d	152	152	**100**	97.6	100	**2.57**	2.22	2.97	131	131	**100**	97.2	100	**1125.3**	946.2	1338.3
046	Unprim	60	60	**100**	94.0	100	**6.48**	4.98	8.44	56	56	**100**	93.6	100	**4978.9**	3857.8	6425.9

		ELISA								OPA							
			≥ 0.2µg/ml				GMC				≥ 8				GMT		
Study	Group	N	n	%	95%CI		Value	95%CI		N	n	%	95%CI		Value	95%CI	
Serotype 18C																	
013	< 6 Mo pd3	131	127	**96.9**	92.4	99.2	**1.84**	1.50	2.26	41	38	**92.7**	80.1	98.5	**181.8**	120.8	273.5
	7-11Mo	114	114	**100**	96.8	100	**9.40**	8.04	10.98	38	38	**100**	90.7	100	**1332.9**	926.3	1918.0
	12-23Mo	133	133	**100**	97.3	100	**9.20**	8.22	10.29	51	51	**100**	93.0	100	**1765.3**	1330.5	2342.2
	≥24Mo	140	140	**100**	97.4	100	**4.65**	4.06	5.31	38	38	**100**	90.7	100	**2051.4**	1558.3	2700.5
002	10Pn_3d	153	152	**99.3**	96.4	100	**3.42**	2.87	4.07	131	126	**96.2**	91.3	98.7	**218.6**	176.1	271.4
046	Unprim	60	60	**100**	94.0	100	**22.28**	18.14	27.36	56	56	**100**	93.6	100	**3984.5**	3187.9	4980.2
Serotype 19F																	
013	< 6 Mo pd3	130	122	**93.8**	88.2	97.3	**1.61**	1.28	2.02	42	37	**88.1**	74.4	96.0	**194.7**	101.7	372.7
	7-11Mo	114	112	**98.2**	93.8	99.8	**5.71**	4.68	6.97	38	35	**92.1**	78.6	98.3	**513.1**	265.8	990.2
	12-23Mo	133	131	**98.5**	94.7	99.8	**5.45**	4.63	6.41	50	47	**94.0**	83.5	98.7	**592.7**	367.3	956.4
	≥24Mo	140	140	**100**	97.4	100	**5.26**	4.34	6.39	41	39	**95.1**	83.5	99.4	**634.3**	400.2	1005.4
002	10Pn_3d	152	146	**96.1**	91.6	98.5	**4.43**	3.60	5.45	128	120	**93.8**	88.1	97.3	**356.7**	263.2	483.4
046	Unprim	60	60	**100**	94.0	100	**17.03**	13.38	21.68	56	56	**100**	93.6	100	**1772.5**	1285.9	2443.3
Serotype 23F																	
013	< 6 Mo pd3	131	114	**87.0**	80.0	92.3	**0.62**	0.50	0.76	41	35	**85.4**	70.8	94.4	**925.8**	422.6	2028.3
	7-11Mo	114	110	**96.5**	91.3	99.0	**1.65**	1.33	2.03	40	39	**97.5**	86.8	99.9	**1770.0**	1148.4	2728.0
	12-23Mo	133	122	**91.7**	85.7	95.8	**0.88**	0.73	1.05	49	47	**95.9**	86.0	99.5	**1656.4**	1063.6	2579.6
	≥24Mo	139	93	**66.9**	58.4	74.6	**0.37**	0.30	0.47	41	37	**90.2**	76.9	97.3	**1575.2**	802.6	3091.7
002	10Pn_3d	152	118	**77.6**	70.2	84.0	**0.52**	0.42	0.63	129	126	**97.7**	93.4	99.5	**1233.7**	991.7	1534.7
046	Unprim	60	56	**93.3**	83.3	98.2	**1.09**	0.81	1.45	57	57	**100**	93.7	100	**5095.5**	3992.3	6503.6
Serotype 1																	
013	< 6 Mo pd3	131	128	**97.7**	93.5	99.5	**1.20**	1.02	1.42	44	24	**54.5**	38.8	69.6	**17.3**	10.9	27.5
	7-11Mo	114	114	**100**	96.8	100	**1.77**	1.55	2.02	40	36	**90.0**	76.3	97.2	**234.1**	127.4	430.2
	12-23Mo	133	132	**99.2**	95.9	100	**1.22**	1.06	1.40	51	23	**45.1**	31.1	59.7	**14.2**	9.0	22.4
	≥24Mo	140	135	**96.4**	91.9	98.8	**0.77**	0.66	0.89	41	19	**46.3**	30.7	62.6	**17.5**	9.4	32.3
002	10Pn_3d	151	149	**98.7**	95.3	99.8	**1.23**	1.07	1.42	132	83	**62.9**	54.0	71.1	**26.5**	19.8	35.4
046	Unprim	60	60	**100**	94.0	100	**2.81**	2.25	3.51	56	50	**89.3**	78.1	96.0	**103.0**	67.6	157.0

		ELISA								OPA							
			≥ 0.2µg/ml				GMC				≥ 8				GMT		
Study	Group	N	n	%	95%CI		Value	95%CI		N	n	%	95%CI		Value	95%CI	
Serotype 5																	
013	< 6 Mo pd3	131	130	**99.2**	95.8	100	**2.04**	1.75	2.37	42	36	**85.7**	71.5	94.6	**52.6**	33.7	82.2
	7-11Mo	114	114	**100**	96.8	100	**2.88**	2.48	3.34	39	39	**100**	91.0	100	**243.0**	151.6	389.7
	12-23Mo	133	131	**98.5**	94.7	99.8	**1.80**	1.57	2.06	50	42	**84.0**	70.9	92.8	**47.5**	30.2	74.8
	≥24Mo	138	135	**97.8**	93.8	99.5	**1.16**	0.99	1.36	39	22	**56.4**	39.6	72.2	**14.1**	9.1	22.0
002	10Pn_3d	149	149	**100**	97.6	100	**1.85**	1.63	2.10	130	118	**90.8**	84.4	95.1	**68.4**	54.0	86.5
046	Unprim	60	60	**100**	94.0	100	**3.54**	2.96	4.23	56	55	**98.2**	90.4	100	**127.6**	92.7	175.6
Serotype 7F																	
013	< 6 Mo pd3	131	130	**99.2**	95.8	100	**2.03**	1.76	2.33	43	41	**95.3**	84.2	99.4	**1775.1**	1057.8	2978.8
	7-11Mo	114	114	**100**	96.8	100	**3.73**	3.24	4.28	40	40	**100**	91.2	100	**3726.8**	2759.4	5033.3
	12-23Mo	133	133	**100**	97.3	100	**3.62**	3.22	4.06	48	47	**97.9**	88.9	99.9	**4164.2**	2840.4	6105.0
	≥24Mo	140	140	**100**	97.4	100	**2.60**	2.25	3.01	38	37	**97.4**	86.2	99.9	**3282.2**	2105.1	5117.6
002	10Pn_3d	152	151	**99.3**	96.4	100	**2.14**	1.90	2.40	131	129	**98.5**	94.6	99.8	**2176.5**	1759.2	2692.7
046	Unprim	60	60	**100**	94.0	100	**6.10**	4.99	7.46	55	55	**100**	93.5	100	**6213.1**	4793.1	8053.7
Serotype 6A																	
013	< 6 Mo pd3	132	40	**30.3**	22.6	38.9	**0.10**	0.08	0.12	41	12	**29.3**	16.1	45.5	**14.4**	7.5	27.6
	7-11Mo	114	81	**71.1**	61.8	79.2	**0.55**	0.42	0.73	36	32	**88.9**	73.9	96.9	**302.2**	168.7	541.5
	12-23Mo	133	70	**52.6**	43.8	61.3	**0.23**	0.18	0.29	50	38	**76.0**	61.8	86.9	**150.7**	80.7	281.3
	≥24Mo	138	65	**47.1**	38.6	55.8	**0.24**	0.19	0.31	35	28	**80.0**	63.1	91.6	**324.6**	142.6	738.6
002	10Pn_3d	146	35	**24.0**	17.3	31.7	**0.09**	0.07	0.11	121	69	**57.0**	47.7	66.0	**41.0**	27.9	60.1
046	Unprim	60	49	**81.7**	69.6	90.5	**0.58**	0.42	0.79	52	50	**96.2**	86.8	99.5	**715.2**	487.3	1049.6
Serotype 19A																	
013	< 6 Mo pd3	131	34	**26.0**	18.7	34.3	**0.09**	0.07	0.11	43	4	**9.3**	2.6	22.1	**5.1**	3.9	6.6
	7-11Mo	114	97	**85.1**	77.2	91.1	**0.99**	0.78	1.25	37	20	**54.1**	36.9	70.5	**36.8**	16.2	83.8
	12-23Mo	133	121	**91.0**	84.8	95.3	**0.86**	0.71	1.05	49	25	**51.0**	36.3	65.6	**39.5**	19.0	81.9
	≥24Mo	138	116	**84.1**	76.9	89.7	**0.65**	0.53	0.82	38	20	**52.6**	35.8	69.0	**31.8**	14.3	70.7
002	10Pn_3d	150	80	**53.3**	45.0	61.5	**0.19**	0.16	0.24	130	46	**35.4**	27.2	44.2	**15.8**	11.2	22.3
046	Unprim	60	58	**96.7**	88.5	99.6	**1.97**	1.46	2.65	53	50	**94.3**	84.3	98.8	**406.4**	227.3	726.9

Study 013: <6Mo = 3 doses of 10Pn-PD-DiT + DTPa-IPV/Hib (3, 4, 5 months); 7-11Mo = 2 doses 10Pn-PD-DiT (4 weeks interval) + 1 dose at least 3 months after the last dose; 12-23Mo = 2 doses of 10Pn-PD-DiT (12-23, 14-25 months); >=24Mo = 1 dose 10Pn-PD-DiT (24 months - 5 Years); Data timepoints were one month post Dose III (<6Mo), one month post dose II (7-11Mo & 12-23Mo) and one month post dose I (≥24Mo)

Study 002: 10Pn_3d = 3 doses of 10Pn-PD-DiT (2, 3, 4 months) + DTPa-(HBV)-IPV/Hib (2, 4 months); Data timepoint was 7-10 days post dose I

Study 046: Unprim = 2 doses of 10Pn-PD-DiT (36-46 and 38-48 months) ; Data timepoint was one month post dose II

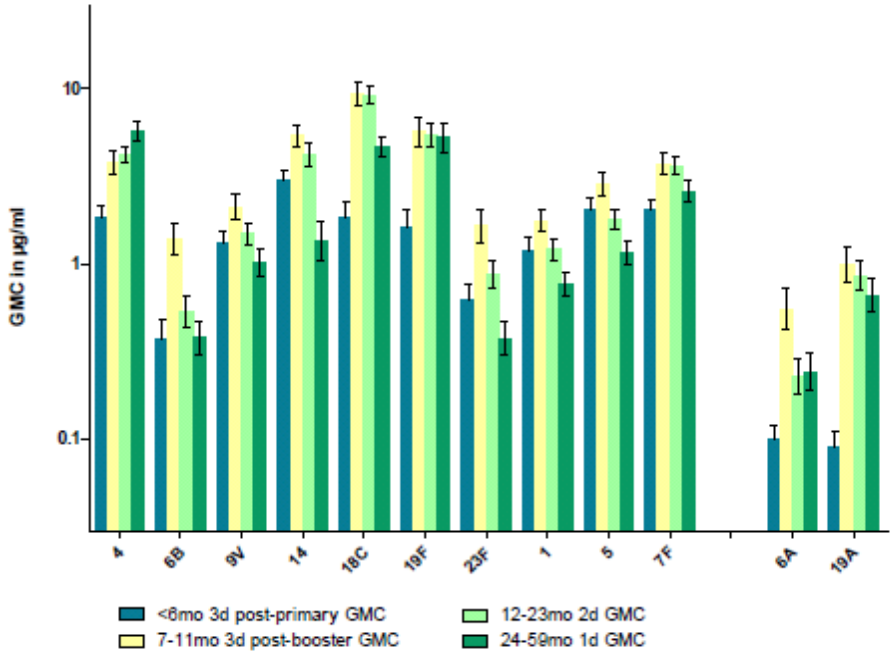
Table 4. Protein D in studies 10PN-PD-DIT-013, -002 and -046

Anti-PD			≥ 100 EL.U/ml				GMC		
Study	Group	N	n	%	95% CI		value	95% CI	
013	<6 Mo pd3	131	131	**100**	97.2	100	**1637.7**	1430.9	1874.3
	7-11Mo	114	113	**99.1**	95.2	100	**1942.0**	1614.5	2335.9
	12-23Mo	133	129	**97.0**	92.5	99.2	**660.0**	554.9	785.1
	≥24Mo	139	106	**76.3**	68.3	83.1	**224.8**	185.2	272.7
002	10Pn_3d	148	148	**100**	97.5	100	**1223.3**	1066.5	1403.2
046	Unprim	60	59	**98.3**	91.1	100	**960.4**	752.7	1225.5

Study 013: <6Mo = 3 doses of 10Pn-PD-DiT + DTPa-IPV/Hib (3, 4, 5 months); 7-11Mo = 2 doses 10Pn-PD-DiT (4 weeks interval) + 1 dose at least 3 months after the last dose; 12-23Mo = 2 doses of 10Pn-PD-DiT (12-23, 14-25 months); >=24Mo = 1 dose 10Pn-PD-DiT (24 months - 5 Years); Data timepoints were one month post Dose III (<6Mo), one month post dose II (7-11Mo & 12-23Mo) and one month post dose I (≥24Mo)
Study 002: 10Pn_3d = 3 doses of 10Pn-PD-DiT (2, 3, 4 months) + DTPa-(HBV)-IPV/Hib (2, 4 months); Data timepoint was 7-10 days post dose I
Study 046: Unprim = 2 doses of 10Pn-PD-DiT (36-46 and 38-48 months) ; Data timepoint was one month post dose II

In study 10PN-PD-DIT-013 for the ≥24 Mo group, one month post-dose I, at least 91.4% of the subjects had antibody concentrations ≥0.2 μg/ml, for each of the vaccine pneumococcal serotypes except for serotypes 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 after a 3-dose primary series (non-overlap of CIs) (Figure 2). The observed percentage of subjects with ELISA antibody concentrations ≥0.2 μg/ml was lower for serotypes 14 and 23F and higher for serotype 19F compared to the <6 Mo control group.

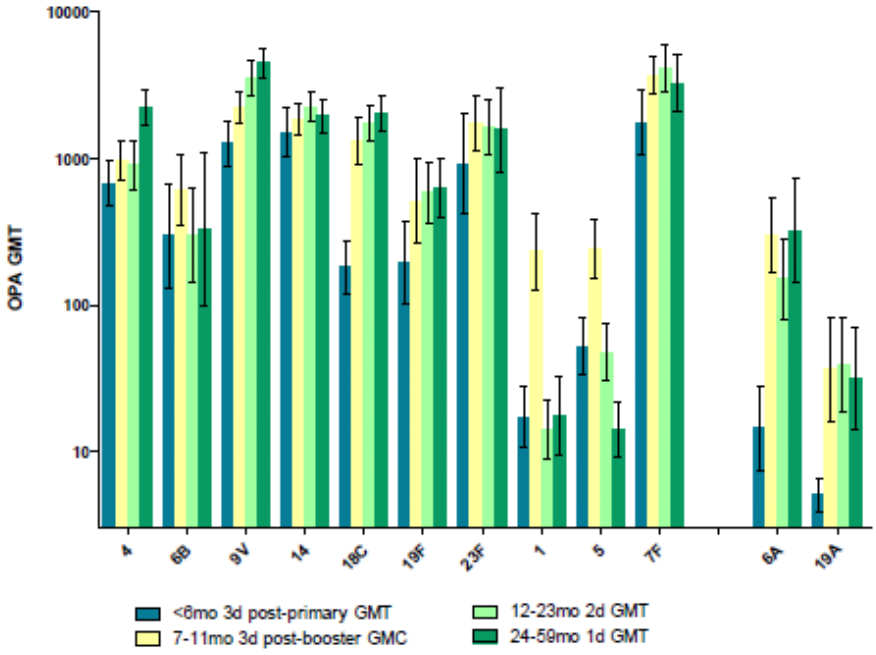
Figure 2 Geometric mean antibody concentration in all groups in study 013



In study 10PN-PD-DIT-013 for the ≥24 Mo group, one month post-dose I, at least 90.2% of the subjects had an OPA titre ≥ 8, for each of the vaccine pneumococcal serotypes except for serotypes 1 (46.3%), 5 (56.4%) and 6B (64.7%). The observed 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 (non-overlap of CIs) (Figure 3).

In all three catch-up immunization 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.

Figure 3: Geometric mean opsonophagocytic titre in all groups in study 013



The anti-PD GMC [224.8 EL. U/ml (95% CI: 185.2-272.7)] and the proportion of subjects [76.3% (68.3-83.1)] 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, i.e. a GMC of 1637.7 (1430.9-1874.3) and 100% (97.2-100) of subjects with measurable anti-PD antibody concentrations.

Discussion on clinical efficacy

From these results it can be concluded that one dose in 2-5 year olds was immunogenic but that the response was not as high as the response after 3 doses in infancy for some serotypes, and Protein D.
In study 013 higher antibody GMCs and OPA GMTs against serotype 6B were observed one month post-dose 1 in children >2 years old at the time of vaccination, compared to those in the 2 years old group (no overlap of 95% CIs).
No statistically significant differences could be observed for the other serotypes, although conclusions need to be drawn with caution given the small sample sizes. No consistent differences were observed between age groups, with for some serotypes a trend for a higher response in the above 2 years old subgroup and for other serotypes a trend for higher responses in the 2 years old group. However, in the OPA analysis, consistently higher GMTs were observed in the older subgroup. It is of note that OPA activity was tested only in one third of the subjects, i.e. approximately 50 subjects per age group.

The number of subjects 3-5 years of age is limited to 40 subjects, which is considered very low. No firm conclusions with respect to vaccine immunogenicity and safety could be drawn.

In study 046, the immune responses following 2-dose catch-up vaccination with the pneumococcal conjugate vaccine during the 4th year of life showed robust increases in ELISA antibody GMCs and OPA GMTs one month after the second dose of vaccine as compared to the pre-vaccination status. All subjects had pneumococcal antibody concentrations ≥0.2 μg/ml for each vaccine serotype except for serotypes 6B and 23F (both 93.3%). One month after the second dose of vaccine, all subjects had an OPA titre ≥8 for each vaccine serotype except for serotypes 1 (89.3%), 5 (98.2%) and 6B (93.0%). The results of study 046 are summarised in Tables 3 and 4.

For each of the pneumococcal serotypes, 2 doses resulted in higher GMCs and GMTs compared to a 3-dose primary vaccination course in infants (at 2, 3 and 4 months of age) in study-002. Also, the proportion of subjects reaching an antibody concentration ≥0.2 μg/ml or an OPA titre ≥8 was greater after 2 doses when compared to 3 doses in the first 6 months of life for all serotypes. Although this study was not designed to compare to the 3-dose primed group in the preceding study-002 and comparison should be done with caution, it is reassuring to observe that 2 doses in previously unvaccinated older children result in higher immune responses compared to the primary vaccination in infants.

Of note, the OPA GMTs 1 month after the second dose in the unprimed group were lower than 7 days after the first dose for serotypes 1, 4, 5, 7F, 9V, remained at the same levels for serotype 18C and 23F, and increased for serotypes 6B, 14 and 19F. In contrast, the IgG-specific antibody responses as measured by ELISA did not follow the same kinetics. This observation suggests that the OPA GMTs resulted from the combined opsonic activity of different immunoglobulin classes i.e. IgG, IgM or IgA. Early kinetics of these immunoglobulin classes upon PCV vaccination are poorly described in the literature, especially in paediatric populations. However, ELISA results available in toddlers, adults and elderly populations indicated that the observed immunoglobulin profile (IgG, IgM, IgA), magnitude of immune responses and the pneumococcal natural immunity may vary from serotype to serotype. Although the IgM and IgA composition of the samples was not investigated in study 046, a high level of IgM at 7 days post-vaccination could explain the observed OPA titre in absence of IgG while at 30 days post-vaccination the opsonisation would be mainly mediated by IgG. The different OPA kinetic profiles between serotypes might depend on pre-existing immunity which may have evolved differently over time. The lack of knowledge in the OPA kinetics during the course of the vaccination schedule makes it difficult to draw final conclusions on these observations.

One month after the second dose of vaccine, the observed percentage of subjects with measurable anti-PD antibody concentrations (≥100 EL.U/ml) was 98.3% and anti-PD GMC was 960.4 EL.U/ml (95% CI 752.7-1225.5). This was in the same range as the response after a 3-dose primary vaccination course in study-002, i.e. 100% with measurable anti-PD antibody concentrations and a GMC of 1223.3 EL. U/ml (95% CI 1066.5-1403.2).

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.

The results of study 046 indicate that 2 doses given to children 3-4 years of age result in immune responses that are higher than what was seen in children ≤ 6 months receiving the 3-dose priming schedule. Higher immune responses are expected among older children, as they are more likely to have some previous exposure to pneumococci. Thus, in conclusion, two doses should be given to children above 2 years of age for optimal immune responses.

Clinical safety

Methodology of safety monitoring

The evaluation of the safety of the catch-up vaccinations schedules included in both study 013 and study 046 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°C or axillary/oral/tympanic temperature ≥37.5°C; 3 fever was defined as rectal temperature >40.0°C or axillary/oral/tympanic temperature >39.5°C). 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. Large swelling reactions involving the entire vaccinated limb are a well-recognised phenomenon following booster vaccination with many vaccines including DTPa, DT, and DTPw vaccines from all manufacturers and with Prevenar. The cause of these large swelling reactions is not fully understood, they are however generally not associated with significant impairment of function, and resolve without sequelae. The occurrence of large swelling reactions was solicited following catch-up vaccination in both studies.

Solicited adverse events

Study 013

The age distribution of the subjects vaccinated in the ≥ 24 months - 5 years of age group in catch-up study 10PN-PD-DIT-013 is shown below. Of the 150 subjects vaccinated in this age group, 100 subjects were 2 years of age and in total 50 subjects were older than 2 years. Therefore the safety and immunogenicity analyses were done according to two subcategories; 2 year old subjects (24 - 35 months of age) (N=100) and subjects above 2 years of age (≥ 36 months of age) (N=50). The safety analysis included only the solicited AEs.

Number of subjects by age category for the ≥ 24 months of age group (Total vaccinated cohort)

	≥ 24Mo N = 150	
Age at vaccination	n	%
24 - 35 months	100	66.7
36 - 47 months	17	11.3
48 - 59 months	23	15.3
≥ 60 months	10	6.7

Source: Module 2, Section 2.7, page 12 Table 4

A trend towards a higher incidence of local solicited symptoms was reported in subjects who started catch-up immunization at an older age, but differences with the younger age group were not statistically significant. Due to the small sample size of the dataset, one cannot exclude a slight increase of local symptoms when administering the vaccine beyond 36 months of age. There was no evidence of imbalance between age groups when comparing the incidence of solicited general symptoms.

The solicited symptoms (local and general) following catch-up immunization, are shown in Table 5 and Table 6. 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 (60 % and 68.9%, respectively, for any reaction and 11.3% and 16.2% respectively, for grade 3 reactions) were previously documented for the licensed Prevenar vaccine.

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.
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, following no more than 2.4% of doses. There were no cases of fever > 40.0°C in any of the catch-up groups.

Table 5. Study 10PN-PD-DIT-013: Incidence of solicited local symptoms at the 10Pn-PD-DiT injection site during the 4-day follow up period after catch-up vaccination, overall doses (Total vaccinated cohort)

		7-11 months (two doses) N=295				7-11 months (third dose) N=145				12-23 months N=292				≥ 24 months N=148			
				95%CI				95%CI				95%CI				95%CI	
Symptom	Intensity	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Pain	Any	93	31.5	26.3	37.2	64	44.1	35.9	52.6	177	60.6	54.8	66.3	102	68.9	60.8	76.3
	Grade 3	5	1.7	0.6	3.9	3	2.1	0.4	5.9	33	11.3	7.9	15.5	24	16.2	10.7	23.2
Redness	Any	153	51.9	46	57.7	73	50.3	41.9	58.7	109	37.3	31.8	43.2	65	43.9	35.8	52.3
	> 20 mm	28	9.5	6.4	13.4	6	4.1	1.5	8.8	12	4.1	2.1	7.1	14	9.5	5.3	15.4
	>30 mm	13	4.4	2.4	7.4	5	3.4	1.1	7.9	5	1.7	0.6	4	9	6.1	2.8	11.2
Swelling	Any	87	29.5	24.3	35.1	45	31	23.6	39.2	77	26.4	21.4	31.8	32	21.6	15.3	29.1
	> 20 mm	28	9.5	6.4	13.4	10	6.9	3.4	12.3	20	6.8	4.2	10.4	10	6.8	3.3	12.1
	> 30 mm	16	5.4	3.1	8.7	7	4.8	2	9.7	13	4.5	2.4	7.5	7	4.7	1.9	9.5

7-11 months of age group received 10Pn-PD-DiT at 7-11, 8-12, 12-15 months of age
12-23 months of age group received 10Pn-PD-DiT at 12-23 and 14-25 months of age
≥ 24 months of age group received 10Pn-PD-DiT at 24 months - 5 years of age
N = number of documented doses; n/% = number/percentage of doses with at least one local symptom ; 95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit;
Grade 3 pain: cried when limb was moved/was spontaneously painful

Source: Module 2, Section 2.5, page 22 Table 6

Table 6. Study 10PN-PD-DIT-013: Incidence of solicited general symptoms following 10Pn-PD-DiT catch-up vaccination during the 4-day follow up period after vaccination, overall doses (Total vaccinated cohort)

		7-11 months (two doses) N = 295				7-11 months (third dose) N=145				12-23 months N = 292				≥ 24 months N = 148			
				95%CI				95%CI				95%CI				95%CI	
Symptom	Intensity	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Drowsiness	Any	121	41	35.3	46.9	57	39.3	31.3	47.8	111	38	32.4	43.9	55	37.2	29.4	45.5
	Grade 3	1	0.3	0	1.9	3	2.1	0.4	5.9	3	1	0.2	3	1	0.7	0	3.7
Irritability	Any	168	56.9	51.1	62.7	71	49	40.6	57.4	152	52.1	46.2	57.9	62	41.9	33.8	50.3
	Grade 3	5	1.7	0.6	3.9	3	2.1	0.4	5.9	7	2.4	1	4.9	2	1.4	0.2	4.8
Loss of appetite	Any	77	26.1	21.2	31.5	35	24.1	17.4	31.9	77	26.4	21.4	31.8	41	27.7	20.7	35.7
	Grade 3	0	0	0	1.2	3	2.1	0.4	5.9	4	1.4	0.4	3.5	0	0	0	2.5
Fever (rectal temperature)	≥38.0°C	68	23.1	18.4	28.3	33	22.8	16.2	30.5	54	18.5	14.2	23.4	10	6.8	3.3	12.1
	>39.0°C	4	1.4	0.4	3.4	8	5.5	2.4	10.6	6	2.1	0.8	4.4	1	0.7	0	3.7
	>40.0°C	0	0	0	1.2	0	0	0	2.5	0	0	0	1.3	0	0	0	2.5

7-11 months of age group received 10Pn-PD-DiT at 7-11, 8-12, 12-15 months of age
12-23 months of age group received 10Pn-PD-DiT at 12-23 and 14-25 months of age
≥ 24 months of age group received 10Pn-PD-DiT at 24 months - 5 years of age
N = number of documented doses; n/% = number/percentage of doses with at least one general symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Source: Module 2, Section 2.5, page 23 Table 7

Study 046

The incidences of solicited events (local and general) are presented in Table 7 and Table 8. Pain at injection site was the most frequently reported solicited local adverse event (72.6% dose 1, 51.6% dose 2 and 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 adverse events.
There was no increase in incidence of events with consecutive doses.

Table 7. Study 10PN-PD-DIT -046: Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period after each dose and overall doses (Total vaccinated cohort)

		Unprim				
					95 % CI	
Symptom	Type	N	n	%	LL	UL
Dose 1						
Pain	All	62	45	72.6	59.8	83.1
	Grade 3	62	5	8.1	2.7	17.8
Redness (mm)	All	62	36	58.1	44.8	70.5
	>20.0	62	14	22.6	12.9	35.0
	>30.0	62	12	19.4	10.4	31.4
Swelling (mm)	All	62	22	35.5	23.7	48.7
	>20.0	62	11	17.7	9.2	29.5
	>30.0	62	5	8.1	2.7	17.8
Dose 2						
Pain	All	62	32	51.6	38.6	64.5
	Grade 3	62	1	1.6	0.0	8.7
Redness (mm)	All	62	33	53.2	40.1	66.0
	>20.0	62	8	12.9	5.7	23.9
	>30.0	62	5	8.1	2.7	17.8
Swelling (mm)	All	62	22	35.5	23.7	48.7
	>20.0	62	6	9.7	3.6	19.9
	>30.0	62	4	6.5	1.8	15.7
Overall/dose						
Pain	All	124	77	62.1	52.9	70.7
	Grade 3	124	6	4.8	1.8	10.2
Redness (mm)	All	124	69	55.6	46.5	64.6
	>20.0	124	22	17.7	11.5	25.6
	>30.0	124	17	13.7	8.2	21.0
Swelling (mm)	All	124	44	35.5	27.1	44.6
	>20.0	124	17	13.7	8.2	21.0
	>30.0	124	9	7.3	3.4	13.3

Unprim = Unprimed / 2 doses of 10Pn-PD-DiT; For each dose: N= number of subjects with at least one documented dose; n/%= number/percentage of subjects reporting at least once the symptom.
For Overall/dose: N= number of documented doses n/%= number/percentage of doses followed by at least one type of symptom; 95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Table 8. Study 10PN-PD-DIT-046: Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period after each dose and overall doses (Total vaccinated cohort)

		Unprim				
					95 % CI	
Symptom	Type	N	n	%	LL	UL
Dose 1						
Drowsiness	All	62	11	17.7	9.2	29.5
	Grade 3	62	0	0.0	0.0	5.8
	Related	62	11	17.7	9.2	29.5
	Grade 3*Related	62	0	0.0	0.0	5.8
Fever (Rectal) (°C)	All	62	6	9.7	3.6	19.9
	>38.5	62	4	6.5	1.8	15.7
	>39.0	62	2	3.2	0.4	11.2
	>39.5	62	0	0.0	0.0	5.8
	>40.0	62	0	0.0	0.0	5.8
	Related	62	5	8.1	2.7	17.8
	>40.0*Related	62	0	0.0	0.0	5.8
Irritability	All	62	17	27.4	16.9	40.2
	Grade 3	62	0	0.0	0.0	5.8
	Related	62	17	27.4	16.9	40.2
	Grade 3*Related	62	0	0.0	0.0	5.8
Loss of appetite	All	62	5	8.1	2.7	17.8
	Grade 3	62	0	0.0	0.0	5.8
	Related	62	5	8.1	2.7	17.8
	Grade 3*Related	62	0	0.0	0.0	5.8
Dose 2						
Drowsiness	All	62	12	19.4	10.4	31.4
	Grade 3	62	0	0.0	0.0	5.8
	Related	62	12	19.4	10.4	31.4
	Grade 3*Related	62	0	0.0	0.0	5.8
Fever (Rectal) (°C)	All	62	2	3.2	0.4	11.2
	>38.5	62	0	0.0	0.0	5.8
	>39.0	62	0	0.0	0.0	5.8
	>39.5	62	0	0.0	0.0	5.8
	>40.0	62	0	0.0	0.0	5.8
	Related	62	2	3.2	0.4	11.2
	>40.0*Related	62	0	0.0	0.0	5.8
Irritability	All	62	10	16.1	8.0	27.7
	Grade 3	62	0	0.0	0.0	5.8
	Related	62	9	14.5	6.9	25.8
	Grade 3*Related	62	0	0.0	0.0	5.8
Loss of appetite	All	62	10	16.1	8.0	27.7
	Grade 3	62	0	0.0	0.0	5.8
	Related	62	10	16.1	8.0	27.7
	Grade 3*Related	62	0	0.0	0.0	5.8

Table 8: Study 10PN-PD-DIT-046: Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period after each dose and overall doses (Total vaccinated cohort) –cont.

		Unprim				
					95 % CI	
Symptom	Type	N	n	%	LL	UL
Overall/dose						
Drowsiness	All	124	23	18.5	12.1	26.5
	Grade 3	124	0	0.0	0.0	2.9
	Related	124	23	18.5	12.1	26.5
	Grade 3*Related	124	0	0.0	0.0	2.9
Fever(Rectal) (°C)	All	124	8	6.5	2.8	12.3
	>38.5	124	4	3.2	0.9	8.1
	>39.0	124	2	1.6	0.2	5.7
	>39.5	124	0	0.0	0.0	2.9
	>40.0	124	0	0.0	0.0	2.9
	Related	124	7	5.6	2.3	11.3
	>40.0*Related	124	0	0.0	0.0	2.9
Irritability	All	124	27	21.8	14.9	30.1
	Grade 3	124	0	0.0	0.0	2.9
	Related	124	26	21.0	14.2	29.2
	Grade 3*Related	124	0	0.0	0.0	2.9
Loss of appetite	All	124	15	12.1	6.9	19.2
	Grade 3	124	0	0.0	0.0	2.9
	Related	124	15	12.1	6.9	19.2
	Grade 3*Related	124	0	0.0	0.0	2.9

Unprim = Unprimed / 2 doses of 10Pn-PD-DiT
For each dose: N= number of subjects with at least one documented dose; n/%= number/percentage of subjects reporting at least once the symptom
For Overall/dose: N= number of documented doses; n/%= number/percentage of doses followed by at least one type of symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Unsolicited adverse events

Study 013

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 (Table 9). The most common unsolicited adverse event considered to be causally related to vaccination was injection site induration in the two groups receiving two 10Pn-PD-DiT doses. In the ≥24 months of age group, the most common related adverse event was headache (2.0%).

Table 9. Study 10PN-PD-DIT-013: Percentage of doses followed by unsolicited adverse events within the 31-day (Days 0-30) follow-up period after catch-up vaccination (Total vaccinated cohort)

	7-11 months (two doses) N=297				7-11 months (third dose) N=145				12-23 months N=295				≥ 24 months N=150			
			95%CI				95%CI				95%CI				95%CI	
Doses followed by	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Any unsolicited AEs	168	56.6	50.7	62.3	63	43.4	35.2	51.9	141	47.8	42	53.7	54	36	28.3	44.2
Vaccine related unsolicited AEs	43	14.5	10.7	19	11	7.6	3.8	13.2	36	12.2	8.7	16.5	17	11.3	6.7	17.5
Grade 3 unsolicited AEs	19	6.4	3.9	9.8	8	5.5	2.4	10.6	26	8.8	5.8	12.6	2	1.3	0.2	4.7

7-11 months of age group received 10Pn-PD-DiT at 7-11, 8-12, 12-15 months of age
12-23 months of age group received 10Pn-PD-DiT at 12-23 and 14-25 months of age
≥ 24 months of age group received 10Pn-PD-DiT at 24 months - 5 years of age
At least one AE = at least one adverse event experienced
N = number of administered doses; n/% = number/percentage of doses with reported unsolicited AEs
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Study 046

Study population
The number of subjects included in the analyses of study 046 is summarised in the table below.

Number of subjects	Total	10Pn-2d	10Pn-3d	unprimed
Number of subjects planned	210	70	70	70
Number of subjects enrolled	172	51	59	62
Number of subjects completed	171	51	58	62
Total vaccinated cohort	172	51	59	62
According to Protocol (ATP) for safety/persistence	172	51	59	62
According to Protocol (ATP) for immunogenicity	167	51	57	60

The mean age in the unprimed group was 40.3 months (38 months in the other two groups) and the range was 36-45 months.

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 adverse events considered to be causally related to vaccination were nausea, vomiting, injection site hematoma, pyrexia and rhinitis (all reported after 1.6% of the doses).

Table 10. Study 10PN-PD-DIT-046: Percentage of doses followed by unsolicited adverse events within the 31-day (Days 0-30) follow-up period after catch-up vaccination (Total vaccinated cohort)

Doses followed by	Unprim N = 124			
	n	%	95%CI	
			LL	UL
Any unsolicited adverse events	50	40.3	31.6	49.5
Vaccine related unsolicited adverse events	10	8.1	3.9	14.3
Grade 3 unsolicited adverse events	6	4.8	1.8	10.2

Unprim = Unprimed / 2 doses of 10Pn-PD-DiT
At least one AE = at least one adverse event experienced
N = number of administered doses; n/% = number/percentage of doses with reported unsolicited AEs
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Serious adverse events

Study 013

In study 10PN-PD-DIT-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 (data lock point 15 June 2008). None of the subjects reported a causally related SAE or an SAE with a fatal outcome.

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.

Following assessment of the submitted documentation, some concerns were raised. The major objection concerned the limited data in children above 4 years of age.

Additional supporting safety data

Study 10PN-PD-DIT-070 is a double-blind, randomized controlled trial conducted in Kenya. This study is a GSK-supported conducted at the Kenya Medical Research Institute (KEMRI). The main objectives of the study are to determine the immunogenicity and reactogenicity of 1 or 2 doses of Synflorix in children aged 12-59 months and to determine the effect of vaccination on the carriage prevalence of Synflorix types. A total of 600 children aged 12-59 months were enrolled in three study groups as follows:

Vaccination schedule

	Group A	Group B	Group C
	N=200	N=200	N=200
Day 0	Synflorix	Synflorix	Havrix[1]
Day 60	Synflorix	Infanrix[2]	Infanrix
Day 180	Infanrix[2]	Synflorix	Havrix[1] + Synflorix

[1]Havrix: GSK's Hepatitis A vaccine
[2]Infanrix: GSK's DTPa vaccine

This study provided safety data from 600 children aged 12-59 months exposed to two doses of Synflorix.
The occurrence of solicited local and general symptoms reported within 3 days after vaccination has been calculated across age groups (12-23 months; 24-35 months; 36-47 months; 48-59 months).

Table 11 and Table 12 summarise the reactogenicity data following the first dose of Synflorix (pooled Groups A+B: N ~100 per age group) or control vaccine Havrix (Group C: N ~50 per age group), respectively. The occurrences of solicited symptoms were comparable between Synflorix and the control vaccine in all age groups. Most importantly, no increase of occurrence of solicited symptoms was observed in children aged 48 months and above as compared to younger children for either Synflorix or control vaccine. There were no reports of grade 3 solicited local and general symptoms across all age groups, except grade 3 drowsiness which was documented in one child after the first dose of Synflorix.
The occurrences of solicited symptoms across all age groups and overall after a second dose of Synflorix (Group A: N ~ 50) or after control vaccine Infanrix at Day 60 (pooled Groups B+C: N ~100) are shown in Table 4 and Table 5, respectively. Similar to the reporting of solicited symptoms observed after the first dose of Synflorix, there was no trend towards higher reactogenicity with increasing age after the second dose of Synflorix. The occurrences of solicited symptoms following a second dose of Synflorix and following the control vaccine Infanrix at day 60 were comparable.

The results from Table 11 and Table 13 show that the reactogenicity profile for solicited local and general symptoms following one dose of Synflorix was generally higher than that following the second dose of Synflorix across all age groups. Serious adverse events (SAEs) were documented in 6 of 400 children (1.5%) in the groups receiving at least one dose of Synflorix (groups A+B) and 1 of 200 children (0.5%) in the control group C. All SAEs were considered to be unrelated to vaccination.

It is acknowledged that the safety profile of Synflorix in European population may differ from that obtained in the Kenyan population due to ethnic factors, clinical settings or health conditions in Africa. However, the data are reassuring in that the reactogenicity profile for the subjects in the 48-59 months age group was not higher than in the other age groups, either following one dose or two doses of Synflorix. In addition, the reactogenicity profile in the 48-59 months age group following two doses

of Synflorix tended to be lower than that following one dose of Synflorix. Finally the reporting of solicited local and general symptoms following vaccination with Synflorix was similar to that following the control vaccines (Havrix and Infanrix).

Table 11. Occurrence of side effects with Synflorix within 3 days following dose 1 (pooled Group A and Group B)

	Group A + Group B: Synflorix																			
	All ages				12-23 months				24-35 months				36-47 months				48-59 months			
N	400				94				104				101				101			
Side effect	n	%	LL 95%CI	UL 95%CI	n	%	LL 95%CI	UL 95%CI	n	%	LL 95%CI	UL 95%CI	n	%	LL 95%CI	UL 95%CI	n	%	LL 95%CI	UL 95%CI
Swelling grade 3	0	0.0	0.0	0.9	0	0.0	0.0	3.8	0	0.0	0.0	3.5	0	0.0	0.0	3.6	0	0.0	0.0	3.6
Swelling any	198	49.5	44.5	54.5	49	52.1	41.6	62.5	51	49.0	39.1	59.0	55	54.5	44.2	64.4	43	42.6	32.8	52.8
Redness grade 3	0	0.0	0.0	0.9	0	0.0	0.0	3.8	0	0.0	0.0	3.5	0	0.0	0.0	3.6	0	0.0	0.0	3.6
Redness any	44	11.0	8.1	14.5	12	12.8	6.8	21.2	9	8.7	4.0	15.8	15	14.9	8.6	23.3	8	7.9	3.5	15.0
Pain grade 3	0	0.0	0.0	0.9	0	0.0	0.0	3.8	0	0.0	0.0	3.5	0	0.0	0.0	3.6	0	0.0	0.0	3.6
Pain any	338	84.5	80.6	87.9	86	91.5	83.9	96.3	91	87.5	79.6	93.2	84	83.2	74.4	89.9	77	76.2	66.7	84.1
Any local reaction	347	86.8	83.0	89.9	89	94.7	88.0	98.3	92	88.5	80.7	93.9	87	86.1	77.8	92.2	79	78.2	68.9	85.8
Irritability grade 3	0	0.0	0.0	0.9	0	0.0	0.0	3.8	0	0.0	0.0	3.5	0	0.0	0.0	3.6	0	0.0	0.0	3.6
Irritability any	264	66.0	61.1	70.6	76	80.9	71.4	88.2	75	72.1	62.5	80.5	62	61.4	51.2	70.9	51	50.5	40.4	60.6
Drowsiness grade 3	1	0.3	0.0	1.4	1	1.1	0.0	5.8	0	0.0	0.0	3.5	0	0.0	0.0	3.6	0	0.0	0.0	3.6
Drowsiness any	30	7.5	5.1	10.5	10	10.6	5.2	18.7	10	9.6	4.7	17.0	5	5.0	1.6	11.2	5	5.0	1.6	11.2
Temp ≥ 39.0°	0	0.0	0.0	0.9	0	0.0	0.0	3.8	0	0.0	0.0	3.5	0	0.0	0.0	3.6	0	0.0	0.0	3.6
Fever any	163	40.8	35.9	45.7	44	46.8	36.4	57.4	41	39.4	30.0	49.5	35	34.7	25.5	44.8	43	42.6	32.8	52.8
Any systemic reaction	322	80.5	76.3	84.3	84	89.4	81.3	94.8	90	86.5	78.4	92.4	77	76.2	66.7	84.1	71	70.3	60.4	79.0

Table 12. Occurrence of side effects with Havrix with 3 days following dose 1 (Group C)

	Group C: Havrix																			
	All ages				12-23 months				24-35 months				36-47 months				48-59 months			
N	200				48				48				51				53			
Side effect	n	%	LL 95%CI	UL 95%CI	n	%	LL 95%CI	UL 95%CI	n	%	LL 95%CI	UL 95%CI	n	%	LL 95%CI	UL 95%CI	n	%	LL 95%CI	UL 95%CI
Swelling grade 3	0	0.0	0.0	1.8	0	0.0	0.0	7.4	0	0.0	0.0	7.4	0	0.0	0.0	7.0	0	0.0	0.0	6.7
Swelling any	87	43.5	36.5	50.7	21	43.8	29.5	58.8	16	33.3	20.4	48.4	24	47.1	32.9	61.5	26	49.1	35.1	63.2
Redness grade 3	0	0.0	0.0	1.8	0	0.0	0.0	7.4	0	0.0	0.0	7.4	0	0.0	0.0	7.0	0	0.0	0.0	6.7
Redness any	16	8.0	4.6	12.7	3	6.3	1.3	17.2	3	6.3	1.3	17.2	4	7.8	2.2	18.9	6	11.3	4.3	23.0
Pain grade 3	0	0.0	0.0	1.8	0	0.0	0.0	7.4	0	0.0	0.0	7.4	0	0.0	0.0	7.0	0	0.0	0.0	6.7
Pain any	157	78.5	72.2	84.0	41	85.4	72.2	93.9	37	77.1	62.7	88.0	39	76.5	62.5	87.2	40	75.5	61.7	86.2
Any local reaction	166	83.0	77.1	87.9	42	87.5	74.8	95.3	39	81.3	67.4	91.1	41	80.4	66.9	90.2	44	83.0	70.2	91.9
Irritability grade 3	0	0.0	0.0	1.8	0	0.0	0.0	7.4	0	0.0	0.0	7.4	0	0.0	0.0	7.0	0	0.0	0.0	6.7
Irritability any	131	65.5	58.5	72.1	38	79.2	65.0	89.5	33	68.8	53.7	81.3	30	58.8	44.2	72.4	30	56.6	42.3	70.2
Drowsiness grade 3	0	0.0	0.0	1.8	0	0.0	0.0	7.4	0	0.0	0.0	7.4	0	0.0	0.0	7.0	0	0.0	0.0	6.7
Drowsiness any	12	6.0	3.1	10.2	4	8.3	2.3	20.0	3	6.3	1.3	17.2	4	7.8	2.2	18.9	1	1.9	0.0	10.1
Temp ≥ 39.0°	1	0.5	0.0	2.8	1	2.1	0.1	11.1	0	0.0	0.0	7.4	0	0.0	0.0	7.0	0	0.0	0.0	6.7
Fever any	52	26.0	20.1	32.7	15	31.3	18.7	46.3	15	31.3	18.7	46.3	11	21.6	11.3	35.3	11	20.8	10.8	34.1
Any systemic reaction	145	72.5	65.8	78.6	41	85.4	72.2	93.9	38	79.2	65.0	89.5	32	62.7	48.1	75.9	34	64.2	49.8	76.9

Table 13. Occurrence of side effects with Synflorix with 3 days following dose 2 (Group A)

	Group A: PCV																			
	All ages				12-23 months				24-35 months				36-47 months				48-59 months			
N	197				46				49				50				52			
Side effect	n	%	LL 95%CI	UL 95%CI	n	%	LL 95%CI	UL 95%CI	n	%	LL 95%CI	UL 95%CI	n	%	LL 95%CI	UL 95%CI	n	%	LL 95%CI	UL 95%CI
Swelling grade 3	0	0.0	0.0	1.9	0	0.0	0.0	7.7	0	0.0	0.0	7.3	0	0.0	0.0	7.1	0	0.0	0.0	6.8
Swelling any	35	17.8	12.7	23.8	7	15.2	6.3	28.9	7	14.3	5.9	27.2	11	22.0	11.5	36.0	10	19.2	9.6	32.5
Redness grade 3	0	0.0	0.0	1.9	0	0.0	0.0	7.7	0	0.0	0.0	7.3	0	0.0	0.0	7.1	0	0.0	0.0	6.8
Redness any	1	0.5	0.0	2.8	1	2.2	0.1	11.5	0	0.0	0.0	7.3	0	0.0	0.0	7.1	0	0.0	0.0	6.8
Pain grade 3	0	0.0	0.0	1.9	0	0.0	0.0	7.7	0	0.0	0.0	7.3	0	0.0	0.0	7.1	0	0.0	0.0	6.8
Pain any	80	40.6	33.7	47.8	21	45.7	30.9	61.0	22	44.9	30.7	59.8	21	42.0	28.2	56.8	16	30.8	18.7	45.1
Any local reaction	95	48.2	41.1	55.4	22	47.8	32.9	63.1	26	53.1	38.3	67.5	26	52.0	37.4	66.3	21	40.4	27.0	54.9
Irritability grade 3	0	0.0	0.0	1.9	0	0.0	0.0	7.7	0	0.0	0.0	7.3	0	0.0	0.0	7.1	0	0.0	0.0	6.8
Irritability any	26	13.2	8.8	18.7	12	26.1	14.3	41.1	8	16.3	7.3	29.7	4	8.0	2.2	19.2	2	3.8	0.5	13.2
Drowsiness grade 3	0	0.0	0.0	1.9	0	0.0	0.0	7.7	0	0.0	0.0	7.3	0	0.0	0.0	7.1	0	0.0	0.0	6.8
Drowsiness any	2	1.0	0.1	3.6	0	0.0	0.0	7.7	2	4.1	0.5	14.0	0	0.0	0.0	7.1	0	0.0	0.0	6.8
Temp ≥ 39.0°	0	0.0	0.0	1.9	0	0.0	0.0	7.7	0	0.0	0.0	7.3	0	0.0	0.0	7.1	0	0.0	0.0	6.8
Fever any	53	26.9	20.8	33.7	13	28.3	16.0	43.5	14	28.6	16.6	43.3	12	24.0	13.1	38.2	14	26.9	15.6	41.0
Any systemic reaction	72	36.5	29.8	43.7	22	47.8	32.9	63.1	19	38.8	25.2	53.8	15	30.0	17.9	44.6	16	30.8	18.7	45.1

Table 14. Occurrence of side effects with Infanrix with 3 days following dose 2 (pooled Group B and Group C)

	Group B + Group C: Infanrix																			
	All ages				12-23 months				24-35 months				36-47 months				48-59 months			
N	390				93				99				97				101			
Side effect	n	%	LL 95%CI	UL 95%CI	n	%	LL 95%CI	UL 95%CI	n	%	LL 95%CI	UL 95%CI	n	%	LL 95%CI	UL 95%CI	n	%	LL 95%CI	UL 95%CI
Swelling grade 3	0	0.0	0.0	0.9	0	0.0	0.0	3.9	0	0.0	0.0	3.7	0	0.0	0.0	3.7	0	0.0	0.0	3.6
Swelling any	70	17.9	14.3	22.1	10	10.8	5.3	18.9	20	20.2	12.8	29.5	20	20.6	13.1	30.0	20	19.8	12.5	28.9
Redness grade 3	0	0.0	0.0	0.9	0	0.0	0.0	3.9	0	0.0	0.0	3.7	0	0.0	0.0	3.7	0	0.0	0.0	3.6
Redness any	2	0.5	0.1	1.8	1	1.1	0.0	5.8	0	0.0	0.0	3.7	0	0.0	0.0	3.7	1	1.0	0.0	5.4
Pain grade 3	0	0.0	0.0	0.9	0	0.0	0.0	3.9	0	0.0	0.0	3.7	0	0.0	0.0	3.7	0	0.0	0.0	3.6
Pain any	140	35.9	31.1	40.9	37	39.8	29.8	50.5	36	36.4	26.9	46.6	34	35.1	25.6	45.4	33	32.7	23.7	42.7
Any local reaction	172	44.1	39.1	49.2	40	43.0	32.8	53.7	46	46.5	36.4	56.8	44	45.4	35.2	55.8	42	41.6	31.9	51.8
Irritability grade 3	0	0.0	0.0	0.9	0	0.0	0.0	3.9	0	0.0	0.0	3.7	0	0.0	0.0	3.7	0	0.0	0.0	3.6
Irritability any	38	9.7	7.0	13.1	21	22.6	14.6	32.4	10	10.1	5.0	17.8	5	5.2	1.7	11.6	2	2.0	0.2	7.0
Drowsiness grade 3	0	0.0	0.0	0.9	0	0.0	0.0	3.9	0	0.0	0.0	3.7	0	0.0	0.0	3.7	0	0.0	0.0	3.6
Drowsiness any	5	1.3	0.4	3.0	3	3.2	0.7	9.1	0	0.0	0.0	3.7	1	1.0	0.0	5.6	1	1.0	0.0	5.4
Temp ≥ 39.0°	1	0.3	0.0	1.4	0	0.0	0.0	3.9	1	1.0	0.0	5.5	0	0.0	0.0	3.7	0	0.0	0.0	3.6
Fever any	115	29.5	25.0	34.3	24	25.8	17.3	35.9	38	38.4	28.8	48.7	25	25.8	17.4	35.7	28	27.7	19.3	37.5
Any systemic reaction	148	37.9	33.1	43.0	44	47.3	36.9	57.9	45	45.5	35.4	55.8	29	29.9	21.0	40.0	30	29.7	21.0	39.6

Supportive data from studies conducted in Europe

The safety and reactogenicity data of a single dose of Synflorix in children 24-71 months of age in study 10PN-PD-DIT-013 and two doses in children 36-45 months of age in study 10PN-PD-DIT-046 was previously submitted and assessed. Synflorix was well tolerated in both studies. There was no increase of local and general symptoms with increasing age, except for injection site pain of any severity in study 013, which was higher in the ≥24 months age group (68.9%) than in the 12-23 months and 7-11 months age groups (60.6% and 44.1%, respectively).

A new analysis of study 013 has been performed to determine if this trend towards higher injection site pain with age is observed in the 48-59 months age group and the 60-71 months age group. The results indicated that the occurrences of local adverse events of any severity and grade 3 by age group are generally similar in the 36-47 months, 48-59 months and 60-71 months age groups.

With regards to the solicited general symptoms, higher incidences were not observed in children in of 48-59 months of age and 60-71 months of age in study 013 with the exception of fever of any severity in the 60-71 months of age group (22%). No grade 3 cases of fever, drowsiness, irritability and loss of appetite were reported in children of 48-59 months of age and 60-71 months of age.

In addition to this new analysis, the solicited local and general symptoms after one dose of Synflorix in children of 46-48 months of age from study 10PN-PD-DIT-061 are also presented. Study 10PN-PD-DIT-061 is a phase III, open, multicentre, extension study in Germany to assess the immune response following administration of an additional dose of Synflorix or Prevenar at approximately 4 years of age in children previously vaccinated with three primary doses of a pneumococcal conjugate vaccine in study 10PNPD- DIT-003 and a booster dose of 23-valent pneumococcal plain polysaccharide vaccine in study 10PN-PD-DIT-008 BST: 003. In total, 52 subjects were enrolled in study 061, of which 27 subjects received one dose of Synflorix and 25 subjects received one dose of Prevenar. The percentages of subjects reporting any adverse event (solicited and unsolicited, local and general) within the 31-day post-additional dose period were 80.8% in the Synflorix group and 72.0% in the Prevenar group. The percentages of subjects reporting at least one unsolicited adverse event in the 31-day post-additional dose period were 22.2% in the Synflorix group and 32.0% in the Prevenar group. No grade 3 unsolicited adverse events were reported within the 31-day post-additional dose period. No serious adverse events were reported and none of the subjects was withdrawn due to an adverse event.

In study 061, the reporting of solicited local and general symptoms (Table 15 and Table 16 respectively) were generally similar to the reporting in study 013 for the similar age groups (i.e. 36-47 months of age and 48-59 months of age) except for higher fever of any severity in study 061 (26.9% of subjects versus 0% and 4.3% in the 36-47 months of age and 48-59 months of age groups in study 013 respectively).

Table 15. Study 061: Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-additional dose period (Total vaccinated cohort)

		46-48 months				
					95 % CI	
Symptom	Type	N	n	%	LL	UL
Pain	All	26	16	**61.5**	40.6	79.8
	Grade 3	26	2	**7.7**	0.9	25.1
Redness (mm)	All	26	14	**53.8**	33.4	73.4
	>20mm	26	4	**15.4**	4.4	34.9
	>30mm	26	3	**11.5**	2.4	30.2
Swelling (mm)	All	26	9	**34.6**	17.2	55.7
	>20mm	26	5	**19.2**	6.6	39.4
	>30mm	26	1	**3.8**	0.1	19.6

46-48 months = Subjects receiving an additional dose of 10Pn-PD-DiT vaccine at approximately 4 years of age
N= number of subjects with the documented dose
n/%= number/percentage of subjects reporting at least once the symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Table 16. Study 061: Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-additional dose period (Total vaccinated cohort)

		46-48 months				
					95 % CI	
Symptom	Type	N	n	%	LL	UL
Drowsiness	All	26	11	42.3	23.4	63.1
	Grade 3	26	1	3.8	0.1	19.6
	Related	26	8	30.8	14.3	51.8
	Grade 3 & Related	26	0	0.0	0.0	13.2
Fever (Rectally) (°C)	All	26	7	26.9	11.6	47.8
	>38.5°C	26	1	3.8	0.1	19.6
	>39.0°C	26	0	0.0	0.0	13.2
	>39.5°C	26	0	0.0	0.0	13.2
	>40.0°C	26	0	0.0	0.0	13.2
	Related	26	6	23.1	9.0	43.6
	>40.0°C & Related	26	0	0.0	0.0	13.2
Irritability	All	26	9	34.6	17.2	55.7
	Grade 3	26	1	3.8	0.1	19.6
	Related	26	7	26.9	11.6	47.8
	Grade 3 & Related	26	0	0.0	0.0	13.2
Loss of appetite	All	26	11	42.3	23.4	63.1
	Grade 3	26	2	7.7	0.9	25.1
	Related	26	7	26.9	11.6	47.8
	Grade 3 & Related	26	1	3.8	0.1	19.6

46-48 months = Subjects receiving an additional dose of 10Pn-PD-DiT vaccine at approximately 4 years of age
N= number of subjects with the documented dose
n/%= number/percentage of subjects reporting at least once the symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

As noted previously, there was no increase of occurrence of solicited local and general symptoms with consecutive vaccine doses in study 046.

Worldwide marketing experience

There were 41 spontaneous reports when Synflorix was used in subjects older than 2 years of age (data lock point 10 June 2010). Out of the 41 reports, there were 21 cases concerning children between 2 and 6 years of age. The Company 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. Since launch up to 10 December 2010, 379 spontaneous cases were reported after Synflorix vaccination. Of these 379 cases, 28 occurred in subjects who were aged from 2 to 5 years old at the time they received Synflorix vaccination. Data presented within these 28 cases did not highlight any particular safety concern regarding cases reported in children aged from 2 to 5 years old.

Discussion on clinical safety

The safety and reactogenicity of a single dose of Synflorix has been documented in 206 children 36 to 48 months of age (studies 013, 046, 061 and 070), 124 children of 48 to 59 months of age (studies 013 and 070) and 9 subjects of 60 to 71 months of age (study 013). Reporting of adverse events following a second dose of Synflorix was studied in 62 subjects of 36 to 45 months of age in study 046 and 52 children of 48 to 59 months of age in study 070. It should be noted that the number of children of 3 to 4 years of age (36 months to 59 months) in these studies are similar to that the number of children found in for PCV13 indication in children 2-5 years of age (N=152 in PCV13 study 3002) (EPAR, 2009).

A further analysis by age of the data from study 013 in children of 24 to 71 months of age showed that local and general solicited symptoms were similar in children of 36 to 47 months of age, 48-59 months of age and 60 to 71 months of age, except for fever of any severity in the 61 to 71 months of age group. Study 061 provided additional data in children of 46 to 48 months of age with reporting of local and general solicited symptoms generally similar to the reporting in study 013 for the age groups 36 to 47 months of age and 48 to 59 months of age.

The recently available data from study 070 in Kenya indicate that Synflorix was well tolerated in children of 12 to 59 months of age and are of special interest as they provide safety and reactogenicity data for children of 48 to 59 months of age following one or two doses of Synflorix. The reporting of solicited symptoms for oldest age group in the study (48 to 59 months of age) was similar to the other age groups that received Synflorix and also similar to that in children of 48 to 59 months of age receiving control vaccine Havrix (except for higher number of children reporting fever in the Synflorix group) or control vaccine Infanrix.

Following the first round of assessment, some concerns were raised. The major objection concerned the limited data in children above 4 years of age. This concern was satisfactorily resolved upon the assessment of additional supporting safety data.
Furthermore, a new analysis of safety data from previous studies conducted in Europe provided additional evidence that there are no trends towards higher reactogenicity in children above 48 months of age receiving one or two doses of Synflorix.

In conclusion, one dose of Synflorix has been shown to be well tolerated in children of 2 up to 5 years of age in studies 013 and 061 with similar reporting of solicited symptoms in the older children of 3 up to 5 years of age and, in study 046, there was no increase in reporting of solicited symptoms following a second dose of Synflorix in children of 3 years of age. A review of the available post-marketing surveillance safety data did not reveal any safety concerns in children of 2 to 5 years of age. The data from Kenya can support the conclusions reached for the safety and tolerability of two doses of Synflorix when administered to children from 2 up to 5 years of age (i.e. up to 59 months of age).

The evidence presented supports the safety and tolerability of two doses of Synflorix in children of 2 up to 5 years of age and supports the changes to the SmPC to increase the upper age limit to 5 years of age and the inclusion of immunogenicity data and new safety data.

Overall Conclusion and Benefit-Risk assessment

Benefits

Beneficial effects

Two doses of Synflorix were shown to elicit immune responses in children aged 3-4 years old in study 046, which are at least of the same magnitude as the responses to the approved 3+1 and 2+1 primary vaccination schedule in infants.

Uncertainty in the knowledge about the beneficial effects

There are limited data in children 48-60 months of age, and there are no data on children in this age group receiving two doses. The immune responses after two doses in children 3-4 years of age were lower than those seen in children of the same age who had received a priming course of 3+1 or 2+1 doses and a booster dose at 36-46 months of age. The implication of this lower response on long-term immunity is currently unknown. The lack of immunogenicity data following 2 doses in children >4 and

<6 years of age are of some concern, but it is likely that immune responses in 2-4 year old children are also representative of children 4-5 years of age.

Risks

Unfavourable effects

The reactogenicity is generally similar to what has been shown previously in younger children. However, the frequency of pain at the injection site was shown to increase with increasing age in study 013.

Uncertainty in the knowledge about the unfavourable effects

There are no data on children 48-60 years of age receiving two doses. Considering the observed increased frequency of pain at the injection site in study 013, there is a need for more data on the risks. The MAH provided additional analysis from study 013 for age groups 24-35 months, 36-47 months, 48-59 months and 60-71 months, which do not indicate a clear increase in reactogenicity with increasing age, although the age segments are small, e.g. the 60-71 month group only includes 9 individuals. In addition, a Kenyan study in children 12-59 months of age do not support increased reactogenicity with increasing age. However, data in the oldest children, i.e. 48-60 months of age receiving two doses are scarce, and the MAH is requested to closely monitor adverse reactions in children 2-5 years and report in upcoming PSURs.

Balance

Importance of favourable and unfavourable effects

The incidence of pneumococcal infection is greatest among children below 5 years of age, and therefore there is a need to vaccinate this age group. The lack of immunogenicity data following 2 doses in children older than 4 years of age is a deficiency, but it is likely that the results from the younger children can be extrapolated to the older children. The lack of safety data in the initial dossier was identified by CHMP as a major objection, mainly due to the observed increase in frequency of injection site pain with increasing age. However, in response to the major objection raised, the MAH has presented additional data that do not support an overall increase in reactogenicity by increasing age.

Benefit-risk balance

The incidence of disease caused by *S. pneumoniae* is highest in children up to 5 years of age, thus there is a need to vaccinate children up to 5 years of age. The results of study 013 indicated that a single dose given to children over 2 years of age did not result in sufficient immune responses. In study 046, it was shown that 2 doses given to children 3-4 years of age resulted in immune responses that were at least comparable to the responses seen in younger children following primary immunisation. It is considered that the immunogenicity data from the 3-4 year old children can be extrapolated to children up to 5 years of age.
There was an increase in the incidence of pain at the injection site with increasing age in study 013, but no increase in systemic reactions. These data were not supported by a Kenyan study 070, which did not support increased reactogenicity with increasing age and by further analysis of the 013 data by age group. Thus, there is no specific safety concern with increasing age, and the safety data from younger children can be extrapolated to children up to 5 years of age.

Thus, the benefit of vaccinating children up to 5 years of age is considered to outweigh the risks of vaccination.

As the overall safety database in children 2-5 years of age is very limited, the CHMP recommended performing an active safety surveillance, and closely monitoring vaccine safety in this age group. All serious listed and unlisted adverse events should be continuously reported and accordingly be presented cumulatively in future PSURs.

Changes to the Product Information

The changes to the Product Information include updating the indication Section 4.1 to increase the upper age limit of infants and children from 2 years to 5 years and updating all relevant sections of the Summary of Product Characteristics (SmPC), i.e. 4.1, 4.2, 4.8 and 5.1 and Package Leaflet.

Amend the version number of the RMP mentioned in Annex II in order to reflect the latest approved RMP version 5.0.

The CHMP agreed with the changes to the Product Information. The SmPC has been modified as indicated in Annex 1.

Outcome

Based on the CHMP review of data on safety and efficacy, the CHMP considers that the benefit risk balance of Synflorix for active immunisation against invasive disease and acute otitis media caused by *Streptococcus pneumoniae* in infants in children 2-5 years is considered acceptable. The MAH took the opportunity to amend the version number of the RMP mentioned in Annex II in order to reflect the latest approved RMP version 5.0.

The CHMP recommends performing an active safety surveillance and closely monitoring vaccine safety in this age group. All serious listed and unlisted adverse events should be continuously reported and accordingly be presented cumulatively in future PSURs.

The CHMP is of the opinion that study 10PN-PD-DIT-046 EXT: 002, which is contained in the agreed Paediatric Investigation Plan and has been completed after 26 January 2007, is considered significant.

2. Conclusion

On 23 June 2011 the CHMP considered this Type II variation to be approvable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet:

Variation requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Furthermore, the CHMP reviewed the available paediatric data subject to the agreed Paediatric Investigation Plan and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate the Package Leaflet.

In accordance with Article 45(3) of Regulation EC(No)1901/2006 as amended, significant studies in the agreed paediatric investigation plan have been completed after the entry into force of that Regulation

Follow-up measures undertaken by the marketing authorisation holder

As requested by the CHMP, the MAH agreed to perform an active safety surveillance, and closely monitoring vaccine safety in this age group. All serious listed and unlisted adverse events will be continuously reported and accordingly be presented cumulatively in future PSURs.