24 October 2013
EMA/73592/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Synflorix

International non-proprietary name: PNEUMOCOCCAL POLYSACCHARIDE CONJUGATE VACCINE (ADSORBED)

Procedure No. EMEA/H/C/000973/II/0052

Note

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

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1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline Biologicals submitted to the European Medicines Agency on 14 September 2012 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**Common name:**	**Presentations:**
Synflorix	PNEUMOCOCCAL POLYSACCHARIDE CONJUGATE VACCINE (ADSORBED)	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.1.6 a)	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for a an extension of the indication for the prevention of pneumonia caused by *Streptococcus pneumoniae* in infants and children from 6 weeks up to 5 years of age. Consequently, the MAH proposed the update of sections 4.1, 4.4 and 5.1 of the Summary of Product Characteristics.

The Package Leaflet was proposed to be updated in accordance.

The variation proposed amendments to the SmPC and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision [P/0162/2012] on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP [P/0162/2012] was not yet completed as some measures were deferred.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Pieter Neels

Submission date:	14 September 2012
Start of procedure:	19 October 2012
Rapporteur's preliminary assessment report circulated on:	12 December 2012
Co-Rapporteur's preliminary assessment report circulated on:	16 December 2012
Joint Rapporteur's updated assessment report circulated on:	11 January 2013

Request for supplementary information and extension of timetable adopted by the CHMP on:	17 January 2013
MAH's responses submitted to the CHMP on:	23 May 2013
Joint Rapporteur's preliminary assessment report on the MAH's responses circulated on:	11 June 2013
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	20 June 2013
Further Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	25 June 2013
Joint Rapporteur's updated assessment report following CHMP discussion circulated on:	27 June 2013
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	27 June 2013
MAH's responses submitted to the CHMP on:	22 August 2013
Joint Rapporteur's preliminary assessment report on the MAH's responses circulated on:	18 October 2013
CHMP opinion:	24 October 2013

2. Scientific discussion

2.1. Introduction

Synflorix is a pneumococcal conjugate vaccine, containing 10 serotypes, 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. It was first approved in the EU in March 2009. The current variation aims to extend the indication to also include prevention of pneumonia. To support the extension of indication an interim report on efficacy from the Clinical Otitis Media and Pneumonia Study (COMPAS) was submitted.

COMPAS is a Phase III, double blind (using observer blind methodologies), randomised and controlled study. The primary objective of this study is to demonstrate the efficacy of a three dose primary course of *Haemophilus influenzae* protein D conjugate vaccine, Synflorix in infants (followed by a booster dose in the second year of life) against first episode of "likely bacterial" community-acquired pneumonia (B-CAP). Planned interim analysis of the primary objective for B-CAP and analyses of other important CAP efficacy objectives, as well as the final analyses for immunogenicity, have been performed.

During the variation application procedure, the MAH submitted to CHMP additional CAP efficacy data as well as safety data from the COMPAS end-of-study analysis

Interaction with Regulatory Authorities

The MAH has conducted three formal European Regulatory Agency consultations to discuss major amendments to the COMPAS protocol and to propose a new timing for the follow-up measure (FUM008) with the Committee for Medicinal Products for Human Use (CHMP).

Protocol Amendment 5: The MAH met with representatives from the MPA, Sweden (Rapporteur), FAGG-AFMPS, Belgium (Co-Rapporteur) and the EMA (Project Leader) on 26 November, 2009. The discussion focussed on the Company's proposed changes to the co-primary endpoints of the study.

In protocol amendment 4, two analyses of the study had been planned as follows:

- An interim analysis when 628 episodes of B-CAP and 628 episodes of C-AOM became available.
- A final analysis when 1,200 episodes of B-CAP and 1,200 episodes of C-AOM became available and when all subjects had completed their 22 months of follow-up (24-27 months of age).

The MAH proposed to amend the protocol to dissociate the co-primary endpoints by demoting C-AOM from a co-primary endpoint to a first secondary endpoint. Hence, the C-AOM endpoint would not be analysed at the time of the interim analysis. Vaccine efficacy against B-CAP remained as the only primary objective, but still with a planned interim analysis. The MAH proposed to perform the interim analysis when at least 535 cases of B-CAP had become available. As there was no longer any need to adjust the alpha level to account for two primary endpoints, the total number of B-CAP cases required to demonstrate vaccine efficacy at final analysis was revised to 1,045 first B-CAP cases, provided each subject would be at least 24 months old. All other endpoints and analyses were unchanged. Both the Rapporteur and Co-Rapporteur agreed with these proposed changes to the protocol.

Protocol Amendment 6: The MAH discussed its proposal for a further protocol amendment (amendment 6) with representatives from the MPA, Sweden; FAGG-AFMPS, Belgium; the PDCO representative from Sweden and the EMA Paediatric Coordinator on the 30 July 2010.

In the initial CXR reading process, WHO case definitions had been used to categorise pneumonia cases. However, WHO training material for CXR interpretation was not available at study start. Each CXR was evaluated by two primary readers, and if a third reader agreed with one of the previous readers this was the final diagnosis. If not the CXR entered a full second round. If discrepancy persisted the CXR was considered as 'no pneumonia'. This process resulted in an unexpected low level of concordance (~20%) between the three readers. As requested by the Independent Data Monitoring Committee (IDMC), the MAH proposed to improve the CXR reading process by establishing an Expert Panel of two readers to resolve by consensus discordant readings from the two primary readers. Two out of three readers were replaced and all readers were regularly re-trained according to available WHO training materials. Hence, the initial process was stopped, all previous results were disregarded, and all CXRs were re-evaluated with the new process. The availability of the WHO training materials led to a much greater concordance (~60%) amongst primary readers. As a consequence of the MAH's improvement to the CXR reading process, fewer confirmed B-CAP cases were observed, i.e., by December 2008 with the revised process, 221 B-CAP cases had been identified compared to 400 B-CAP cases identified with the previous methodology. Following the teleconference, final agreement was reached via e-mail exchange. The final wording in protocol amendment 6 is as follows:

"The study end will depend on the outcome of the planned B-CAP interim analysis. If the outcome on the primary endpoint is conclusive, the study end (completion of contact 10 for each subject) will be organized as soon as possible. If the outcome is not conclusive, the study end will be organized approximately between September and December 2011." As requested by PDCO during the PIP procedure, another change to the protocol was to include clarification of the pathogen-specific AOM endpoint.

In 2009, the MAH committed to report vaccine efficacy against pneumonia, AOM and IPD, as well as the impact of Synflorix on NPC from COMPAS, by March 2012 (Post-authorisation measure 008 [MEA 008]). During a teleconference on 28 February 2012, the MAH informed the Rapporteurs, the EMA Project Leader and the EMA Paediatric Coordinator of a delay in COMPAS end-of-study analysis and

proposed to submit the pneumonia efficacy results from the interim analysis by September 2012. The MAH acknowledged that issues have been identified (e.g. ICF [Informed Consent Form] issues with minor parents in Panama), which have impacted the conduct of the study but clarified that the corrective actions undertaken, which are in accordance with EMA guidelines, support the validity of the study data. Subsequent to re-monitoring activities, the COMPAS end-of-study analysis was agreed to be submitted in June 2013.

2.2. Clinical efficacy

2.2.1. Main study

An interim study report was submitted for study 10PN-PD-DIT-028: Clinical Otitis Media and Pneumonia Study (COMPAS): a phase III, double-blind, randomized, controlled, multicentre study to demonstrate the efficacy of the 10-valent pneumococcal conjugate vaccine against Community Acquired Pneumonia (CAP) and Acute Otitis Media (AOM).

The interim report presents the efficacy data related to the primary objective and some of the secondary objectives. In addition the final immunogenicity data are presented.

- Study initiation date: 28 June 2007
- Data lock point for Primary objective: 31 August 2010
- Database freeze for Immunogenicity objectives: 30 July 2012
- Date of interim report: 20 August 2012

Methods

Study design:

Multicentre study conducted in Argentina (42 centres), Panama (16 centres) and Colombia (3 centres), randomized, double blind (using observer-blind methodology), controlled trial with two parallel groups:

- 10Pn group: approximately 12,000 subjects who received 10-valent pneumococcal conjugate vaccine
- Control group: approximately 12,000 subjects who received a non-pneumococcal control vaccine regimen

Three subsets were defined:

- “Immuno and reacto” subset: first 1,000 subjects enrolled in defined centres in Panama and Argentina (500 subjects per country), for assessment of immunogenicity and reactogenicity
- “Carriage” subset: next 2000 subjects enrolled in defined centres in Panama, for assessment of nasopharyngeal carriage
- “Additional immune” subset: 3,500 subjects enrolled in Panama (not participating in the “Immuno and reacto” subset), for assessment of immunogenicity

Blood sampling:

- Four blood samples were collected from subjects in the “Immuno and reacto” subset for assessment of immunogenicity: one month post dose III, prior to booster vaccination, one month post-booster vaccination and at the last scheduled visit. Two blood samples were collected from

subjects in the “Additional immune” subset for exploratory laboratory assays to explore the correlation between protection against AOM caused by (non-typeable) *Haemophilus influenzae* and the serological response to protein D: prior to booster vaccination and one month post booster vaccination

Nasopharyngeal swabs:

- Six samples were collected from subjects in the “Carriage” subset: at 7 months of age, at 12-15 months of age, at the booster vaccination visit (15-18 months of age), approximately one month and 3 months after the booster dose, and at 24-27 months of age.

Objectives:

This interim report addresses the primary objective and some of the secondary objectives related to the efficacy of the 10Pn-PD-DiT vaccine against first episodes of various definitions of community acquired pneumonia (CAP). In addition, final evaluation of the secondary objectives related to immunogenicity was performed. All other secondary objectives will be addressed in the end-of-study report.

Primary:

To demonstrate the efficacy of a 3-dose primary course followed by a booster dose in the second year of life with the 10Pn-PD-DiT vaccine against likely bacterial CAP cases (B-CAP) in the entire study cohort. Likely bacterial CAP is defined as radiologically confirmed CAP cases with either alveolar consolidation/pleural effusion on the chest X-ray (CXR), or with non-alveolar infiltrates but with CRP ≥ 40 mg/L.

Criteria for efficacy:

Efficacy against likely bacterial CAP will be demonstrated if the one-sided p-value calculated for the null hypothesis H0= [B-CAP vaccine efficacy (VE) ≤ 0%] is lower than 1.75%.

Secondary:

To assess the efficacy of the 10Pn-PD-DiT vaccine against CAP with alveolar consolidation or pleural effusion on chest X-ray (C-CAP)

- To document the impact of the 10Pn-PD-DiT vaccine against suspected CAP cases
- To document the impact of the 10Pn-PD-DiT vaccine against CAP cases with any abnormal CXR
- To document the impact of the 10Pn-PD-DiT vaccine against CAP cases with either alveolar consolidation/pleural effusion on the chest X-ray or with non-alveolar infiltrates with CRP ≥80 mg/L
- To document the impact of the 10Pn-PD-DiT vaccine against CAP cases with either alveolar consolidation/pleural effusion on the chest X-ray or with non-alveolar infiltrates with CRP ≥120 mg/L
- To assess the immune response to the 10Pn-PD-DiT vaccine, one month after dose III, before, one month and approximately 8 months after the booster dose in terms of serotype specific ELISA antibody concentrations, serotype specific opsonophagocytic activity and anti-PD antibody responses (in a subset of 500 children in Argentina and Panama, up to a total of 1,000)

Diagnosis and criteria for inclusion:

- Male or female between, and including, 6 and 16 weeks of age (between 42 and 118 days) at the time of the first vaccination. Preterm infants (born after a gestation period < 37 weeks) could be included in the study starting from 8 weeks of chronological age at the time of first vaccination and up to 16 weeks of chronological age (between 56 and 118 days).
- In each site, subjects living in the area covered by the surveillance system for CAP, ID and AOM.
- Written informed consent obtained from the parent or guardian of the subject.
- Free of any known or suspected health problems (as established by medical history and clinical examination before entering into the study), that would contraindicate the initiation of routine immunizations outside a clinical trial context.
- Subjects for whom the investigator believed that their parents/guardians could and would comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits).
- For Colombia: infants with birth weight ≥ 2,500g.

Study vaccine, dose, mode of administration

All vaccines were administrated intramuscularly in the right (10Pn-PD-DiT and HBV or HAV vaccines) or the left (DTPa-HBV-IPV/Hib or DTPa-IPV/Hib vaccines) thigh (primary doses) or deltoid (booster dose). In addition to the study vaccines the following vaccines were concomitantly administered: Havrix vaccine, Varilrix vaccine, NeisVac C and Rotarix vaccine.

Criteria for evaluation:

For the interim report the primary endpoint (i.e. efficacy to prevent the first episode of B-CAP) was to be evaluated when at least 535 first B-CAP episodes were reported from 2 weeks after dose III for subjects in the ATP cohort for efficacy. Furthermore some of the secondary endpoints related to CAP were to be partially evaluated such as first episode of CAP only (multiple episodes will be analysed at the time of the final report). In addition, the final analysis of the secondary endpoints related to immunogenicity was performed.

Efficacy:

- Occurrence of likely bacterial CAP cases (B-CAP) defined as radiologically confirmed CAP cases with either alveolar consolidation/pleural effusion on the chest X-ray or with non-alveolar infiltrates but with CRP ≥40 mg/L.
- Occurrence of CAP cases with alveolar consolidation or pleural effusion on the Chest X-ray (CCAP)
- Occurrence of suspected CAP cases
- Occurrence of CAP cases with any abnormal CXR
- Occurrence of CAP cases with either alveolar consolidation/pleural effusion on the chest X-ray or with non-alveolar infiltrates but with CRP ≥80 mg/L
- Occurrence of CAP cases with either alveolar consolidation/pleural effusion on the chest X-ray or with non-alveolar infiltrates but with CRP ≥120 mg/L

- Immunogenicity (in the "Immuno and reacto" subset of 1,000 subjects (500 subjects respectively in Argentina and Panama)):
- Antibody concentrations against pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (22F-inhibition ELISA), one month post dose III , pre-booster, one month post-booster and at Visit 9
- Opsonophagocytic activity (OPA) against pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, one month post dose III, pre-booster, one month post-booster and at Visit 9
- Antibody concentrations to protein D (ELISA), one month post dose III, pre-booster, one month post-booster and at Visit 9.

Statistical methods:

Sample size calculation:

If the true VE is 25%, the study has 87.6% power to be conclusive at the interim analysis. If the interim is not conclusive, one can consider that the total number of evaluable B-CAP cases at the final analysis will be between 600 and 700.

Therefore if the true VE is 20%, considering a number of 600 cases at final analysis, and the interim analysis was not to be conclusive despite a 66% power at the interim, there was to be at least 9.7% chance to conclude at the final analysis with a global power of at least 75.7%.

Statistical analyses

Statistical analyses for this interim report were performed, as described in the protocol, by an independent statistician as the study was still ongoing and blinded at the time of the analyses.

Demography-descriptive analysis:

- Demographic characteristics (age, gender, race) of the ATP cohort for efficacy for CAP and of the Total vaccinated cohort were tabulated per group.

Efficacy (ATP cohort for efficacy):

- For all first episodes of a defined CAP, the vaccine efficacy (VE) and its 95% confidence interval (CI) was estimated as 1 minus the hazard ratio obtained from a Cox regression model including the treatment group as only regressor.
- The number of first episodes, follow-up years, associated rate and cumulative hazard curve were presented by group, for each considered endpoint.
- In order to check the statistical significance of the primary endpoint at the time of this interim analysis, one-sided p-value for the Wald-Test obtained from the Cox proportional hazard model was calculated for B-CAP reported 2 weeks after dose III in the ATP cohort for efficacy. The success of the primary objective will be established if the one-sided nominal p-value calculated for the null hypothesis H0=[B-CAP VE $\leq$0%] is lower than 1.75%.

Immunogenicity (ATP cohort for "Immuno and reacto" subset):

- Geometric mean antibody concentrations/titres (GMCs/GMTs) with 95% CIs were tabulated for each group and for each appropriate antigen/serotype at each applicable blood sampling timepoint.
- Seropositivity rates were calculated with 95% CIs for each group and for each antigen/serotype at each applicable blood sampling time point.
- Distribution of antibody concentrations/titres was displayed using tables and/or reverse cumulative distribution curves for each appropriate antigen/serotype at each applicable blood sampling time point
- For each pneumococcal serotype, at each time point that a blood-sample result was available, geometric mean of ratios of Opsonophagocytic (OPA) titres/ELISA concentrations were tabulated with 95% CIs.
- Geometric mean ratios of ELISA concentrations or OPA titres between various blood sample time points were calculated with 95% CIs.

Results

GCP Issues

A number of GCP issues have been raised during the COMPAS trial. A summary of the issues is described below:

During the early phase of study conduct, issues related to the quality of the monitoring services (e.g. source data verification, implementation/follow-up of identified actions) provided by the CRO (Contract Research Organisation) were encountered. As no improvement in the services was observed after agreement of corrective actions the collaboration with the implicated CRO was terminated in December 2009 and another CRO was contracted to perform the study monitoring activities. The CRO performed a quality check in Argentina on the monitoring of 20% of the reported CAP cases.

From the end of 2007 until mid-2008 the study was increasingly discussed in the local media and on the internet. This media coverage focused on two issues: the reporting of deaths of some children enrolled in the study, and that the recruitment process at one study centre was allegedly not conducted appropriately. This media coverage ultimately led to further investigations by the local regulatory authorities in Argentina and Colombia. While the local regulatory authorities concluded that the study could continue as planned, the media coverage adversely impacted the rate of enrolment of new subjects into the trial, as well as the willingness of many parents of enrolled children to let their children continue to participate in the study. To enhance enrolment the recruitment period was extended through end of 2008.

Local regulatory authorities in Argentina and Colombia performed inspections in 2007 and 2008, partially triggered by the above described media coverage of the study. In Argentina concerns were raised during the inspections regarding the following:

- The informed consent process (e.g. lack of documentation of the relationship between parents and LAR (legally authorized representative) of subject and ICFs signed after randomization).
- The compliance with the inclusion/exclusion/elimination criteria
- Monitoring/surveillance by the Sponsor (e.g. source data verification and loss of source data).
- The 30 minutes safety follow-up after vaccination and follow-up of AEs/SAEs (e.g. reporting of AEs and SAEs).

The concerns were investigated by the MAH and additional information was provided to the authorities. Additionally, appropriate corrective actions were put in place and communicated to the authorities who were in agreement that the study should be allowed to continue. Nevertheless, the authorities issued fines to the MAH and the study investigators in 2009. The MAH disagreed with the allegations and initiated appeals that lasted over a period of several years. However in 2012, whilst continuing to disagree with the assessment of the fines, the MAH decided to conclude the judicial processes by withdrawing its appeals so that it could focus its attention on completing the study. In Colombia, the regulatory inspections raised concerns about the progress of the implementation of the regulation for Independent Ethics Committees (IECs) from INVIMA of July 2008 at two IECs that were overseeing the study. Therefore it was agreed with INVIMA to also submit the study to an IEC that already complied with the INVIMA regulation. This latter IEC also approved the study.

In June 2008, the IDMC (Independent Data Monitoring Committee) noted an imbalance in reporting of fatal adverse events in the study. At the request of the IDMC, the enrolment of the study was put on hold to allow the IDMC to further investigate this observation. All analyses requested by the IDMC were performed by an independent statistician to ensure the blinding of the study. The IDMC concluded that no safety concern could be identified for children enrolled in the COMPAS study compared to baseline mortality. The IDMC recommended therefore that enrolment could be restarted. The study was on hold from 23 June 2008 to 02 July 2008.

In June 2009, after noting a high number of discrepancies in CXR diagnoses between the readers in the CXR panel, the IDMC recommended improving the robustness of the CXR review process. In agreement with the IDMC, the review process was enhanced, some of the CXR readers were replaced and regular trainings on WHO case definitions for pneumonia were provided. Following implementation of these changes (January 2010), all CXRs were re-assessed according to the new process and previous diagnoses were not considered for any analysis.

During the data validation process for the interim analysis, errors were detected in the completion of several electronic case report form (eCRF) fields at a specific study centre. It was concluded that these findings had no impact on the data for the interim analysis but during the investigation an under-reporting of non-serious adverse events (AEs) was detected. Corrective actions were taken.

Additional quality checks and selective re-monitoring activities were implemented after completion of the interim analysis. After completion of the interim analysis and after the last study contact in 2011, a further quality check at the 2 centres with the highest recruitment in Panama revealed some under reporting of S-CAP cases, AOM cases, serious adverse events (SAEs) and AEs. Therefore, prior to the database freeze and unblinding for the final analysis, the MAH decided to perform a re-monitoring of all recorded data in all centres in Panama and to do a quality check of the data recorded respectively for at least 10% and 20% of the subjects in each of the centres in Argentina and Colombia, before closing of the database. These activities revealed issues with ICFs for some subjects of which 144 could not be resolved: 60 subjects for whom re-consent had not been obtained (i.e. 59 subjects minor parents/guardians who could not be re-contacted when becoming 18 years of age and 1 subject whose parents/guardian did not re-consent); 53 subjects for whom the age of the parents/guardians could not be definitively confirmed; and 31 subjects for whom the original signed ICFs were lost during the re-monitoring activities initiated after study end.

Participant flow

Study population

Number of subjects	Total	PHiD-CV group	Control group
Planned	24000	12000	12000
Total vaccinated cohort for efficacy	23738	11875	11863
ATP cohort for efficacy for CAP	20496	10295	10201
Primary Total vaccinated cohort for immunogenicity	737	373	364
Primary ATP cohort for immunogenicity	665	334	331
Booster Total vaccinated cohort for immunogenicity	675	345	330
Booster ATP cohort for immunogenicity	447	232	215

Protocol deviations

The number of subjects enrolled into the study as well as the number of subjects eliminated from ATP analysis for efficacy with reasons for elimination is listed in Table 1. Subjects are listed in the table based on the lowest elimination code as more than one elimination code could be assigned to the same subject.

Table 1 Number of subjects enrolled into the study as well as the number of subjects excluded from ATP analysis for efficacy, with reasons for exclusion

	Total			10Pn		Control		NOGRP	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**
Total cohort	**23821**			**11911**		**11908**		**2**	
ICF signature not valid as per Colombian Law or subjects from Colombia with low birth weight (< 2,500g) (code 900)	81	81		36	36	45	45	0	0
Study vaccine dose not administered but subject number allocated (code 1030)	2	2		0	0	0	0	2	2
Total vaccinated cohort for efficacy	**23738**		**100**	**11875**		**11863**		**0**	**0**
Subjects who received forbidden vaccine within one month before 1st study vaccine dose (code 1500)	67	68		26	27	41	41		
Age at study vaccine dose 1 not according-to-protocol (code 2010)	19	19		7	7	12	12		
Administration of any medication forbidden by the protocol (code 2040)	58	58		29	29	29	29		
Underlying medical condition forbidden by the protocol (code 2050)	34	41		12	15	22	26		
Subject with no contact beyond 14 days after dose 3 (code 3010)	2051	2102		1002	1023	1049	1077		
Administration of pneumococcal concomitant vaccine(s) other than the study vaccines during the entire study period (code 3040)	47	56		17	23	30	33		
Wrong vial at a defined primary dose (code 3070)	21	21		10	10	11	11		
Non compliance with primary vaccination schedule (code 3080)	945	1004		477	505	468	499		
ATP cohort for efficacy for CAP	**20496**		**86.3**	**10295**		**10201**		**-**	**-**

10Pn = Primed with 10Pn-PD-DiT + DTPa-HBV-IPV/Hib and boosted with 10Pn-PD-DiT + DTPa-IPV/Hib
Control = Primed with HBV + DTPa-IPV/Hib and boosted with HAV + DTPa-IPV/Hib
NOGRP = No assigned group
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort

Demographic characteristics

The demographic characteristics of the ATP cohort for efficacy for CAP and the Total vaccinated cohort at first vaccination and at booster vaccination are shown respectively in Table 2. The demographic profile of the 10Pn and Control groups was comparable with respect to mean age at first vaccination and at booster vaccination, gender and race.

Table 2 Summary of demographic characteristics (ATP cohort for efficacy for CAP)

		10Pn N = 10295		Control N = 10201		Total N = 20496	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age (weeks) at dose 1	Mean	9.2	-	9.2	-	9.2	-
	SD	1.91	-	1.91	-	1.91	-
	Median	9.0	-	9.0	-	9.0	-
	Minimum	6	-	6	-	6	-
	Maximum	16	-	16	-	16	-
Age (months) at booster dose	Mean	16.1	-	16.1	-	16.1	-
	SD	1.55	-	1.55	-	1.55	-
	Median	16.0	-	16.0	-	16.0	-
	Minimum	14	-	13	-	13	-
	Maximum	32	-	33	-	33	-
	Unknown	816	-	771	-	1587	-
Gender	Female	5072	49.3	4987	48.9	10059	49.1
	Male	5223	50.7	5214	51.1	10437	50.9
Race	African heritage / African American	90	0.9	75	0.7	165	0.8
	American Indian or Alaskan native	246	2.4	252	2.5	498	2.4
	Asian - central/south Asian heritage	0	0.0	0	0.0	0	0.0
	Asian - east Asian heritage	1	0.0	2	0.0	3	0.0
	Asian - Japanese heritage	0	0.0	0	0.0	0	0.0
	Asian - south east Asian heritage	0	0.0	0	0.0	0	0.0
	Native Hawaiian or other pacific Islander	0	0.0	0	0.0	0	0.0
	White - Arabic / north African heritage	25	0.2	21	0.2	46	0.2
	White - Caucasian / European heritage	5933	57.6	5897	57.8	11830	57.7
	Other*	4000	38.9	3954	38.8	7954	38.8

10Pn = Primed with 10Pn-PD-DiT + DTPa-HBV-IPV/Hib and boosted with 10Pn-PD-DiT + DTPa-IPV/Hib
Control = Primed with HBV + DTPa-IPV/Hib and boosted with HAV + DTPa-IPV/Hib
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
*Other: mainly mixed race

Efficacy results

Vaccine efficacy against likely bacterial CAP (B-CAP)

The occurrence of first episodes of B-CAP cases and the VE for time to first episodes of B-CAP anytime from 2 weeks after the administration of dose III are presented in Table 3 and Table 4.

Table 3 Occurrence (number and percentage) of first episodes of likely bacterial CAP (B-CAP) anytime from 2 weeks after the administration of dose III - DLP = 31AUG2010 (ATP cohort for efficacy for CAP)

	10Pn N = 10295				Control N = 10201			
			95% CI				95% CI	
Categories	n	%	LL	UL	n	%	LL	UL
Likely Bacterial CAP	240	2.3	2.0	2.6	304	3.0	2.7	3.3

10Pn = Primed with 10Pn-PD-DiT + DTPa-HBV-IPV/Hib and boosted with 10Pn-PD-DiT + DTPa-IPV/Hib
Control = Primed with HBV + DTPa-IPV/Hib and boosted with HAV + DTPa-IPV/Hib
N = total number of subjects

n/% = number/percentage of subjects reporting a first episode of likely bacterial CAP (B-CAP) cases from 2 weeks after the administration of dose III
95% I = exact 95% confidence interval, LL = lower limit, UL = upper limit
Note: Censoring variables were taken into account to compute the occurrence of cases

Table 4 Vaccine Efficacy (with p-value) for time to first occurrence of likely bacterial CAP (B-CAP) anytime from 2 weeks after the administration of dose III - DLP = 31AUG2010 (ATP cohort for efficacy for CAP)

					VE			
						95% CI		
Event Type	Group	N	n	T (year)	%	LL	UL	1-SIDED P-VALUE COX
Likely Bacterial CAP	10Pn	10295	240	19512.99	**22.033**	7.656	34.172	**0.0020**
	Control	10201	304	19260.15	-	-	-	.

10Pn = Primed with 10Pn-PD-DiT + DTPa-HBV-IPV/Hib and boosted with 10Pn-PD-DiT + DTPa-IPV/Hib
Control = Primed with HBV + DTPa-IPV/Hib and boosted with HAV + DTPa-IPV/Hib
N = number of subjects
n = number of subjects reporting at least one event(s) = number of first event(s)
T (year) = sum of follow-up period expressed in years censored at the first occurrence of event in each group
VE (%) = Vaccine efficacy (Cox regression model)
95% CI = 95% confidence interval derived from Cox regression model; LL = Lower Limit, UL = Upper Limit
One-sided p-value from Cox regression model to test H0 = [VE≤ 0%] (Y = Time to Event) - significance level = 1.75%
Note: Censoring variables were taken into account to compute the occurrence of cases

As the primary objective was met, the occurrence of first episodes of several kinds of CAP and the VE for time to first episodes of several kinds of CAP anytime from 2 weeks after the administration of dose III has been evaluated and is presented in Table 5.

Table 5 Vaccine Efficacy (with p-value) for time to first occurrence of several kinds of CAP anytime from 2 weeks after the administration of dose III - DLP = 31AUG2010 (ATP cohort for efficacy for CAP)

					VE			
						95% CI		
Event Type	Group	N	n	T (year)	%	LL	UL	1-SIDED P-VALUE COX
CAP with alveolar consolidation or pleural effusion (C-CAP)	10Pn	10295	155	19611.18	25.650	8.423	39.637	0.0027
	Control	10201	206	19368.99	-	-	-	-
Suspected CAP (S-CAP)	10Pn	10295	1916	17465.61	6.695	0.676	12.349	0.0149
	Control	10201	2019	17129.55	-	-	-	-
CAP with any abnormal chest X-ray	10Pn	10295	625	19050.86	13.275	3.436	22.112	0.0047
	Control	10201	711	18767.06	-	-	-	-
C-CAP or non-consolidated CAP with CRP ≥ 80 mg/L	10Pn	10295	179	19582.74	23.409	6.903	36.989	0.0037
	Control	10201	231	19344.42	-	-	-	-
C-CAP or non-consolidated CAP with CRP ≥ 120 mg/L	10Pn	10295	164	19598.83	24.612	7.625	38.475	0.0032
	Control	10201	215	19358.95	-	-	-	-

10Pn = Primed with 10Pn-PD-DiT + DTPa-HBV-IPV/Hib and boosted with 10Pn-PD-DiT + DTPa-IPV/Hib
Control = Primed with HBV + DTPa-IPV/Hib and boosted with HAV + DTPa-IPV/Hib
N = number of subjects
n = number of subjects reporting at least one event(s) = number of first event(s)
T (year) = sum of follow-up period expressed in years censored at the first occurrence of event in each group
VE (%) = Vaccine efficacy (Cox regression model)
95% CI = 95% confidence interval derived from Cox regression model; LL = Lower Limit, UL = Upper Limit
One-sided p-value from Cox regression model to test H0 = [VE≤ 0%]
Note: Censoring variables were taken into account to compute the occurrence of cases

Sensitivity analysis

Following the interim analysis performed in March 2011, further re-monitoring activities were performed as described above. These activities revealed issues with ICFs for some subjects being part of primary objective analyses.

In order to further confirm the validity of the interim analysis, a descriptive sensitivity analysis on the primary objective has been performed as recommended in ICH E9 (Note for Guidance on Statisitical Principles for Clinical Trials) with reference to the further exploration of the sensitivity of conclusions and as also recommended in the EMA guidance of 2008 (Ethical Considerations For Clinical Trials On Medicinal Products Conducted With The Paediatric Population) in the case of submission of non GCP compliant data ("the quality of the data, the study results, and consequently the validity of the marketing authorisation application should be scrutinised. Sensitivity analysis should be performed within the GCP-compliant full data set and in some cases also in comparison with all GCP-non compliant data").

Therefore, for this sensitivity analysis, a total of 144 subjects were excluded for the reasons described above. The database used for this sensitivity analysis was the same as the one used for the initial interim analysis with the above identified subjects eliminated from the ATP cohort for efficacy for CAP. Note that the subjects identified above will also be eliminated from all end-of-study study analyses. The VE against the first episode of likely bacterial CAP reported in the updated ATP cohort for efficacy for sensitivity analysis, anytime from 2 weeks after the administration of dose III was 22.3% (95% CI [7.9 ; 34.4] versus 22.0% (95% CI [7.7 ; 34.2]) before exclusion of the above mentioned subjects.

End of study results

Subsequent to interim results reported above, the study activities for completion of the study were conducted and the end-of-study analysis was performed, including descriptive analyses of community acquired pneumonia (CAP). In these analyses, the mean efficacy follow-up from 2 weeks after the administration of dose 3 in the ATP cohort was 30 months (range from 0 to 44 months). The efficacy of Synflorix against first B-CAP episodes in COMPAS measured in the end-of-study analysis is consistent with the point estimate from the confirmatory analysis result from the event-driven (interim) analysis. Vaccine efficacy was also shown against other pneumonia endpoints of public health importance (S-CAP, C-CAP and CXR-CAP) investigated as descriptive secondary objectives. In these analyses, a stratification by age was performed to evaluate whether the VE against CAP endpoints varied by age in light of previous observations with other pneumococcal conjugate vaccines. Using the comparable standardized WHO endpoint the VE against first episodes of C-CAP in the ATP cohort in subjects <24 months of age and ≥24 months of age was 25.4% (95%CI, 5.6; 41.1) and 15.0% (95%CI, -20.0; 39.8), respectively. The VE against all episodes of C-CAP was in line with the VE against first episodes (24.0% and 12.5% respectively). The results of the TVC were consistent with those obtained for the ATP cohort.

Since in the COMPAS study, the observation period extended beyond 2 years of age, a descriptive analysis, stratifying for each year of age, was performed in order to better understand what age stratification makes the most sense based on the efficacy data. For C-CAP, the standardized WHO endpoint, there is evidence of efficacy up to 36 months of age with point estimates of 15.1%, 31.8% and 20.7% vaccine efficacy for the children under 12 months of age, 12-24 months of age and 24 to 36 months of age respectively (Table 6). A similar pattern is seen for B-CAP but with a lower point estimate at 24 to 36 months of age (vaccine efficacy of 5.9%) perhaps reflecting the increasing lack of specificity of this case definition in older children.

Table 6 Vaccine Efficacy (with p-value) for time to first occurrence of C-CAP and B-CAP subdivided per age-groups anytime from 2 weeks after the administration of dose III (ATP cohort for vaccine efficacy analysis) – 10PN-PD-DIT-028 (COMPAS)

Event	Group	N	n	T (year)	VE			One sided p-value
					%	95% CI		
						LL	UL	
Consolidated CAP / < 12 months of age	10Pn	10211	53	25136.95	15.11	-22.48	41.17	0.1905
	Control	10140	62	24940.32	-	-	-	-
Consolidated CAP / ≥ 12 - < 24 months of age	10Pn	10211	68	25142.31	31.84	7.19	49.94	0.0075
	Control	10140	99	24905.17	-	-	-	-
Consolidated CAP / ≥ 24 - < 36 months of age	10Pn	10211	48	25210.87	20.73	-15.87	45.76	0.1152
	Control	10140	60	25021.15	-	-	-	-
Consolidated CAP / > 36 months of age	10Pn	10211	12	25249.29	-19.32	-176.16	48.45	0.6600
	Control	10140	10	25071.33	-	-	-	-
Likely bacterial CAP / < 12 months of age	10Pn	10211	80	25081.94	13.69	-16.47	36.03	0.1678
	Control	10140	92	24878.24	-	-	-	-
Likely bacterial CAP / ≥ 12 - < 24 months of age	10Pn	10211	105	25079.04	31.96	12.77	46.92	0.0012
	Control	10140	153	24814.73	-	-	-	-
Likely bacterial CAP / ≥ 24 - < 36 months of age	10Pn	10211	74	25181.20	5.94	-29.28	31.57	0.3529
	Control	10140	78	25006.82	-	-	-	-
Likely bacterial CAP / > 36 months of age	10Pn	10211	16	25246.78	-59.20	-250.80	27.76	0.8756
	Control	10140	10	25071.33	-	-	-	-

10Pn = Primed with 10Pn-PD-DiT + DTPa-HBV-IPV/Hib and boosted with 10Pn-PD-DiT + DTPa-IPV/Hib
Control = Primed with HBV + DTPa-IPV/Hib and boosted with HAV + DTPa-IPV/Hib
N = number of subjects
n = number of subjects reporting at least one event
T (year) = sum of follow-up expressed in years censored at the first occurrence of event
VE (%) = Vaccine efficacy (Cox regression model)
95% CI = 95% confidence interval derived from Cox regression model LL = Lower Limit, UL = Upper Limit
Descriptive P-value from Cox regression model when at least 1 event - no adjustment for multiplicity
Note: Censoring variables are taken into account to compute the occurrence of cases

Based on this analysis and the observation that there still appeared to be vaccine efficacy against C-CAP and B-CAP in the age cohort 24-36 months of age, the MAH has performed an additional analysis considering the age cohort of children up to 36 months of age and above 36 months of age; with vaccine efficacy of greater than 15% efficacy in the age stratified analysis for C-CAP up to 3 years of age and only decreasing after that for some of the endpoints, 36 months of age represents a logical break, rather than 24 months of age, as initially explored (Table 6).

The results for this analysis for first episodes in the ATP cohort are presented in Table 7 (results for any episode and Total vaccinated cohort are presented in Annex Additional COMPAS analysis) and show that the vaccine efficacy in children less than 36 months of age was positive for all endpoints with notably statistically significant results (based on positive lower limit of the non-adjusted 95% CI around VE) for C-CAP (24.2% [95% CI, 7.4; 38.0]) and B-CAP (20.6% [95% CI, 6.5; 32.6]). Therefore, the results from COMPAS provide evidence that Synflorix protects children vaccinated in infancy against C-CAP and B-CAP up to the age of 36 months at least.

Given the limited number of C-CAP and B-CAP cases in children ≥ 36 months of age and thus the large confidence intervals for the point estimates for this age cohort, it was difficult to interpret the calculated VE in this age group. As pneumococcal pneumonia may also be contributing to endpoints other than C-CAP in older children, it may be relevant, however, to consider that VE estimates in the ≥36 months of age group for both suspected CAP and for CAP with an abnormal X-ray were 12-36% (depending on ATP or TVC cohort – first episodes), with statistical significance (based on positive lower limit of the non-adjusted 95% CI around VE) achieved for suspected CAP in that age group in all instances. Although a decrease of VE against C-CAP or B-CAP in children ≥36 months of age cannot be

excluded, the above data indicates that efficacy against some pneumonia-related endpoints could be detected even in children ≥36 months of age.

Table 7 Vaccine Efficacy (with p-value) for time to first occurrence of several kinds of CAP subdivided before or after 36 months of age anytime from 2 weeks after the administration of dose III (ATP cohort for vaccine efficacy analysis) – 10PN-PD-DIT-028 (COMPAS)

Event	Group	N	n	T (year)	VE			One sided p-value
					%	95% CI		
						LL	UL	
Suspected CAP / < 36 months of age	10Pn	10211	2058	21713.75	6.15	0.30	11.65	0.0198
	Control	10140	2159	21302.70	-	-	-	-
Suspected CAP / ≥ 36 months of age	10Pn	10211	50	25232.50	36.43	9.33	55.43	0.0062
	Control	10140	78	25042.53	-	-	-	-
Consolidated CAP / < 36 months of age	10Pn	10211	169	24978.40	24.24	7.44	37.99	0.0033
	Control	10140	221	24715.57	-	-	-	-
Consolidated CAP / ≥ 36 months of age	10Pn	10211	12	25249.29	-19.32	-176.16	48.45	0.6600
	Control	10140	10	25071.33	-	-	-	-
Likely bacterial CAP / < 36 months of age	10Pn	10211	259	24830.46	20.64	6.55	32.61	0.0028
	Control	10140	323	24548.71	-	-	-	-
Likely bacterial CAP / ≥ 36 months of age	10Pn	10211	16	25246.78	-59.20	-250.80	27.76	0.8756
	Control	10140	10	25071.33	-	-	-	-
Non-consolidated CAP / < 36 months of age	10Pn	10211	523	24372.23	6.47	-5.40	17.00	0.1363
	Control	10140	554	24117.03	-	-	-	-
Non-consolidated CAP / ≥ 36 months of age	10Pn	10211	16	25249.21	36.37	-19.18	66.03	0.0790
	Control	10140	25	25064.59	-	-	-	-
CAP with any abnormal X-Ray / < 36 months of age	10Pn	10211	658	24142.74	11.61	1.81	20.43	0.0107
	Control	10140	736	23814.82	-	-	-	-
CAP with any abnormal X-Ray / ≥ 36 months of age	10Pn	10211	23	25245.31	18.24	-41.93	52.91	0.2371
	Control	10140	28	25063.72	-	-	-	-

10Pn = Primed with 10Pn-PD-DiT + DTPa-HBV-IPV/Hib and boosted with 10Pn-PD-DiT + DTPa-IPV/Hib
Control = Primed with HBV + DTPa-IPV/Hib and boosted with HAV + DTPa-IPV/Hib
N = number of subjects
n = number of subjects reporting at least one event
T (year) = sum of follow-up expressed in years censored at the first occurrence of event
VE (%) = Vaccine efficacy (Cox regression model)
95% CI = 95% confidence interval derived from Cox regression model LL = Lower Limit, UL = Upper Limit
Descriptive P-value from Cox regression model - no adjustment for multiplicity
Note: Censoring variables are taken into account to compute the occurrence of cases

Immunogenicity results

Immune response to the 10Pn-PD-DiT vaccine after primary vaccination

The GMCs of antibodies against the vaccine pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F), measured by 22F-inhibition ELISA, and the percentage of subjects with pneumococcal antibody concentrations ≥the cut-off of the assay of 0.05 µg/mL and ≥the threshold value of 0.20 µg/mL, one month post-dose III overall are shown in Table 8.

For each of the vaccine pneumococcal serotypes the percentage of subjects with antibody concentrations ≥0.20 µg/mL in the 10Pn group one month post-dose III was at least 93.1%.

Table 8 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 one month after the 3-dose primary vaccination course (Primary ATP cohort for immunogenicity)

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-1	10Pn	PIII(M5)	334	333	99.7	98.3	100	333	99.7	98.3	100	2.51	2.29	2.75
	Control	PIII(M5)	312	88	28.2	23.3	33.5	13	4.2	2.2	7.0	0.04	0.03	0.04
ANTI-4	10Pn	PIII(M5)	334	333	99.7	98.3	100	332	99.4	97.9	99.9	3.26	2.98	3.56
	Control	PIII(M5)	328	48	14.6	11.0	18.9	11	3.4	1.7	5.9	0.03	0.03	0.04
ANTI-5	10Pn	PIII(M5)	334	334	100	98.9	100	333	99.7	98.3	100	4.20	3.86	4.57
	Control	PIII(M5)	324	153	47.2	41.7	52.8	22	6.8	4.3	10.1	0.05	0.04	0.05
ANTI-6B	10Pn	PIII(M5)	334	324	97.0	94.6	98.6	311	93.1	89.8	95.6	1.34	1.18	1.52
	Control	PIII(M5)	322	48	14.9	11.2	19.3	8	2.5	1.1	4.8	0.03	0.03	0.03
ANTI-7F	10Pn	PIII(M5)	334	333	99.7	98.3	100	333	99.7	98.3	100	3.86	3.56	4.19
	Control	PIII(M5)	330	116	35.2	30.0	40.6	28	8.5	5.7	12.0	0.04	0.04	0.05
ANTI-9V	10Pn	PIII(M5)	334	331	99.1	97.4	99.8	330	98.8	97.0	99.7	3.15	2.84	3.50
	Control	PIII(M5)	331	68	20.5	16.3	25.3	19	5.7	3.5	8.8	0.04	0.03	0.04
ANTI-14	10Pn	PIII(M5)	334	333	99.7	98.3	100	328	98.2	96.1	99.3	4.55	4.07	5.10
	Control	PIII(M5)	330	234	70.9	65.7	75.8	77	23.3	18.9	28.3	0.09	0.08	0.11
ANTI-18C	10Pn	PIII(M5)	334	333	99.7	98.3	100	330	98.8	97.0	99.7	5.32	4.73	5.99
	Control	PIII(M5)	328	92	28.0	23.3	33.2	21	6.4	4.0	9.6	0.04	0.04	0.04
ANTI-19F	10Pn	PIII(M5)	334	331	99.1	97.4	99.8	325	97.3	94.9	98.8	5.33	4.70	6.06
	Control	PIII(M5)	327	176	53.8	48.3	59.3	40	12.2	8.9	16.3	0.06	0.05	0.07
ANTI-23F	10Pn	PIII(M5)	334	328	98.2	96.1	99.3	321	96.1	93.4	97.9	1.99	1.76	2.26
	Control	PIII(M5)	331	78	23.6	19.1	28.5	15	4.5	2.6	7.4	0.04	0.03	0.04

10Pn = Primed with 10Pn-PD-DiT + DTPa-HBV-IPV/Hib and boosted with 10Pn-PD-DiT + DTPa-IPV/Hib
Control = Primed with HBV + DTPa-IPV/Hib and boosted with HAV + DTPa-IPV/Hib
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

The GMTs of opsonophagocytic activity (OPA) against the vaccine pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) and the percentage of subjects with opsonophagocytic activity ≥ 8 one month post-dose III overall are shown in Table 9. One month post-dose III, for each of the vaccine pneumococcal serotypes, at least 90.8% of subjects in the 10Pn group had opsonophagocytic activity ≥8.

Table 9 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 one month after the 3-dose primary vaccination course (Primary ATP cohort for immunogenicity)

				≥ 8				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
OPSONO-1	10Pn	PIII(M5)	306	280	91.5	87.8	94.4	139.5	116.8	166.5
	Control	PIII(M5)	305	25	8.2	5.4	11.9	4.8	4.5	5.3
OPSONO-4	10Pn	PIII(M5)	310	306	98.7	96.7	99.6	771.7	686.5	867.6
	Control	PIII(M5)	299	15	5.0	2.8	8.1	5.1	4.5	5.8
OPSONO-5	10Pn	PIII(M5)	313	303	96.8	94.2	98.5	224.8	196.0	257.8
	Control	PIII(M5)	314	13	4.1	2.2	7.0	4.5	4.2	4.8
OPSONO-6B	10Pn	PIII(M5)	315	286	90.8	87.0	93.7	689.7	553.2	859.7
	Control	PIII(M5)	309	16	5.2	3.0	8.3	5.4	4.6	6.2
OPSONO-7F	10Pn	PIII(M5)	302	302	100	98.8	100	4656.7	4175.6	5193.3
	Control	PIII(M5)	266	162	60.9	54.8	66.8	110.4	78.8	154.7
OPSONO-9V	10Pn	PIII(M5)	312	311	99.7	98.2	100	1690.4	1489.4	1918.7
	Control	PIII(M5)	302	98	32.5	27.2	38.0	14.6	11.6	18.2
OPSONO-14	10Pn	PIII(M5)	308	306	99.4	97.7	99.9	908.5	795.2	1038.1
	Control	PIII(M5)	273	95	34.8	29.2	40.8	16.5	12.9	21.1
OPSONO-18C	10Pn	PIII(M5)	308	290	94.2	90.9	96.5	310.9	259.4	372.6
	Control	PIII(M5)	317	8	2.5	1.1	4.9	4.4	4.1	4.7
OPSONO-19F	10Pn	PIII(M5)	304	277	91.1	87.3	94.1	383.0	308.5	475.5
	Control	PIII(M5)	314	16	5.1	2.9	8.1	4.7	4.3	5.2
OPSONO-23F	10Pn	PIII(M5)	317	311	98.1	95.9	99.3	2167.4	1863.4	2521.1
	Control	PIII(M5)	282	68	24.1	19.2	29.5	14.5	11.0	19.1

10Pn = Primed with 10Pn-PD-DiT + DTPa-HBV-IPV/Hib and boosted with 10Pn-PD-DiT + DTPa-IPV/Hib
Control = Primed with HBV + DTPa-IPV/Hib and boosted with HAV + DTPa-IPV/Hib
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

The GMCs of antibodies against the cross-reactive pneumococcal serotypes 6A and 19A, measured by 22F-inhibition ELISA, and the percentage of subjects with pneumococcal antibody concentrations ≥the cut-off of the assay of 0.05 µg/mL and ≥the threshold value of 0.20 µg/mL, one month post-dose III overall are presented in Table 10. The OPA GMTs against the cross-reactive pneumococcal serotypes 6A and 19A and the percentage of subjects with opsonophagocytic activity ≥8 one month post-dose III overall are shown in Table 11.

Table 10 Seropositivity rates and GMCs for ANTI-6A and ANTI-19A antibodies one month after the 3-dose primary vaccination course (Primary ATP cohort for immunogenicity)

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-6A	10Pn	PIII(M5)	334	306	91.6	88.1	94.4	215	64.4	59.0	69.5	0.32	0.27	0.37
	Control	PIII(M5)	321	77	24.0	19.4	29.0	5	1.6	0.5	3.6	0.03	0.03	0.04
ANTI-19A	10Pn	PIII(M5)	334	303	90.7	87.1	93.6	204	61.1	55.6	66.3	0.29	0.25	0.33
	Control	PIII(M5)	326	120	36.8	31.6	42.3	18	5.5	3.3	8.6	0.04	0.04	0.05

10Pn = Primed with 10Pn-PD-DiT + DTPa-HBV-IPV/Hib and boosted with 10Pn-PD-DiT + DTPa-IPV/Hib
Control = Primed with HBV + DTPa-IPV/Hib and boosted with HAV + DTPa-IPV/Hib
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

Table 11 Seropositivity rates and GMTs for OPSONO-6A and OPSONO-19A one month after the 3-dose primary vaccination course (Primary ATP cohort for immunogenicity)

				≥ 8				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
OPSONO-6A	10Pn	PIII(M5)	297	232	78.1	73.0	82.7	156.9	121.8	202.1
	Control	PIII(M5)	305	16	5.2	3.0	8.4	5.0	4.5	5.5
OPSONO-19A	10Pn	PIII(M5)	302	121	40.1	34.5	45.8	18.2	14.5	22.9
	Control	PIII(M5)	309	5	1.6	0.5	3.7	4.1	4.0	4.3

10Pn = Primed with 10Pn-PD-DiT + DTPa-HBV-IPV/Hib and boosted with 10Pn-PD-DiT + DTPa-IPV/Hib
Control = Primed with HBV + DTPa-IPV/Hib and boosted with HAV + DTPa-IPV/Hib
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

Supporting immunogenicity data

To date, the evaluation of vaccine efficacy in children receiving their primary vaccination course after 7 months of age is limited thus complicating the evaluation of the ideal number of doses to be given as catch up vaccination schedule in children above 7 months of age. However, recent data from the FinIP clinical study provided the first evidence of efficacy of Synflorix to protect against pneumonia in children receiving catch-up vaccination at greater than 7 months of age, in European children.

Effectiveness against hospital-diagnosed pneumonia was assessed as secondary objective. There were two catch-up cohorts in this study in which children received the number of doses as recommended in the European SmPC, i.e. children of 7-11 months of age received two primary doses of Synflorix with an interval of at least 4 weeks, followed by a booster dose with an interval of preferably 6 months since the previous vaccine dose [minimum 4 months] and children of 12-18 months of age received a 2-dose vaccination with Synflorix with an interval of at least and preferably 6 months between doses. Data on pneumonia was collected using one main national register: Finnish Care Register for Social Welfare and Health Care (maintained by THL).

In this study, VE against hospital-diagnosed pneumonia endpoints any time after the administration of the first vaccine dose was shown for both age cohorts with efficacy against hospital-diagnosed pneumonia of 33.2% (95% CI [3.0; 53.4]) and 22.4% (95% CI [-8.7: 44.8]) in children enrolled between 7 and 11 months of and between 12 and 18 months of age respectively (Catch-up vaccinated cohort). Considering that in FinIP study the observation period lasted 15-34 months from subject recruitment, some children at the end of observation were up to 45 months of age for the catch-up group of 7-11 months of age at recruitment and up to 53 months of age for catch up group of 12-18 months of age at recruitment. Therefore, the observed vaccine effect following catch-up vaccination included children in their 4th and 5th year of life.

The immunogenicity observed in the catch up cohort of children 3-4 years of age in Study 10PN-PD-DIT-046 (conducted in Sweden and Slovakia) has been compared to the immunogenicity in a similar population, in which efficacy against pneumonia has been shown, i.e. the Study 10PN-PD-DIT-053, nested study of FinIP with catch up vaccination schedules in children of 7-11 months of age at first vaccination (2 primary doses with an interval of at least 4 weeks, followed by a booster dose with an interval of preferably 6 months since the previous vaccine dose [minimum 4 months]) and in children of 12-18 months of age at first vaccination (a 2-dose vaccination schedule with Synflorix with an interval of at least and preferably 6 months between doses). As shown in Table 12, the immune responses in terms of antibody GMCs 1 month after completion of the primary vaccination in the children of 3-4 years of age are comparable or higher to that in study 053 (1 month post booster

vaccination in children of 7-11 months of age and 1 month post dose 2 in children of 12-18 months of age).

Table 12 Antibody responses in studies 053 and 046 (ATP cohort for analysis of immunogenicity)

Antibody	Study 053* 7-11 month old cohort			Study 053** 12-18 month old cohort			Study 046*** (children 3-4 years of age)		
	GMC	95% CI		GMC	95% CI		GMC	95% CI	
	value	LL	UL	value	LL	UL	value	LL	UL
ANTI-1	2.62	2.33	2.94	1.87	1.67	2.09	2.81	2.25	3.51
ANTI-4	5.45	4.85	6.14	5.28	4.77	5.84	8.44	7.16	9.94
ANTI-5	4.11	3.71	4.56	3.45	3.05	3.90	3.54	2.96	4.23
ANTI-6B	1.06	0.85	1.31	0.69	0.57	0.83	1.11	0.84	1.46
ANTI-7F	5.44	4.80	6.15	3.95	3.58	4.35	6.10	4.99	7.46
ANTI-9V	2.81	2.44	3.23	1.60	1.42	1.81	2.22	1.74	2.82
ANTI-14	8.38	7.42	9.47	6.04	5.37	6.79	6.48	4.98	8.44
ANTI-18C	19.87	17.08	23.12	21.27	18.70	24.19	22.28	18.14	27.36
ANTI-19F	11.73	9.73	14.13	12.10	10.38	14.11	17.03	13.38	21.68
ANTI-23F	2.04	1.71	2.43	1.27	1.07	1.50	1.09	0.81	1.45

GMC = geometric mean antibody concentration
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
*ELISA GMCs one month post-booster vaccination.
**ELISA GMCs one month after dose 2.
***ELISA GMCs one month after dose 2.

2.2.2. Discussion on clinical efficacy

A number of GCP issues occurred, however the CHMP considered that appropriate corrective actions have been taken and therefore the quality of the study is acceptable.

The interim results of the COMPAS study demonstrated an efficacy of 22% against likely bacterial pneumonia. These were statistically significant and of clinical relevance when considering the burden of disease. The protective efficacy against likely bacterial pneumonia was supported by the results for other definitions of CAP, and by the sensitivity analysis excluding subjects with remaining ICF issues. The argumentation provided related to the impact of the S-CAP cases retrieved during remonitoring was considered reasonable and the CHMP concurred with the MAH that the impact of these cases on the overall results was very limited. The data from the COMPAS trial conducted in children from the age of 6 weeks until 2 years were not considered sufficient to extrapolate pneumonia indication to the population of children up to 5 years. From the submitted documentation for this variation application, it was not clear on which basis the extension concerned older children. Pneumococcal pneumonia may represent a smaller percentage of pneumonia in children older than 2 years, which would affect the vaccine efficacy in this group. Therefore, the CHMP requested to discuss further evidence of efficacy against pneumonia up to the age of 5 years as well as the end of study results. The MAH provided the end of study results as well as additional analyses on stratification by age to evaluate whether the VE against CAP endpoints varied by age. From these analyses the CHMP noted that waning of protection against pneumonia cannot be excluded as the confidence intervals for efficacy were wide, which could be due to waning protection or replacement of other pathogens in older children. However, it can be concluded based on immunological data that vaccinating older children up to 5 years of age will result in similar or higher antibody responses compared to the youngest age groups, which makes protection against vaccine serotype pneumococcal pneumonia highly likely to be of at least similar magnitude in older and younger children. The current dose recommendations for older children are considered adequate also for the pneumonia indication, although efficacy against pneumonia has not been demonstrated in the older children. As a consequence, protective efficacy in different age groups is described in the SPC, section 5.1.

The results of other CAP definitions generally supported the results of the primary analysis. The sensitivity analysis was supportive of the conclusion on protection against pneumonia in the COMPAS trial. The immune responses as measured by ELISA were in line with previously presented results. The proportion of subjects with OPA titres ≥8 was also in agreement with previously presented results. The ELISA and OPA responses to serotypes 6A and 19A were as well in agreement with previously presented results.

The MAH provided supporting evidence of the potential for Synflorix to prevent against pneumococcal pneumonia up to 5 years of age in children of 7-11 months of age that receive two primary doses of Synflorix, followed by a booster dose, and in children of 12-23 months of age that receive a 2-dose vaccination with Synflorix in these age groups. The MAH considered that the efficacy observed in the FinIP study can be extrapolated to the older age group of children, i.e. 2 to 5 years olds. Based on these results, with an immune response at least comparable between the children of 12-18 months of age that received 2 doses of Synflorix and the children of 3-4 years of age who also received 2 doses of Synflorix, it can be considered that the posology in children of 2-5 years of age is 2 doses, as for the IPD and AOM indications.

The disease burden is substantial because of the high incidence of CAP among children and significant CAP-related morbidity and mortality worldwide. This disease burden is preventable with vaccination. Infection due to *Streptococcus pneumoniae* is considered one of the most common causes of CAP. The incidence of pneumonia in Latin America is generally estimated to be higher than in the EU. It is difficult to determine whether the results of the COMPAS could be extrapolated to a European setting, but in general vaccines have been shown to be more efficacious in developed countries compared to developing countries, while the opposite has rarely been demonstrated.

Vaccination with Synflorix in Europe would reduce the disease burden because the vaccine serotypes target the paediatric population that has the greatest rates of pneumococcal disease. The presence of 1, 5 and 7F serotypes in Synflorix would contribute substantially to this effect since these serotypes are among the most prevalent in European countries. The MAH argued that the serotype distribution for pneumonia in the COMPAS study does not significantly differ from a European setting, and that the results of the study are in agreement with other PCV trials in other regions. The factor most likely to cause a lower efficacy in Europe would be a different pneumonia serotype distribution, predominated by non-vaccine serotypes. This may be the case if widespread coverage is achieved as a result of vaccination, and serotype replacement occurs to a significant degree. The CHMP noted that the arguments provided favoured a similar protection in a European setting compared to Latin America, however, from the presented data be concluded that the data can be fully extrapolated to a European setting and this fact should be reflected in the SmPC.

There are mainly two ways to estimate the contribution of Synflorix to pneumonia prevention in European and non-European countries, one is by measuring the impact of the vaccine following universal mass vaccination (UMV, in which the impact is best captured by comparing hospitalizations due to pneumonia before and after vaccination), and the second is by applying vaccine-attributable reduction (VAR) from studies like COMPAS as an endpoint to determine the potential public health impact of Synflorix on the reduction of the burden of pneumonia. So far the assessment of impact of Synflorix on pneumonia comprehends a short period after vaccine introduction and further assessment of the impact of the vaccine in European and non-European countries is currently underway, especially in those where the vaccine has been introduced in the national immunization program (e.g. Finland, Kenya, etc). The prospective analysis over the upcoming period of time post vaccine introduction will ensure the generation of additional data on the impact of Synflorix in these countries.

The issue of strain coverage is important in the case of the 19A serotype given uncertainty as to the cross-protection afforded by the 19F serotype present in Synflorix. The emergence of this serotype in

the CAP aetiology following nearly universal use of PCV vaccines in EU should not be neglected. Close epidemiological surveillance in order to continuously assess the benefit of vaccinating with Synflorix is needed. The replacement of vaccine serotype with non-vaccine types might reduce the vaccine efficacy against pneumococcal pneumonia. This potential reduction of the vaccine benefit should not be underestimated and deserves close monitoring. Since routine infant immunization with Synflorix has only recently been implemented in EU countries, for example in Finland, data on long-term effectiveness and serotype replacement will have to be awaited. At this stage, the magnitude of the benefit of vaccination can be considered to be higher than the risk of replacement. The MAH should monitor vaccine efficacy against pneumonia, AOM and IPD as well as the impact of the vaccine on nasopharyngeal carriage of *S. pneumoniae, H. influenzae* and other bacterial pathogens.

Besides serotype replacement, emergence of antibiotic resistance in non-vaccine pneumococcal serotypes and any modification in the clinical manifestations of the disease should be specifically monitored. The CHMP endorsed these conclusions.

The CHMP expressed some concerns on potential risks with Synflorix vaccination such as serotype replacement and microbiological shifts to other pathogenic agents in pneumonia and requested that surveillance studies including close monitoring of pneumonia and carriage with respect to serotype replacement and bacteriological shifts as well as patterns of antibiotic resistance in the EU need to be outlined in an updated RMP. The MAH provided an overview of multiple supporting studies, which report on pneumonia and carriage with respect to serotype replacement and bacteriological shifts as well as patterns of antibiotic resistance in countries which have introduced Synflorix into their national vaccination programs. The MAH did not address how such investigations relate to the RMP. However, the CHMP noted that an updated RMP was submitted as part of the renewal application.

2.2.3. Conclusions on the clinical efficacy

The results of the COMPAS study that was conducted in Latin America demonstrated vaccine efficacy of 22% against likely bacterial community acquired pneumonia. These results were considered statistically significant and of clinical relevance when taking into account the burden of disease. In addition, the observed protective efficacy against likely bacterial pneumonia was supported by the results for other definitions of CAP and by sensitivity analysis. Similar protection is expected in a European setting. The end-of-study results showed a vaccine efficacy of 18% with a 100% efficacy against bacteraemic pneumococcal pneumonia or empyema due to vaccine serotypes. The protection was greatest in children < 36 months of age compared to children > 36 months of age suggesting a waning of protection. The persistence of protection against pneumonia beyond the age of 36 months is currently not established.

2.3. Clinical safety

Overall extent of exposure

In COMPAS, a total of 11,798 subjects received at least one dose of Synflorix and 11,799 subjects received at least one dose of control vaccine and were analysed for safety. Approximately 84% of the subjects received a full four dose course, i.e. 3 primary doses of Synflorix co-administered with Infanrix hexa followed by a booster dose of Synflorix co-administered with Infanrix-IPV/Hib for subjects in the 10Pn group or 3 primary doses of Engerix-B co-administered with Infanrix-IPV/Hib followed by a dose of Havrix, also co-administered with Infanrix-IPV/Hib for subjects in the Control group.

The total vaccinated cohort is presented in Table 13

The analysis of solicited AEs was performed on the Total Vaccinated cohort from the 'Immuno and reacto' subset. The analysis of unsolicited AEs was performed on the Total Vaccinated cohort enrolled in Panama, while the analysis of SAEs was performed on the Total Vaccinated cohort.

Table 13 COMPAS - Number and percentage of subjects who received study vaccine doses by vaccine (Total vaccinated cohort)

Total number of doses received	10Pn						Control					
	Synflorix N = 11798		*Infanrix hexa* N = 11798		*Infanrix-IPV/Hib* N = 11798		*Infanrix-IPV/Hib* N = 11799		*Havrix* N = 11799		*Engerix-B* N = 11799	
	n	%	n	%	n	%	n	%	n	%	n	%
0	0	0.0	0	0.0	1861	15.8	0	0.0	1893	16.0	0	0.0
1	563	4.8	567	4.8	9937	84.2	608	5.2	9906	84.0	609	5.2
2	367	3.1	375	3.2	-	-	364	3.1	-	-	375	3.2
3	946	8.0	10856	92.0	-	-	936	7.9	-	-	10815	91.7
4	9922	84.1	-	-	-	-	9891	83.8	-	-	-	-
Any	11798	100	11798	100	9937	84.2	11799	100	9906	84.0	11799	100

10Pn = Primed with Synflorix + Infanrix hexa and boosted with Synflorix + Infanrix-IPV/Hib
Control = Primed with Engerix-B + Infanrix-IPV/Hib and boosted with Havrix + Infanrix-IPV/Hib
N = number of subjects in each group included in the considered cohort
n/% = number/percentage of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least one dose

Demographic and Other Characteristics of Study Population

Demographic information for subjects in COMPAS included in the TVC and therefore included in the analysis of safety for SAEs is provided in Table 14. The mean age at first vaccination was 9.2 weeks (range 5 to 18 weeks) and 51% of the study population was male. Overall 57.2% of the subjects were White-Caucasian and 39.4% were mainly as mixed race (Other).

Table 15 presents the demographic characteristics of the cohorts analysed for specific AEs; solicited AEs during the 4-day period after each vaccination for 739 subjects enrolled in Panama and Argentina and unsolicited AEs for 7214 subjects enrolled in Panama. The mean ages at first vaccination of both these cohorts (9.4 weeks and 9.0 weeks, respectively) and the gender (49.4% and 51% of male, respectively) were similar to what was observed in the TVC as a whole. Overall, for both of these cohorts, 66.1% and 0.4% of the subjects were White-Caucasian; 32.2% and 98.5% of the subjects were mainly as mixed race (Other).

The study duration was at least 22 months for each subject (approximately up to 9 months after the booster dose) with last follow-up contact for SAEs at the end of the study (e.g. up to 48 months as for CAP/IPD efficacy analysis).

Table 14 COMPAS - Summary of demographic characteristics (Total vaccinated cohort)

		10Pn N = 11798		Control N = 11799		Total N = 23597	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (weeks) at vaccination dose: 1	Mean	9.2	-	9.2	-	9.2	-
	SD	1.93	-	1.92	-	1.92	-
	Median	9.0	-	9.0	-	9.0	-
	Minimum	6	-	5	-	5	-
	Maximum	16	-	18	-	18	-
Gender	Female	5796	49.1	5767	48.9	11563	49.0
	Male	6002	50.9	6032	51.1	12034	51.0
Race	African heritage / African American	116	1.0	99	0.8	215	0.9
	American Indian or Alaskan native	265	2.3	267	2.3	532	2.3
	Asian - central/south Asian heritage	0	0.0	0	0.0	0	0.0
	Asian - east Asian heritage	2	0.0	3	0.0	5	0.0
	Asian - Japanese heritage	0	0.0	0	0.0	0	0.0
	Asian - south east Asian heritage	0	0.0	0	0.0	0	0.0
	Native Hawaiian or other pacific islander	0	0.0	0	0.0	0	0.0
	White - Arabic / north African heritage	27	0.2	25	0.2	52	0.2
	White - Caucasian / European heritage	6729	57.2	6726	57.1	13455	57.2
	Other	4630	39.3	4652	39.5	9282	39.4
	Unknown	29	0.2	27	0.2	56	0.2

10Pn = Primed with Synflorix + Infanrix hexa and boosted with Synflorix + Infanrix-IPV/Hib
Control = Primed with Engerix-B + Infanrix -IPV/Hib and boosted with Havrix + Infanrix-IPV/Hib
N = total number of subjects; n/% = number / percentage of subjects in a given category
Value = value of the considered parameter; SD = standard deviation

Table 15 COMPAS - Summary of demographic characteristics in cohorts analysed for adverse events

		Total vaccinated cohort for solicited AEs analysis						Total vaccinated cohort for unsolicited AEs analysis					
		10Pn N = 374		Control N = 365		Total N = 739		10Pn N = 3602		Control N = 3612		Total N = 7214	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (weeks) at vaccination dose: 1	Mean	9.4	-	9.5	-	9.4	-	9.0	-	9.0	-	9.0	-
	SD	1.75	-	1.56	-	1.66	-	1.26	-	1.28	-	1.27	-
	Median	9.0	-	9.0	-	9.0	-	9.0	-	9.0	-	9.0	-
	Minimum	6	-	6	-	6	-	6	-	6	-	6	-
	Maximum	16	-	15	-	16	-	16	-	16	-	16	-
Gender	Female	185	49.5	189	51.8	374	50.6	1762	48.9	1775	49.1	3537	49.0
	Male	189	50.5	176	48.2	365	49.4	1840	51.1	1837	50.9	3677	51.0
Race	African heritage / African American	0	0.0	1	0.3	1	0.1	17	0.5	18	0.5	35	0.5
	American Indian or Alaskan native	4	1.1	3	0.8	7	0.9	20	0.6	19	0.5	39	0.5
	Asian - central/south Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - east Asian heritage	0	0.0	0	0.0	0	0.0	1	0.0	2	0.1	3	0.0
	Asian - Japanese heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - south east Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Native Hawaiian or other pacific islander	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Arabic / north African heritage	2	0.5	2	0.5	4	0.5	0	0.0	0	0.0	0	0.0
	White - Caucasian / European heritage	246	66.0	242	66.3	488	66.1	14	0.4	15	0.4	29	0.4
	Other	121	32.4	117	32.1	238	32.2	3521	98.5	3531	98.5	7052	98.5
	Unknown	1	0.3	0	0.0	1	0.1	29	0.8	27	0.8	56	0.8

10Pn = Primed with Synflorix + Infanrix hexa and boosted with Synflorix + Infanrix-IPV/Hib
Control = Primed with Engerix-B + Infanrix-IPV/Hib and boosted with Havrix + Infanrix-IPV/Hib
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Analysis of adverse events

Solicited local and general AEs were only solicited in subjects that were part of the 'immuno and reacto' subset, i.e., approximately 1,000 subjects (500 subjects respectively in Argentina and Panama) were planned to be included in this analysis. Unsolicited symptoms were only collected in subjects that were enrolled in Panama. Therefore, the overall incidences of AEs (solicited or unsolicited, local and/ or general) are presented for subjects from the TVC who were enrolled in Panama and were part of the 'immuno and reacto' subset.

Out of the 1,001 subjects who were enrolled in the 'Immuno and reacto' subset, 262 subjects from Panama were excluded because their parents/LAR(s)/guardian(s) could not be re-contacted (236 subjects) or did not agree to the use of the subject's immunogenicity and reactogenicity data after they had been informed that they had signed an incorrect version of the ICF (26 subjects). As a consequence, the TVC for solicited AEs analysis actually included 739 subjects (374 subjects in the 10Pn group and 365 subjects in the Control group). Of these subjects, 713 subjects (96.5%; 362 subjects in the 10Pn group and 351 subjects in the Control group) received a full primary vaccination course and 667 (90.3%; 346 subjects in the 10Pn group and 331 subjects in the Control group) received the complete primary and booster course.

Out of the 7359 subjects who were enrolled in Panama 145 subjects were excluded because the signed ICF was not valid (142 subjects) or they did not receive any vaccination (3 subjects). Thus the TVC for unsolicited AEs analysis included 7214 subjects (3602 subjects in the 10Pn groups and 3612 subjects in the Control group).

Primary vaccination course

During the 31- day post-primary vaccination period, the percentage of subjects reporting at least one AE (solicited and/or unsolicited, local and/or general) was similar after subsequent doses of the primary vaccination course in both groups (87.0% after the first dose, 86.4% after the second dose and 82.9% after the third dose in the 10Pn group; 77.9% after the first dose, 73.6% after the second dose and 74.5% after the third dose in the Control group).

During the 31-day post-primary vaccination period at least one AE (solicited and/ or unsolicited, local and/ or general) was reported after 85.5% of doses in the 10Pn group and after 75.4% of doses in the Control group; grade 3 AEs (solicited and/ or unsolicited, local and/ or general) were reported after 9.5% of doses in the 10Pn group and after 7.8% of doses in the Control group. The incidence of local AEs was lower than the incidence of general AEs after each dose.

During the 31-day post-booster vaccination period at least one AE (solicited and/ or unsolicited, local and/ or general) was reported for 67.0% of subjects in the 10Pn group and 52.9% of subjects in the Control group; Grade 3 AEs (solicited and/ or unsolicited, local and/ or general) were reported for 5.5% of subjects in the 10Pn group and for 4.9% of subjects in the Control group.

Common Adverse Events

Solicited local adverse events

Primary vaccination course

The incidence of solicited local AEs reported during the 4-day post-primary vaccination was collected.

During the 4-day post-primary vaccination period, the observed incidence of solicited local (any and grade 3) symptoms overall per dose was higher in infants receiving 3 doses of Synflorix and Infanrix hexa than in infants receiving 3 doses of Engerix-B control vaccine and Infanrix-IPV/Hib.

Pain (independent of the injection site) was the most frequently reported solicited local AE in both groups (52.1% of doses in the 10Pn group and 29.5% of doses in the Control group), followed by redness (34.0% of doses vs. 23.3% of doses, respectively) then swelling (26.2% of doses vs. 17.7% of doses, respectively). Pain was also the local AE most frequently reported as Grade 3 (after 7.9% of doses in the 10Pn group and 3.0% of doses in the Control group). In the 10Pn group, pain (of any intensity and Grade 3 pain) was reported at a similar incidence at the Synflorix and Infanrix hexa injection sites (49.1% [Synflorix] versus 48.8% [Infanrix hexa] of all doses for any pain and 7.5% [Synflorix] versus 6.9% [Infanrix hexa] for Grade 3 pain).

Medical advice was infrequently sought for any local AE (for ≤ 0.5% of all subjects over the primary vaccination course).

Booster vaccination

The most frequently reported solicited local AE within the 4-day period after the booster vaccination was pain (44.2% of subjects) in the 10Pn group and redness in the Control group (33.7% of subjects). In the 10Pn group, the incidence of pain was similar between the two injection sites (40.7% at the injection site of Synflorix and 41.3% at the injection site of Infanrix hexa).

Grade 3 solicited local AEs were reported for a maximum of 4.7% of subjects (pain) in the 10Pn group and 6.3% of subjects (redness) in the Control group.

Medical advice was sought for ≤ 0.6% of all subjects for any local AE after the booster dose.

No large swelling site reactions were reported following booster vaccination.

Solicited general adverse events

Overall, per dose, irritability was the most frequently reported solicited general AE in both groups following 52.1% of doses in the 10Pn group and 35.2% of doses in the Control group.

Rectal temperature > 40°C was experienced following 0.3% of all doses. All episodes of fever > 40°C were considered by the Investigator to be related to vaccination. In the Control group, no fever > 40°C was reported. Medical advice for fever was sought after 0.6% of all doses of the subjects in the 10Pn group and after 0.5% of all doses in the Control group.

Most solicited general AEs were considered by the Investigator to be causally related to vaccination. Irritability was the most frequently reported solicited AE vaccine-related in both groups; reported after 51.2% of doses in the 10Pn group and after 34.7% of doses in the Control group. Grade 3 drowsiness or loss of appetite considered by the Investigator to be related to vaccination were reported after 1.9% and 1.2%, respectively, of all doses in the 10Pn group over the primary vaccination course.

Medical advice for drowsiness and for irritability was sought for only one and two subjects respectively and was not sought for loss of appetite.

Booster vaccination

Irritability was the most frequently reported solicited general AE in both groups, following 38.2% of doses in the 10Pn group and 31.4% of doses in the Control group.

The most frequently reported solicited general AE considered by the Investigator to be causally related was irritability in both groups; reported by 35.6% of subjects in the 10Pn group and by 30.0% of subject in the Control group.

Grade 3 solicited general AEs were reported following a maximum of 0.6% of doses (irritability) in the 10Pn group and 1.7% of doses (loss of appetite) in the Control group.

No subject in the 10Pn group experienced fever > 40°C after the booster dose. Fever > 40°C was reported for 2 subjects in the Ctrl group.

Deaths

During the entire study period, a total of 45 subjects (19 subjects in the 10Pn group and 26 subjects in the Control group) had an SAE with fatal outcome. None of the reported fatal SAEs were considered by the Investigator to be causally related to vaccination.

For 32 subjects (12 subjects from the 10Pn group and 20 subjects from the Control group), death occurred during 1st year of life.

Other serious adverse events

The incidence of SAEs from the administration of the first dose up to study end was collected for the TVC (23,597 vaccinated subjects [11,798 subjects in the 10Pn group and 11,799 subjects in the Control group]) and for the subjects excluded from the TVC.

During the entire study period, SAEs were reported for 5,202 (22.0%) subjects (2,534 [21.5%] subjects in the 10Pn group and 2,668 [22.6%] subjects in the Control group in the TVC. The numbers of events appeared to be evenly distributed across the two treatment groups.

The most commonly reported SAEs (> 1% of subjects in any group) are provided in Table 34, for each event.

The most frequently reported SAE was gastroenteritis in the 10Pn group and pneumonia in the Control group; both events were reported with an incidence of 4.7%.

One SAE reported for one subject in the Control group was considered to be causally related to vaccination by the Investigator. Information about this event is provided in Table 35. Subject 59 developed an apparent life threatening event (coded to the MedDRA SOC Respiratory, thoracic and mediastinal disorders) 12 hours after the administration of the second dose of the control vaccine. The subject was hospitalised and treated. The event resolved within 1 day. The subject had a low birth weight and intrauterine growth retardation, which were considered as risk factors.

Other Significant Adverse Events

Adverse events/serious adverse events leading to study withdrawal

For 72 subjects (32 subjects from the 10Pn group and 40 subjects from the Control group), an SAE leading to premature discontinuation was reported. None of these SAEs were considered by the Investigator to be related to vaccination.

Out of the 32 SAEs reported in the 10Pn group, 19 SAEs had fatal outcome. In the Control group, 25 out of 40 SAEs had fatal outcome.

Six subjects (3 in the 10Pn group and 3 in the Control group) were withdrawn due to non-serious AEs.

Convulsions

There were 33 convulsive episodes reported after the booster dose (12 in the 10Pn group and 21 in the Control group).

In the 10Pn group, 9 convulsive episodes were categorised as “generalised” and 3 as “missing confirmed” i.e. not enough information on the convulsive episode was available to be able to categorise it. In the Control group, 15 convulsive episodes were categorised as “generalised” and 3 as “missing confirmed”.

None of convulsion episodes was considered to be causally related to vaccination by the Investigator.

Analysis of Adverse Events by Organ System or Syndrome

All unsolicited adverse events

Out of the 7359 subjects who were enrolled in Panama, 145 subjects were excluded because the signed ICF was not valid (142 subjects) or they did not receive any vaccination (3 subjects). Thus the TVC for unsolicited AE analysis included 7,214 subjects (3,602 subjects in the 10Pn group and 3,612 subjects in Control group). This summary presents the analysis of unsolicited symptoms which occurred within the 31- day (Days 0-30) period after each vaccination (primary and booster doses).

Primary vaccination course

A total of 63.1% of doses in the 10Pn group and 58.4% of doses in the Control group were followed by at least one unsolicited AE. The most frequently reported unsolicited AE in the 10Pn group were Pyrexia (25.4% of doses) followed by nasopharyngitis (25.2% of doses) and diarrhoea (5.5% of doses). In the Control group, the most frequently reported unsolicited AE were nasopharyngitis (26.6% of doses), pyrexia (15.7% of doses) and diarrhoea (5.0% of doses).

Grade 3 unsolicited AEs were reported following 4.6 % of doses in the 10Pn group and 4.5% of doses in the Control group.

Booster vaccination

At least one unsolicited AE was reported for 50.8% of subjects in the 10Pn group and 49.5% of subjects in the Control group. The most frequently reported unsolicited AE were nasopharyngitis (21.6% of subjects in the 10Pn group and 20.9% of subjects in the Control group), pyrexia (10.7% of subjects in the 10Pn group and 6.9% of subjects in the Control group), and diarrhoea (4.9% of subjects in the 10Pn group and 5.4% of subjects in the Control group).

Grade 3 unsolicited AEs were reported for 4.2% of subjects in the 10Pn group and 3.8% of subjects in the Control group.

2.3.1. Discussion on the clinical safety

There was lack of safety data in the interim report submitted with this variation application, therefore CHMP requested the MAH to provide all available safety data from the COMPAS study. The CHMP noted the multiple analyses performed on various subgroups of smaller size within the COMPAS study as well as differences regarding the choice of denominators for some of the analyses.

The MAH has stated that the TVC included 23,597 (11798 in 10Pn and 11799 in control) subjects which represented > 95% of the according-to-protocol cohort. However, it is noted that only 84.1% of the TVC received the full four dose course (primary vaccination + booster dose). Furthermore, different

populations within the TVC were used to analyse different levels of safety information. An immuno and reacto subset of 1001 subjects enrolled in Panama and Argentina was used to analyse solicited local and general symptoms; there were only 739 subjects used in the analysis due to exclusions. Another subset, subjects from Panama, was used to analyse unsolicited symptoms; there were a total of 7214 subjects for this analysis. The TVC was used to analyse SAEs from the first vaccine dose until the study end as well as the occurrence of a convulsive episode within 30 days after booster vaccination. The CHMP recommended using a conservative approach about reporting results from this trial, as the entire TVC was not followed for the observation of all analysed events (solicited local/general events, unsolicited events).No new safety concerns were observed in the COMPAS study.

2.3.2. Conclusions on the clinical safety

No new safety signals were identified in the submitted final results of the COMPAS study. The current approved SmPC adequately reflects the safety profile of Synflorix and no safety updates are deemed necessary.

2.4. Update of the Product information

4.1 Therapeutic indications

Active immunisation against invasive disease, pneumonia and acute otitis media caused by Streptococcus pneumoniae in infants and children from 6 weeks up to 5 years of age. See sections 4.4 and 5.1 for information on protection against specific pneumococcal serotypes.

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

As a consequence of this new indication, sections 4.4 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed and accepted by the CHMP.

4.4 Special warnings and precautions for use

As with any vaccine, Synflorix may not protect all vaccinated individuals against invasive pneumococcal disease, pneumonia or otitis media caused by the serotypes in the vaccine. Protection against otitis media caused by pneumococcal serotypes in the vaccine and protection against pneumonia is expected to be substantially lower than protection against invasive disease. ~~In addition, a~~As otitis media and pneumonia ~~is~~ are caused by many micro-organisms other than the Streptococcus pneumoniae serotypes represented in the vaccine, the overall protection against ~~otitis media~~these diseases is expected to be limited (see section 5.1).

In clinical trials Synflorix elicited an immune response to all ten serotypes included in the vaccine, but the magnitude of the responses varied between serotypes. The functional immune response to serotypes 1 and 5 was lower in magnitude than the response against all other vaccine serotypes. It is not known whether this lower functional immune response against serotypes 1 and 5 will result in lower protective efficacy against invasive disease, pneumonia or otitis media caused by these serotypes (see section 5.1).

5.1 Pharmacodynamic properties

Epidemiological data

Pneumonia of different aetiologies is a leading cause of childhood morbidity and mortality globally. In prospective studies, Streptococcus pneumoniae was estimated to be responsible for 30-50% of pneumonia cases.

1. Invasive pneumococcal disease (which includes sepsis, meningitis, bacteraemic pneumonia and bacteraemia)

2. Pneumonia
Efficacy against pneumonia was assessed in a large-scale randomised, double-blind clinical trial (Clinical Otitis Media and Pneumonia Study - COMPAS) conducted in Latin America. 23,738 healthy infants received either Synflorix or hepatitis B control vaccine at 2, 4 and 6 months of age followed respectively by either Synflorix or hepatitis A control vaccine at 15 to 18 months of age. The mean duration follow-up from 2 weeks post-dose 3 in the ATP cohort was 23 months (range from 0 to 34 months) for the interim analysis (IA) and 30 months (range from 0 to 44 months) for the end-of-study analysis. At the end of this IA or end-of-study ATP follow-up period, the mean age was 29 months (range from 4 to 41 months) and 36 months (range from 4 to 50 months), respectively. The proportion of subjects who received the booster dose in the ATP cohort was 92.3% in both analyses.

Efficacy of Synflorix against first episodes of likely bacterial Community Acquired Pneumonia (CAP) occurring from 2 weeks after the administration of the 3rd dose was demonstrated in the ATP cohort (P value ≤ 0.002) in the interim analysis (event-driven; primary objective).
Likely bacterial CAP (B-CAP) is defined as radiologically confirmed CAP cases with either alveolar consolidation/pleural effusion on the chest X-ray, or with non alveolar infiltrates but with C reactive protein (CRP) ≥ 40 mg/L.

The vaccine efficacy against B-CAP observed at the interim analysis is presented below (table 3).

Table 3: Numbers and percentages of subjects with first episodes of B-CAP occurring from 2 weeks after the administration of the 3rd dose of Synflorix or control vaccine and vaccine efficacy (ATP cohort)

Synflorix N=10,295		*Control vaccine N=10,201*		*Vaccine efficacy*
n	*% (n/N)*	*n*	*% (n/N)*	
240	*2.3%*	*304*	*3.0%*	*22.0% (95% CI: 7.7; 34.2)*

N number of subjects per group
n/% number/percentage of subjects reporting a first episode of B-CAP anytime from 2 weeks after the administration of the 3rd dose
CI Confidence Interval

In the interim analysis (ATP cohort), the vaccine efficacy against first episodes of CAP with alveolar consolidation or pleural effusion (C-CAP, WHO definition) was 25.7% (95% CI: 8.4; 39.6) and against first episodes of clinically suspected CAP referred for X-ray was 6.7% (95% CI: 0.7; 12.3).

At the end-of-study analysis (ATP cohort), the vaccine efficacy (first episodes) against B-CAP was 18.2% (95% CI: 4.1; 30.3), against C-CAP 22.4% (95% CI: 5.7; 36.1) and against clinically suspected CAP referred for X-ray 7.3% (95% CI: 1.6; 12.6). Efficacy was 100% (95% CI: 41.9; 100) against bacteraemic pneumococcal pneumonia or empyema due to vaccine serotypes. The protection against B-CAP before booster dose and at the time or after booster dose was 13.6% (95% CI: -11.3; 33.0) and 21.7% (95% CI: 3.4; 36.5) respectively. For C-CAP it was 15.1% (95% CI: -15.5; 37.6) and 26.3% (95% CI: 4.4; 43.2) respectively.
The reduction in B-CAP and C-CAP was greatest in children < 36 months of age (vaccine efficacy of 20.6% (95% CI: 6.5; 32.6) and 24.2% (95% CI: 7.4; 38.0) respectively). Vaccine efficacy results in children > 36 months of age suggest a waning of protection. The persistence of protection against B-CAP and C-CAP beyond the age of 36 months is currently not established.

The results of the COMPAS study, which was performed in Latin America, should be interpreted with caution due to possible differences in epidemiology of pneumonia in different geographical locations.

As a consequence of the introduction of pneumonia as a disease caused by *Streptococcus pneumoniae* the numbering in this section as well as the numbering of the Tables have been re-ordered.

Package leaflet

Section 1. What Synflorix is and what it is used for

It is used to help protect your child from 6 weeks up to 5 years of age against:
a bacteria called 'Streptococcus pneumoniae'. This bacteria can cause serious illnesses including meningitis, sepsis ~~or~~ and bacteraemia (bacteria in blood stream) ~~and~~ as well as ear infection ~~and~~ or pneumonia.

2.5. Significance of paediatric studies

The CHMP is of the opinion that study 10PN-PD-DIT-028 (Clinical Otitis Media and Pneumonia Study [COMPAS]) is contained in the agreed Paediatric Investigation Plan, which is not yet completed, is considered as significant.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The primary endpoint results of the COMPAS study demonstrated a vaccine of efficacy of 22% against likely bacterial community acquired pneumonia. These results were considered statistically significant and clinically relevant when the burden of disease is taken into consideration. The end of study results confirmed the interim results. The observed protective efficacy of Synflorix against likely bacterial community acquired pneumonia was supported by results for other definitions of community acquired pneumonia and by sensitivity analysis carried out. The protection was greatest in children < 36 months of age.

Uncertainty in the knowledge about the beneficial effects

The protection against pneumonia caused by pneumococcal vaccine serotypes is expected to be substantially lower than protection against invasive disease. Serotype distribution for pneumonia in the COMPAS study conducted in Latin America does not significantly differ from a European setting and therefore it is expected that a similar benefit of vaccination might be observed in a European population. However, lower efficacy could be observed in Europe depending on pneumonia serotype distribution determined by non-vaccine serotypes. Although the study was not primarily designed to evaluate the duration of protection; waning was observed. The age when no relevant protection can be expected is unknown.

Risks

Unfavourable effects

The reactogenicity is generally similar to what has been shown previously in younger children. No new safety signals were identified in the submitted final results of the COMPAS study. The current approved SmPC adequately reflects the safety profile of Synflorix and no safety updates are warranted.

Benefit-risk balance

Based on the current evidence the CHMP concluded that the benefit-risk balance is favourable in the claimed indication. The use of the vaccine should occur in accordance with official national recommendations.

4. Recommendations

☒ The application for extension of the indication to include active immunisation against pneumonia for Synflorix is approvable as all other concerns have been resolved.

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

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

Extension of indication to include active immunisation against pneumonia for Synflorix.

As a consequence of the new indication, sections 4.4 and 5.1 of the Summary of Product Characteristics have been updated with data from study10PN-PD-DIT-028 - Clinical Otitis Media and Pneumonia Study (COMPAS). The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan [P/0162/2012] and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and in the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include active immunisation against pneumonia for Synflorix.

As a consequence, sections 4.1, 4.4 and 5.1 of the Summary of Product Characteristics have been updated with data from study10PN-PD-DIT-028 - Clinical Otitis Media and Pneumonia Study (COMPAS). The Package Leaflet was updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Summary

Please refer to Assessment Report EMEA/H/C/000973/II/52.