Clinical trial results:
Study to compare immunogenicity of GSK Biologicals' 10Pn-PD-DiT 4-dose presentation to the licensed Synflorix™ (10Pn-PD-DiT) vaccine when co-administered with DTPw-combination vaccine in healthy infants.

Summary

EudraCT number	2014-000750-11
Trial protocol	Outside EU/EEA
Global end of trial date	22 May 2016

Results information

Result version number	v2
This version publication date	08 February 2017
First version publication date	20 November 2016
Version creation reason	• New data added to full data set Primary/ secondary results.

Trial information

Trial identification

Sponsor protocol code	200799

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium, B-1330
Public contact	Clinical Disclosure Advisor, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Disclosure Advisor, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 January 2016
Global end of trial reached?	Yes
Global end of trial date	22 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of 10Pn-PD-DiT vaccine (4-dose presentation) as compared to 10Pn-PD-DiT vaccine (Synflorix™-1-dose presentation) in terms of the immune response to the 10 vaccine pneumococcal serotypes one month after dose 3.
Criterion:
Non-inferiority was demonstrated if the upper limit (UL) of the 2-sided 95% confidence interval (CI) of the geometric mean antibody concentration (GMC) ratios (Synflorix/10Pn_4d) was below a limit of 2-fold for each of the 10 vaccine pneumococcal serotypes.

Protection of trial subjects:

All subjects were supervised for 30 min after vaccination with appropriate medical treatment readily available. Vaccines were administered by qualified and trained personnel. Only eligible subjects that had no contraindications to any components of the vaccines were vaccinated. Subjects were followed-up for 30 days after each/last vaccination.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bangladesh: 320
Worldwide total number of subjects	320
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	320
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Two epochs were defined in the study. The duration of the study was for Epoch 001: Primary starting at Month 0 and ending at Month 4 and for Epoch 002: Booster starting at Month 8 and ending at Month 9.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	320
Number of subjects completed	320

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Observer-blind: during the course of the study, the vaccine recipient and those responsible for the evaluation of any study outcome were all unaware of which vaccine was administered. Vaccine preparation and administration was done by authorised medical personnel who didn't participate in any of the study clinical evaluation.
The laboratory in charge of the laboratory testing was blinded to the treatment, and codes were used to link the subject and study to each sample.

Arms

Are arms mutually exclusive?	Yes
Arm title	10Pn_4d Group

Arm description:

Healthy male or female subjects, between and including 6 to 10 weeks (42-76 days) of age at the time of first vaccination, received 3 doses of the investigational 4-dose presentation 10Pn-PD-DiT vaccine given approximatively at 6, 10 and 18 weeks of age (primary vaccination – Epoch 001) and 3 doses of DTPw-HBV/Hib vaccine given approximatively at 6, 10 and 14 weeks of age (according to the EPI schedule). They also received a booster dose of the 4-dose presentation 10Pn-PD-DiT vaccine at approximatively 9 months of age (Epoch-002).

Arm type	Experimental
Investigational medicinal product name	10Pn-PD-DiT 4-dose presentation
Investigational medicinal product code	GSK1024850A
Other name	10Pn-PD-DiT-4-dose presentation
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3 doses were given approximatively at 6, 10 and 18 weeks of age (primary vaccination) and a booster dose at approximatively 9 months of age. The vaccine was administered by intramuscular injection into the right anterolateral thigh.

Investigational medicinal product name	Tritanrix HB
Investigational medicinal product code	DTPw-HBV
Other name	DTPw-HBV
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Tritanrix HB and Hiberix were used for the preparation of the DTPw-HBV/Hib vaccine: DTPw-HBV component: suspension in monodose vial to be reconstituted with Hib component. 3 doses were given approximatively at 6, 10 and 14 weeks of age (primary vaccination). The vaccine was administered by intramuscular injection into the left anterolateral thigh.

Investigational medicinal product name	Hiberix
Investigational medicinal product code	Hib
Other name	Hib
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Tritanrix HB and Hiberix were used for the preparation of the DTPw-HBV/Hib vaccine: DTPw-HBV component: suspension in monodose vial to be reconstituted with Hib component. 3 doses were given approximatively at 6, 10 and 14 weeks of age (primary vaccination). The vaccine was administered by intramuscular injection into the left anterolateral thigh.

Arm title	Synflorix Group

Arm description:

Healthy male or female subjects, between and including 6 to 10 weeks (42-76 days) of age at the time of first vaccination, received 3 doses of the licensed 1-dose presentation 10Pn-PD-DiT (Synflorix™) vaccine given approximatively at 6, 10 and 18 weeks of age (primary vaccination – Epoch 001) and 3 doses of DTPw-HBV/Hib vaccine given approximatively at 6, 10 and 14 weeks of age (according to the EPI schedule). They also received a booster dose of the 1-dose presentation 10Pn-PD-DiT vaccine at approximatively 9 months of age (Epoch-002).

Arm type	Active comparator
Investigational medicinal product name	Tritanrix HB
Investigational medicinal product code	DTPw-HBV
Other name	DTPw-HBV
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Tritanrix HB and Hiberix were used for the preparation of the DTPw-HBV/Hib vaccine: DTPw-HBV component: suspension in monodose vial to be reconstituted with Hib component. 3 doses were given approximatively at 6, 10 and 14 weeks of age (primary vaccination). The vaccine was administered by intramuscular injection into the left anterolateral thigh.

Investigational medicinal product name	Hiberix
Investigational medicinal product code	Hib
Other name	Hib
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Tritanrix HB and Hiberix were used for the preparation of the DTPw-HBV/Hib vaccine: DTPw-HBV component: suspension in monodose vial to be reconstituted with Hib component. 3 doses were given approximatively at 6, 10 and 14 weeks of age (primary vaccination). The vaccine was administered by intramuscular injection into the left anterolateral thigh.

Investigational medicinal product name	Synflorix™
Investigational medicinal product code	GSK1024850A
Other name	10Pn-PD-DiT-1-dose presentation
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3 doses were given approximatively at 6, 10 and 18 weeks of age (primary vaccination) and a booster dose at approximatively 9 months of age. The vaccine was administered by intramuscular injection into the right anterolateral thigh.

Number of subjects in period 1	10Pn_4d Group	Synflorix Group
Started	160	160
Completed	152	145
Not completed	8	15
Consent withdrawn by subject	-	4
Not included in the Epoch 002	3	2
Death	1	1
Migrated/moved from study area	3	5
Lost to follow-up	1	3

Baseline characteristics

Reporting groups	
Reporting group title	10Pn_4d Group
Reporting group description:	
Healthy male or female subjects, between and including 6 to 10 weeks (42-76 days) of age at the time of first vaccination, received 3 doses of the investigational 4-dose presentation 10Pn-PD-DiT vaccine given approximatively at 6, 10 and 18 weeks of age (primary vaccination – Epoch 001) and 3 doses of DTPw-HBV/Hib vaccine given approximatively at 6, 10 and 14 weeks of age (according to the EPI schedule). They also received a booster dose of the 4-dose presentation 10Pn-PD-DiT vaccine at approximatively 9 months of age (Epoch-002).	
Reporting group title	Synflorix Group
Reporting group description:	
Healthy male or female subjects, between and including 6 to 10 weeks (42-76 days) of age at the time of first vaccination, received 3 doses of the licensed 1-dose presentation 10Pn-PD-DiT (Synflorix™) vaccine given approximatively at 6, 10 and 18 weeks of age (primary vaccination – Epoch 001) and 3 doses of DTPw-HBV/Hib vaccine given approximatively at 6, 10 and 14 weeks of age (according to the EPI schedule). They also received a booster dose of the 1-dose presentation 10Pn-PD-DiT vaccine at approximatively 9 months of age (Epoch-002).	

Reporting group values	10Pn_4d Group	Synflorix Group	Total
Number of subjects	160	160	320
Age categorical Units: Subjects			

Age continuous			
Age continuous description			
Units: weeks			
arithmetic mean	6.9	6.8	
standard deviation	± 1.3	± 1.2	-
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	80	73	153
Male	80	87	167

End points

End points reporting groups

Reporting group title	10Pn_4d Group

Reporting group description:

Healthy male or female subjects, between and including 6 to 10 weeks (42-76 days) of age at the time of first vaccination, received 3 doses of the investigational 4-dose presentation 10Pn-PD-DiT vaccine given approximatively at 6, 10 and 18 weeks of age (primary vaccination – Epoch 001) and 3 doses of DTPw-HBV/Hib vaccine given approximatively at 6, 10 and 14 weeks of age (according to the EPI schedule). They also received a booster dose of the 4-dose presentation 10Pn-PD-DiT vaccine at approximatively 9 months of age (Epoch-002).

Reporting group title	Synflorix Group

Reporting group description:

Healthy male or female subjects, between and including 6 to 10 weeks (42-76 days) of age at the time of first vaccination, received 3 doses of the licensed 1-dose presentation 10Pn-PD-DiT (Synflorix™) vaccine given approximatively at 6, 10 and 18 weeks of age (primary vaccination – Epoch 001) and 3 doses of DTPw-HBV/Hib vaccine given approximatively at 6, 10 and 14 weeks of age (according to the EPI schedule). They also received a booster dose of the 1-dose presentation 10Pn-PD-DiT vaccine at approximatively 9 months of age (Epoch-002).

Primary: Antibody concentrations against pneumococcal serotypes (Epoch 001)

End point title	Antibody concentrations against pneumococcal serotypes (Epoch 001)

End point description:

Antibodies assessed for this outcome measure were those against the vaccine/cross-reactive pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (ANTI-1, -4, -5, -6A, -6B, -7F, -9V, -14, -18C, -19A, -19F and -23F). Antibody concentrations were measured by 22F-inhibition enzyme-linked immunosorbent assay (ELISA), expressed as geometric mean concentrations (GMCs), in micrograms per milliliter (µg/mL). The cut-off of the assay was an antibody concentration higher than or equal to (≥) 0.05 µg/mL. Primary outcome results correspond to antibody concentrations for the 10 vaccine serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.

End point type	Primary

End point timeframe:

At study Month 4, e. g. at one month post-Dose 3 of pneumococcal vaccine

End point values	10Pn_4d Group	Synflorix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	146		
Units: µg/mL				
geometric mean (confidence interval 95%)				
ANTI-1 (N=154,146)	2.78 (2.43 to 3.18)	3.03 (2.6 to 3.54)		
ANTI-4 (N=154,146)	4.23 (3.69 to 4.84)	3.87 (3.33 to 4.51)		
ANTI-5 (N=154,146)	5.12 (4.46 to 5.88)	5.3 (4.59 to 6.12)		
ANTI-6B (N=154,146)	1.23 (0.95 to 1.57)	1.37 (1.05 to 1.79)		
ANTI-7F (N=154,146)	5.52 (4.9 to 6.22)	5.79 (5.06 to 6.62)		

ANTI-9V (N=154,146)	4.6 (3.98 to 5.32)	4.07 (3.34 to 4.95)		
ANTI-14 (N=154,146)	4.97 (4.05 to 6.1)	4.84 (3.91 to 5.99)		
ANTI-18C (N=154,146)	19.58 (16.65 to 23.03)	21.18 (17.9 to 25.06)		
ANTI-19F (N=154,146)	13.24 (11.17 to 15.68)	13.11 (11.16 to 15.41)		
ANTI-23F (N=154,146)	1.59 (1.25 to 2.01)	2.04 (1.61 to 2.58)		
ANTI-6A (N=154,146)	0.31 (0.25 to 0.38)	0.29 (0.23 to 0.36)		
ANTI-19A (N=154,146)	0.76 (0.6 to 0.96)	0.68 (0.54 to 0.86)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

(Synflorix/10Pn_4d) antibody GMCs ratio for ANTI-1 serotype: to demonstrate non-inferiority of 10Pn-PD-DiT vaccine (4-dose presentation) as compared to 10Pn-PD-DiT vaccine (1-dose presentation) in terms of immune response, 1 month after dose 3. Criterion: the upper limit (UL) of the 2-sided 95% confidence interval (CI) of the geometric mean antibody concentration (GMC) ratios (Synflorix/10Pn_4d) should be below a limit of 2-fold for each of the 10 serotypes.

Comparison groups	Synflorix Group v 10Pn_4d Group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	GMCs ratio
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.33

Notes:

[1] - GMCs ratio and its 95 % CI were obtained using an ANOVA model on the logarithm-10 transformed concentrations-pooled variance.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

(Synflorix/10Pn_4d) antibody GMCs ratio for ANTI-4 serotype: to demonstrate non-inferiority of 10Pn-PD-DiT vaccine (4-dose presentation) as compared to 10Pn-PD-DiT vaccine (1-dose presentation) in terms of immune response, 1 month after dose 3. Criterion: the upper limit (UL) of the 2-sided 95% confidence interval (CI) of the geometric mean antibody concentration (GMC) ratios (Synflorix/10Pn_4d) should be below a limit of 2-fold for each of the 10 serotypes.

Comparison groups	Synflorix Group v 10Pn_4d Group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	GMCs ratio
Point estimate	0.92

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.12

Notes:

[2] - GMCs ratio and its 95 % CI were obtained using an ANOVA model on the logarithm-10 transformed concentrations-pooled variance.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

(Synflorix/10Pn_4d) antibody GMCs ratio for ANTI-5 serotype: to demonstrate non-inferiority of 10Pn-PD-DiT vaccine (4-dose presentation) as compared to 10Pn-PD-DiT vaccine (1-dose presentation) in terms of immune response, 1 month after dose 3. Criterion: the upper limit (UL) of the 2-sided 95% confidence interval (CI) of the geometric mean antibody concentration (GMC) ratios (Synflorix/10Pn_4d) should be below a limit of 2-fold for each of the 10 serotypes.

Comparison groups	Synflorix Group v 10Pn_4d Group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	GMCs ratio
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.26

Notes:

[3] - GMCs ratio and its 95 % CI were obtained using an ANOVA model on the logarithm-10 transformed concentrations-pooled variance.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

(Synflorix/10Pn_4d) antibody GMCs ratio for ANTI-6B serotype: to demonstrate non-inferiority of 10Pn-PD-DiT vaccine (4-dose presentation) as compared to 10Pn-PD-DiT vaccine (1-dose presentation) in terms of immune response, 1 month after dose 3. Criterion: the upper limit (UL) of the 2-sided 95% confidence interval (CI) of the geometric mean antibody concentration (GMC) ratios (Synflorix/10Pn_4d) should be below a limit of 2-fold for each of the 10 serotypes.

Comparison groups	Synflorix Group v 10Pn_4d Group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	GMCs ratio
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.61

Notes:

[4] - GMCs ratio and its 95 % CI were obtained using an ANOVA model on the logarithm-10 transformed concentrations-pooled variance.

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

(Synflorix/10Pn_4d) antibody GMCs ratio for ANTI-7F serotype: to demonstrate non-inferiority of 10Pn-PD-DiT vaccine (4-dose presentation) as compared to 10Pn-PD-DiT vaccine (1-dose presentation) in terms of immune response, 1 month after dose 3. Criterion: the upper limit (UL) of the 2-sided 95% confidence interval (CI) of the geometric mean antibody concentration (GMC) ratios (Synflorix/10Pn_4d) should be below a limit of 2-fold for each of the 10 serotypes.

Comparison groups	Synflorix Group v 10Pn_4d Group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	GMCs ratio
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.25

Notes:

[5] - GMCs ratio and its 95 % CI were obtained using an ANOVA model on the logarithm-10 transformed concentrations-pooled variance.

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

(Synflorix/10Pn_4d) antibody GMCs ratio for ANTI-9V serotype: to demonstrate non-inferiority of 10Pn-PD-DiT vaccine (4-dose presentation) as compared to 10Pn-PD-DiT vaccine (1-dose presentation) in terms of immune response, 1 month after dose 3. Criterion: the upper limit (UL) of the 2-sided 95% confidence interval (CI) of the geometric mean antibody concentration (GMC) ratios (Synflorix/10Pn_4d) should be below a limit of 2-fold for each of the 10 serotypes.

Comparison groups	Synflorix Group v 10Pn_4d Group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	GMCs ratio
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.13

Notes:

[6] - GMCs ratio and its 95 % CI were obtained using an ANOVA model on the logarithm-10 transformed concentrations-pooled variance.

Statistical analysis title	Statistical analysis 7

Statistical analysis description:

(Synflorix/10Pn_4d) antibody GMCs ratio for ANTI-14 serotype: to demonstrate non-inferiority of 10Pn-PD-DiT vaccine (4-dose presentation) as compared to 10Pn-PD-DiT vaccine (1-dose presentation) in terms of immune response, 1 month after dose 3. Criterion: the upper limit (UL) of the 2-sided 95% confidence interval (CI) of the geometric mean antibody concentration (GMC) ratios (Synflorix/10Pn_4d) should be below a limit of 2-fold for each of the 10 serotypes.

Comparison groups	Synflorix Group v 10Pn_4d Group

Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	GMCs ratio
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.31

Notes:

[7] - GMCs ratio and its 95 % CI were obtained using an ANOVA model on the logarithm-10 transformed concentrations-pooled variance.

Statistical analysis title	Statistical analysis 8

Statistical analysis description:

(Synflorix/10Pn_4d) antibody GMCs ratio for ANTI-18C serotype: to demonstrate non-inferiority of 10Pn-PD-DiT vaccine (4-dose presentation) as compared to 10Pn-PD-DiT vaccine (1-dose presentation) in terms of immune response, 1 month after dose 3. Criterion: the upper limit (UL) of the 2-sided 95% confidence interval (CI) of the geometric mean antibody concentration (GMC) ratios (Synflorix/10Pn_4d) should be below a limit of 2-fold for each of the 10 serotypes.

Comparison groups	Synflorix Group v 10Pn_4d Group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	GMCs ratio
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.37

Notes:

[8] - GMCs ratio and its 95 % CI were obtained using an ANOVA model on the logarithm-10 transformed concentrations-pooled variance.

Statistical analysis title	Statistical analysis 9

Statistical analysis description:

(Synflorix/10Pn_4d) antibody GMCs ratio for ANTI-19F serotype: to demonstrate non-inferiority of 10Pn-PD-DiT vaccine (4-dose presentation) as compared to 10Pn-PD-DiT vaccine (1-dose presentation) in terms of immune response, 1 month after dose 3. Criterion: the upper limit (UL) of the 2-sided 95% confidence interval (CI) of the geometric mean antibody concentration (GMC) ratios (Synflorix/10Pn_4d) should be below a limit of 2-fold for each of the 10 serotypes.

Comparison groups	Synflorix Group v 10Pn_4d Group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Parameter estimate	GMCs ratio
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.25

Notes:

[9] - GMCs ratio and its 95 % CI were obtained using an ANOVA model on the logarithm-10 transformed concentrations-pooled variance.

Statistical analysis title	Statistical analysis 10

Statistical analysis description:

(Synflorix/10Pn_4d) antibody GMCs ratio for ANTI-23F serotype: to demonstrate non-inferiority of 10Pn-PD-DiT vaccine (4-dose presentation) as compared to 10Pn-PD-DiT vaccine (1-dose presentation) in terms of immune response, 1 month after dose 3. Criterion: the upper limit (UL) of the 2-sided 95% confidence interval (CI) of the geometric mean antibody concentration (GMC) ratios (Synflorix/10Pn_4d) should be below a limit of 2-fold for each of the 10 serotypes.

Comparison groups	Synflorix Group v 10Pn_4d Group
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	GMCs ratio
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.8

Notes:

[10] - GMCs ratio and its 95 % CI were obtained using an ANOVA model on the logarithm-10 transformed concentrations-pooled variance.

Secondary: Titers for opsonophagocytic activity against pneumococcal serotypes (Epoch 001)

End point title	Titers for opsonophagocytic activity against pneumococcal serotypes (Epoch 001)

End point description:

Titers for opsonophagocytic activity assessed for this outcome measure were those for opsonophagocytic activity against the vaccine/cross-reactive pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (OPA-1, -4, -5, -6A, -6B, -7F, -9V, -14, -18C, 19 A ,-19F and -23F). The cut-off of the assay was a titer for opsonophagocytic activity higher than or equal to (≥) 8.

End point type	Secondary

End point timeframe:

At study Month 4, e. g. at one month post-Dose 3 of pneumococcal vaccine

End point values	10Pn_4d Group	Synflorix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	74		
Units: Titers				
geometric mean (confidence interval 95%)				
OPA-1 (N=74,74)	48.3 (34.9 to 67)	52.8 (36 to 77.5)		
OPA-4 (N=75,74)	823.1 (670.9 to 1009.8)	836.8 (644.5 to 1086.6)		
OPA-5 (N=73,74)	179 (140.7 to 227.8)	211 (162.9 to 273.2)		
OPA-6B (N=73,73)	560.6 (336.9 to 932.8)	759.6 (470.2 to 1227.3)		

OPA-7F (N=74,73)	2044 (1669.3 to 2502.9)	2076.8 (1627 to 2650.9)		
OPA-9V (N=75,74)	613.3 (444.9 to 845.4)	821.1 (602.5 to 1119.2)		
OPA-14 (N=73,74)	1563.9 (1105.1 to 2213.2)	1655.8 (1141.1 to 2402.7)		
OPA-18C (N=75,74)	3965.4 (3288.6 to 4781.5)	3809.7 (3067 to 4732.3)		
OPA-19F (N=75,74)	2151.3 (1573.5 to 2941.4)	2879.2 (2348.4 to 3529.9)		
OPA-23F (N=75,74)	524.8 (338.5 to 813.9)	730.2 (495.6 to 1075.7)		
OPA-6A (N=66,69)	50.3 (26.9 to 94)	68.5 (36.8 to 127.7)		
OPA-19A (N=72,71)	98.6 (60.9 to 159.6)	117.1 (71.9 to 190.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against protein D (Anti-PD) (Epoch 001)

End point title	Concentrations of antibodies against protein D (Anti-PD) (Epoch 001)

End point description:

Anti-PD antibody concentrations were measured by enzyme-linked immunosorbent assay (ELISA), expressed as geometric mean concentrations (GMCs), in ELISA Units per milliliter (EL.U/mL). The cut-off of the assay was an anti-PD antibody concentration higher than or equal to (≥) 153 EL.U/mL.

End point type	Secondary

End point timeframe:

At study Month 4, e. g. at one month post-Dose 3 of pneumococcal vaccine

End point values	10Pn_4d Group	Synflorix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	75		
Units: EL.U/mL				
geometric mean (confidence interval 95%)	2410.5 (2029.2 to 2863.5)	2495.4 (2055.7 to 3029.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any and Grade 3 solicited local symptoms (Epoch 001)

End point title	Number of subjects with any and Grade 3 solicited local symptoms (Epoch 001)

End point description:

Assessed local symptoms were pain, redness and swelling. Any = Occurrence of the specified solicited local symptom, regardless of intensity. Grade 3 Pain = Crying when limb was moved/spontaneously painful. Grade 3 Redness/Swelling = Redness/swelling at injection site larger than (>) 30 millimeters (mm). Dose 1 = 10Pn-PD-DIT+DTPw-HBV/Hib at 6 weeks of age. Dose 2 = 10Pn-PD-DIT+DTPw-HBV/Hib at 10 weeks of age. Dose 4 = 10Pn-PD-DIT at 18 weeks of age.

End point type	Secondary

End point timeframe:

Within the 4-day (Days 0-3) post-vaccination period following each primary dose (D) of 10Pn-PD-DiTvaccine

End point values	10Pn_4d Group	Synflorix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Subjects				
Any Pain, post D1 (N=159;156)	82	90		
Grade 3 Pain, post D1 (N=159;156)	4	5		
Any Redness, post D1 (N=159;156)	24	26		
Grade 3 Redness, post D1 (N=159;156)	0	0		
Any Swelling, post D1 (N=159;156)	63	64		
Grade 3 Swelling, post D1 (N=159;156)	0	0		
Any Pain, post D2 (N=158,152)	56	56		
Grade 3 Pain, post D2 (N=158,152)	1	0		
Any Redness, post D2 (N=158,152)	22	26		
Grade 3 Redness, post D2 (N=158,152)	0	0		
Any Swelling, post D2 (N=158,152)	31	37		
Grade 3 Swelling, post D2 (N=158,152)	0	0		
Any Pain, post D4 (N=155,147)	13	15		
Grade 3 Pain, post D4 (N=155,147)	0	0		
Any Redness, post D4 (N=155,147)	9	8		
Grade 3 Redness, post D4 (N=155,147)	0	0		
Any Swelling, post D4 (N=155,147)	11	9		
Grade 3 Swelling, post D4 (N=155,147)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any and Grade 3 solicited general symptoms and with solicited general symptoms with relationship to vaccination (Epoch 001)

End point title	Number of subjects with any and Grade 3 solicited general symptoms and with solicited general symptoms with relationship to vaccination (Epoch 001)

End point description:

Assessed solicited general symptoms were Drowsiness, Irritability/Fussiness (Irr./Fuss.), Loss of appetite (Loss Appet.) and Fever (axillary route - temperature equal or higher than [≥] 37.5 degrees Celsius [°C]),. Any = Occurrence of the specified solicited general symptom, regardless of intensity or

relationship to vaccination. Grade 3 Drowsiness = Drowsiness that prevented normal activity. Grade 3 Irr./Fuss. = Crying that could not be comforted/prevented normal activity. Grade 3 Loss of appetite = Subject did not eat at all. Grade 3 Fever = (axillary) temperature higher than (>) 39.5°C. Related = Occurrence of the specified symptom assessed by the investigator as causally related to vaccination. Dose 1 = 10Pn-PD-DIT+DTPw-HBV/Hib at 6 weeks of age. Dose 2 = 10Pn-PD-DIT+DTPw-HBV/Hib at 10 weeks of age. Dose 4 = 10Pn-PD-DIT at 18 weeks of age.

End point type	Secondary

End point timeframe:

Within the 4-day (Days 0-3) post-vaccination period following each primary dose (D) of 10Pn-PD-DiTvaccine

End point values	10Pn_4d Group	Synflorix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Subjects				
Any Drowsiness, post D1 (N=159,156)	26	31		
Grade 3 Drowsiness, post D1 (N=159,156)	1	5		
Any Irr./Fuss., post D1 (N=159,156)	61	62		
Grade 3 Irr./Fuss., post D1 (N=159,156)	14	8		
Any Loss Appet., post D1 (N=159,156)	43	46		
Grade 3 Loss Appet., post D1 (N=159,156)	4	3		
Any Fever, post D1 (N=159,156)	28	30		
Grade 3 Fever, post D1 (N=159,156)	0	0		
Any Drowsiness, post D2 (N=158,152)	15	23		
Grade 3 Drowsiness, post D2 (N=158,152)	1	1		
Any Irr./Fuss., post D2 (N=158,152)	39	47		
Grade 3 Irr./Fuss., post D2 (N=158,152)	4	5		
Any Loss Appet., post D2 (N=158,152)	24	20		
Grade 3 Loss Appet., post D2 (N=158,152)	3	2		
Any Fever, post D2 (N=158,152)	23	18		
Grade 3 Fever, post D2 (N=158,152)	0	0		
Any Drowsiness, post D4 (N=155,147)	6	8		
Grade 3 Drowsiness, post D4 (N=155,147)	0	1		
Any Irr./Fuss., post D4 (N=155,147)	10	12		
Grade 3 Irr./Fuss., post D4 (N=155,147)	0	1		
Any Loss Appet., post D4 (N=155,147)	5	5		
Grade 3 Loss Appet., post D4 (N=155,147)	0	0		
Any Fever, post D4 (N=155,147)	2	6		
Grade 3 Fever, post D4 (N=155,147)	0	0		
Related Drowsiness, post D1 (N=159,156)	26	29		
Related Irr./Fuss., post D1 (N=159,156)	61	62		
Related Loss Appet., post D1 (N=159,156)	43	46		
Related Fever, post D1 (N=159,156)	28	30		

Related Drowsiness, post D2 (N=158,152)	15	23		
Related Irr./Fuss., post D2 (N=158,152)	39	47		
Related Loss Appet., post D2 (N=158,152)	23	20		
Related Fever, post D2 (N=158,152)	22	18		
Related Drowsiness, post D4 (N=155,147)	6	8		
Related Irr./Fuss., post D4 (N=155,147)	10	12		
Related Loss Appet., post D4 (N=155,147)	5	5		
Related Fever, post D4 (N=155,147)	2	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any unsolicited adverse events (AEs) (Epoch 001)

End point title	Number of subjects with any unsolicited adverse events (AEs) (Epoch 001)

End point description:

An unsolicited AE was defined as any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For the marketed products administered in the study, this also included failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse of the product. Any = Occurrence of an unsolicited AE, regardless of intensity or relationship to vaccination.

End point type	Secondary

End point timeframe:

Within the 31-day (Days 0-30) period post primary vaccination, across doses

End point values	10Pn_4d Group	Synflorix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	160		
Units: Subjects	10	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any serious adverse events (SAEs) (Epoch 001)

End point title	Number of subjects with any serious adverse events (SAEs) (Epoch 001)

End point description:

An SAE was defined as any medical occurrence that resulted in death, was life-threatening, required hospitalization or prolongation of hospitalization, resulted in disability/incapacity in a subject. AE(s)

considered as SAE(s) also included invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that did not result in hospitalization, as per the medical or scientific judgement of the physician. Any = Occurrence of an SAE, regardless of relationship to vaccination.

End point type	Secondary

End point timeframe:

From Month 0 to Month 4

End point values	10Pn_4d Group	Synflorix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	160		
Units: Subjects	4	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody concentrations against pneumococcal serotypes (Epoch 002)

End point title	Antibody concentrations against pneumococcal serotypes (Epoch 002)

End point description:

Antibodies assessed for this outcome measure were those against the vaccine/cross-reactive pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (ANTI-1, -4, -5, -6A, -6B, -7F, -9V, -14, -18C, -19A, -19F and -23F). Antibody concentrations were measured by 22F-inhibition enzyme-linked immunosorbent assay (ELISA), expressed as geometric mean concentrations (GMCs), in micrograms per milliliter (µg/mL). The cut-off of the assay was an antibody concentration higher than or equal to (≥) 0.05 µg/mL.

End point type	Secondary

End point timeframe:

At Month 8 (M8) and Month 9 (M9), e.g.: prior to and at one month post booster vaccination with pneumococcal vaccine

End point values	10Pn_4d Group	Synflorix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	144		
Units: µg/mL				
geometric mean (confidence interval 95%)				
ANTI-1 M8 (N=151,144)	0.93 (0.79 to 1.1)	0.99 (0.81 to 1.19)		
ANTI-1 M9 (N=151,144)	6.37 (5.48 to 7.41)	7.5 (6.28 to 8.97)		
ANTI-4 M8 (N=151,144)	1.9 (1.65 to 2.19)	1.71 (1.45 to 2.01)		
ANTI-4 M9 (N=151,143)	9.68 (8.47 to 11.06)	9.41 (8.16 to 10.86)		
ANTI-5 M8 (N=151,144)	1.75 (1.5 to 2.05)	1.75 (1.48 to 2.08)		

ANTI-5 M9 (N=151,144)	11.53 (10.14 to 13.12)	12.24 (10.65 to 14.05)		
ANTI-6B M8 (N=151,144)	1.14 (0.93 to 1.4)	1.06 (0.84 to 1.32)		
ANTI-6B M9 (N=151,144)	3.76 (3.01 to 4.69)	4.11 (3.21 to 5.25)		
ANTI-7F M8 (N=151,144)	2.86 (2.5 to 3.27)	2.75 (2.4 to 3.16)		
ANTI-7F M9 (N=151,144)	12.84 (11.38 to 14.48)	13.71 (12.01 to 15.65)		
ANTI-9V M8 (N=151,144)	2.32 (1.96 to 2.75)	2.25 (1.83 to 2.76)		
ANTI-9V M9 (N=151,144)	12.07 (10.42 to 13.98)	12.43 (10.22 to 15.13)		
ANTI-14 M8 (N=151,144)	2.98 (2.39 to 3.72)	2.4 (1.9 to 3.04)		
ANTI-14 M9 (N=151,143)	9.84 (8.02 to 12.08)	9.72 (7.92 to 11.93)		
ANTI-18C M8 (N=151,144)	8.37 (7.14 to 9.82)	9.23 (7.82 to 10.9)		
ANTI-18C M9 (N=151,144)	41.64 (36.87 to 47.02)	47.06 (41.88 to 52.88)		
ANTI-19F M8 (N=151,144)	6.36 (5.36 to 7.55)	6.45 (5.5 to 7.57)		
ANTI-19F M9 (N=151,144)	23.43 (19.48 to 28.19)	24.96 (21.07 to 29.57)		
ANTI-23F M8 (N=151,144)	1.09 (0.89 to 1.33)	1.21 (0.96 to 1.53)		
ANTI-23F M9 (N=151,144)	6.69 (5.66 to 7.9)	6.69 (5.33 to 8.41)		
ANTI-6A M8 (N=151,144)	0.31 (0.24 to 0.39)	0.3 (0.24 to 0.38)		
ANTI-6A M9 (N=151,144)	0.97 (0.74 to 1.26)	1.11 (0.83 to 1.49)		
ANTI-19A M8 (N=151,144)	0.7 (0.55 to 0.89)	0.69 (0.54 to 0.88)		
ANTI-19A M9 (N=151,144)	3.03 (2.26 to 4.05)	3.63 (2.73 to 4.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Titers for opsonophagocytic activity against pneumococcal serotypes (Epoch 002)

End point title	Titers for opsonophagocytic activity against pneumococcal serotypes (Epoch 002)

End point description:

Titers for opsonophagocytic activity assessed for this outcome measure were those for opsonophagocytic activity against the vaccine/cross-reactive pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (OPA-1, -4, -5, -6A, -6B, -7F, -9V, -14, -18C, -19A, -19F and -23F). The cut-off of the assay was a titer for opsonophagocytic activity higher than or equal to (≥) 8.

End point type	Secondary

End point timeframe:

At study Month 8 (M8) and Month 9 (M9), e.g.: prior to and at one month post booster vaccination with pneumococcal vaccine

End point values	10Pn_4d Group	Synflorix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	73		
Units: Titers				
geometric mean (confidence interval 95%)				
OPA-1 M8 (N=72,70)	11.5 (8.2 to 16.1)	12.8 (9.1 to 17.9)		
OPA-1 M9 (N=73,71)	227.7 (170.6 to 303.9)	326.7 (238.7 to 447)		
OPA-4 M8 (N=72,70)	248.1 (178.6 to 344.7)	280.5 (193.4 to 406.6)		
OPA-4 M9 (N=76,73)	2025.4 (1641.6 to 2498.8)	2888.7 (2221.6 to 3756.1)		
OPA-5 M8 (N=73,71)	51.3 (37 to 71.3)	62.7 (44.4 to 88.7)		
OPA-5 M9 (N=76,73)	550.6 (437.8 to 692.4)	801.2 (633.2 to 1013.6)		
OPA-6B M8 (N=73,70)	290.3 (177.1 to 475.7)	286.8 (183.5 to 448)		
OPA-6B M9 (N=74,72)	851.3 (533.4 to 1358.6)	1352 (913.9 to 1999.9)		
OPA-7F M8 (N=74,73)	1112.8 (864.8 to 1431.8)	1181.7 (933.4 to 1495.9)		
OPA-7F M9 (N=76,73)	4574.7 (3756.1 to 5571.6)	5635.8 (4561.7 to 6962.9)		
OPA-9V M8 (N=69,72)	415.8 (280.6 to 616.3)	570.6 (408.4 to 797.3)		
OPA-9V M9 (N=76,73)	2308.4 (1903.3 to 2799.7)	3181.9 (2376.9 to 4259.6)		
OPA-14 M8 (N=73,72)	660.1 (432.4 to 1007.6)	745 (513.9 to 1080)		
OPA-14 M9 (N=76,73)	3345.6 (2585 to 4330.1)	3649.1 (2808.6 to 4741.2)		
OPA-18C M8 (N=74,73)	1505.4 (1196.4 to 1894.1)	1735.2 (1373.8 to 2191.7)		
OPA-18C M9 (N=76,73)	7316.1 (6137.6 to 8720.8)	7181.6 (6003.6 to 8590.7)		
OPA-19F M8 (N=74,72)	770.1 (536.6 to 1105.3)	1254.3 (990.8 to 1587.9)		
OPA-19F M9 (N=76,73)	3197.3 (2271.1 to 4501.2)	4757.7 (3772.3 to 6000.4)		
OPA-23F M8 (N=70,69)	267.7 (168.7 to 424.9)	252.7 (154.8 to 412.4)		
OPA-23F M9 (N=76,73)	1250.8 (931.3 to 1679.8)	1465.6 (1002.9 to 2141.7)		
OPA-6A M8 (N=72,68)	52.4 (27.4 to 100.1)	45.5 (24 to 86.5)		

OPA-6A M9 (N=71,68)	192 (102.9 to 358.4)	284.4 (158.4 to 510.6)		
OPA-19A M8 (N=73,71)	42.7 (25.1 to 72.7)	43.6 (26.6 to 71.3)		
OPA-19A M9 (N=76,72)	410.4 (246.7 to 682.8)	591.7 (356.9 to 980.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against protein D (Anti-PD) (Epoch 002)

End point title	Concentrations of antibodies against protein D (Anti-PD) (Epoch 002)

End point description:

Anti-PD antibody concentrations were measured by enzyme-linked immunosorbent assay (ELISA), expressed as geometric mean concentrations (GMCs), in ELISA Units per milliliter (EL.U/mL). The cut-off of the assay was an anti-PD antibody concentration higher than or equal to (≥) 153 EL.U/mL.

End point type	Secondary

End point timeframe:

At study Month 9 (M9), e.g.: at one month post booster vaccination with pneumococcal vaccine

End point values	10Pn_4d Group	Synflorix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	73		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-PD	2672.4 (2285.5 to 3124.8)	2944 (2486.2 to 3486)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any and Grade 3 solicited local symptoms (Epoch 002)

End point title	Number of subjects with any and Grade 3 solicited local symptoms (Epoch 002)

End point description:

Assessed local symptoms were pain, redness and swelling. Any = Occurrence of the specified solicited local symptom, regardless of intensity. Grade 3 Pain = Crying when limb was moved/spontaneously painful. Grade 3 Redness/Swelling = Redness/swelling at injection site larger than (>) 30 millimeters (mm).

End point type	Secondary

End point timeframe:

Within the 4-day (Days 0-3) period after booster vaccination

End point values	10Pn_4d Group	Synflorix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	145		
Units: Subjects				
Any Pain	9	2		
Grade 3 Pain	1	0		
Any Redness	14	5		
Grade 3 Redness	0	0		
Any Swelling	16	8		
Grade 3 Swelling	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any and Grade 3 solicited general symptoms and with solicited general symptoms with relationship to vaccination (Epoch 002)

End point title	Number of subjects with any and Grade 3 solicited general symptoms and with solicited general symptoms with relationship to vaccination (Epoch 002)

End point description:

Assessed solicited general symptoms were Drowsiness, Irritability/Fussiness (Irr./Fuss.), Loss of appetite (Loss Appet.) and Fever (axillary route - temperature equal or higher than [≥] 37.5 degrees Celsius [°C]). Any = Occurrence of the specified solicited general symptom, regardless of intensity or relationship to vaccination. Related = Occurrence of the specified symptom assessed by the investigators as causally related to vaccination. Grade 3 Drowsiness = Drowsiness that prevented normal activity. Grade 3 Irr./Fuss. = Crying that could not be comforted/prevented normal activity. Grade 3 Loss of appetite = Subject did not eat at all. Grade 3 Fever = (Axillary) temperature higher than (>) 39.5°C.

End point type	Secondary

End point timeframe:

Within the 4-day (Days 0-3) period after booster vaccination

End point values	10Pn_4d Group	Synflorix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	145		
Units: Subjects				
Any Drowsiness	8	4		
Grade 3 Drowsiness	0	0		
Related Drowsiness	8	4		
Any Irr./Fuss.	11	5		
Grade 3 Irr./Fuss.	1	0		
Related Irr./Fuss.	11	5		
Any Loss Appet.	8	4		
Grade 3 Loss Appet.	0	0		

Related Loss Appet.	8	4		
Any Fever	4	3		
Grade 3 Fever	0	0		
Related Fever	4	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any unsolicited AEs (Epoch 002)

End point title	Number of subjects with any unsolicited AEs (Epoch 002)

End point description:

An unsolicited AE was defined as any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For the marketed products administered in the study, this also included failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse of the product. Any = Occurrence of an unsolicited AE, regardless of intensity or relationship to vaccination.

End point type	Secondary

End point timeframe:

Within the 31-day (Days 0-30) period post booster vaccination

End point values	10Pn_4d Group	Synflorix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	145		
Units: Subjects				
Any AE(s)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any SAEs during the entire duration of the study

End point title	Number of subjects with any SAEs during the entire duration of the study

End point description:

An SAE was defined as any medical occurrence that resulted in death, was life-threatening, required hospitalization or prolongation of hospitalization, resulted in disability/incapacity in a subject. AE(s) considered as SAE(s) also included invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that did not result in hospitalization, as per the medical or scientific judgement of the physician. Any = Occurrence of an SAE, regardless of relationship to vaccination.

End point type	Secondary

End point timeframe:

From Day 0 to Month 9

End point values	10Pn_4d Group	Synflorix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	160		
Units: Subjects				
Any SAE(s)	4	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited symptoms and Unsolicited AEs: during 31 days post vaccination period; SAEs: during the whole study period (from Day 0 to Month 9).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Synflorix Group

Reporting group description:

Healthy male or female subjects, between and including 6 to 10 weeks (42-76 days) of age at the time of first vaccination, received 3 doses of the licensed 1-dose presentation 10Pn-PD-DiT (Synflorix™) vaccine given approximatively at 6, 10 and 18 weeks of age (primary vaccination – Epoch 001) and 3 doses of DTPw-HBV/Hib vaccine given approximatively at 6, 10 and 14 weeks of age (according to the EPI schedule). They also received a booster dose of the 1-dose presentation 10Pn-PD-DiT vaccine at approximatively 9 months of age (Epoch-002).

Reporting group title	10Pn_4d Group

Reporting group description:

Healthy male or female subjects, between and including 6 to 10 weeks (42-76 days) of age at the time of first vaccination, received 3 doses of the investigational 4-dose presentation 10Pn-PD-DiT vaccine given approximatively at 6, 10 and 18 weeks of age (primary vaccination – Epoch 001) and 3 doses of DTPw-HBV/Hib vaccine given approximatively at 6, 10 and 14 weeks of age (according to the EPI schedule). They also received a booster dose of the 4-dose presentation 10Pn-PD-DiT vaccine at approximatively 9 months of age (Epoch-002).

Serious adverse events	Synflorix Group	10Pn_4d Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 160 (5.63%)	4 / 160 (2.50%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Chemical poisoning			
subjects affected / exposed	1 / 160 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Cerebral palsy			
subjects affected / exposed	1 / 160 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Laryngomalacia			
subjects affected / exposed	1 / 160 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	1 / 160 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 160 (1.25%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	2 / 160 (1.25%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 160 (0.63%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 160 (2.50%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	0 / 160 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 160 (0.00%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	1 / 160 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Synflorix Group	10Pn_4d Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	126 / 160 (78.75%)	120 / 160 (75.00%)	
Nervous system disorders			
Somnolence			
subjects affected / exposed	42 / 160 (26.25%)	38 / 160 (23.75%)	
occurrences (all)	66	55	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	102 / 160 (63.75%)	101 / 160 (63.13%)	
occurrences (all)	163	160	
Pyrexia			
subjects affected / exposed	47 / 160 (29.38%)	51 / 160 (31.88%)	
occurrences (all)	57	59	
Swelling			
subjects affected / exposed	81 / 160 (50.63%)	83 / 160 (51.88%)	
occurrences (all)	118	121	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	40 / 160 (25.00%)	37 / 160 (23.13%)	
occurrences (all)	65	69	

Psychiatric disorders Irritability subjects affected / exposed occurrences (all)	 84 / 160 (52.50%) 126	 77 / 160 (48.13%) 121	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 53 / 160 (33.13%) 75	 58 / 160 (36.25%) 80	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2015	Amendment 1 The protocol amendment has been issued to implement the following guidance from the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B): Following post-study approval discussion with the Ethical Review Committee (ERC) of the ICDDR,B regarding the strengthening of the informed consent process, the presence of one witness has been requested for the informed consent of each subject's parent/legally acceptable representative, irrespective of literacy status. In line with local ICDDR,B guidelines, the ERC required the implementation of a Data and Safety Monitoring Board (DSMB) which will be established by the ERC. The safety monitoring section has been updated accordingly.
21 October 2015	Amendment 2 Recently Synflorix effectiveness against vaccine-related serotype 19A has been added to the product information and Synflorix can be recommended for active immunization against 19A pneumococcal disease in addition to the vaccine serotypes. The purpose of this amendment is to add demonstration of the non-inferiority of the 10Pn-PD-DiT vaccine (4-dose presentation) as compared to 10Pn-PD-DiT vaccine (1-dose presentation) in terms of the immune response to the vaccine-related serotype 19A as a first secondary objective. Following review of the validation package of the anti-protein D (PD) IgG ELISA, the Company decided to fully redevelop and revalidate this assay in order to comply with the latest validation requirements of the Regulatory Authorities. In consequence, the anti-PD ELISA assay cut-off has been changed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported