Clinical trial results:
A phase III, single group, open study to assess the immunogenicity, safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine in Mexico when co-administered with GSK Biologicals' Infanrix hexa (DTPa-HBV-IPV/Hib) vaccine as a 3-dose primary immunization course at 2, 4 and 6 months of age and GSK Biologicals' Rotarix vaccine (HRV) as a 2-dose primary immunization course at 2 and 4 months of age.

Summary

EudraCT number	2015-001510-10
Trial protocol	Outside EU/EEA
Global end of trial date	31 March 2008

Results information

Result version number	v1
This version publication date	22 March 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	109661

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00489554
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 Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, 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	13 August 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the immunogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine in Mexico, one month post dose III, when co-administered with GSK Biologicals' Infanrix hexa and GSK Biologicals' Rotarix vaccines, to the immune responses as observed in the pivotal non-inferiority, lot-to-lot consistency study 10PN-PD-DIT-001 in Europe.

Protection of trial subjects:

All subjects were supervised closely for at least 30 minutes following vaccination with appropriate medical treatment readily available. Vaccines were administered by qualified and trained personnel. Vaccines were administered only to eligible subjects that had no contraindications to any components of the vaccines. The subject's parents/guardians were instructed to contact the investigator immediately should their child manifest any signs or symptoms they perceived as serious. Subjects were followed up for any safety event from the time the subject consented to participate in the study until she/he was discharged.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 July 2007
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	Mexico: 230
Worldwide total number of subjects	230
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)	230
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:

230 subjects were enrolled in the study, all of whom were vaccinated. Study duration was of approximately 5 months (from Day 0, day of 1st vaccination, up to Month 5).

Pre-assignment

Screening details:

During the screening the following steps occurred: check for inclusion/exclusion criteria, contraindications/precautions, medical history of the subjects and signing informed consent forms.

Period 1

Period 1 title	Overall Study (Day 0 to Month 5) (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Synflorix Vaccine Group

Arm description:

Subjects receiving 3 doses of 10Pn-PD-DiT (Synflorix) vaccine co-administered with 3 doses of DTPa-HBV-IPV/Hib (Infanrix hexa) vaccine at 2, 4 and 6 months of age, and co-administered with 2 doses of HRV (Rotarix) vaccine at 2 and 4 months of age. 10Pn-PD-DIT and DTPa-HBV-IPV/Hib vaccines were administered intramuscularly in the thigh, on the right and left side, respectively. HRV vaccine was administered orally.

Arm type	Experimental
Investigational medicinal product name	10-valent pneumococcal and non-typeable H. influenzae protein D conjugate vaccine
Investigational medicinal product code	10Pn-PD-DiT
Other name	Pneumococcal conjugate vaccine GSK1024850A; 10Pn
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection, 3 doses administered in the right thigh.

Investigational medicinal product name	Infanrix hexa
Investigational medicinal product code	DTPa-HBV-IPV/Hib
Other name	
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection, 3 doses administered in the left thigh.

Investigational medicinal product name	Rotarix
Investigational medicinal product code	
Other name	HRV
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Oral use

Dosage and administration details:

Oral, 2 doses.

Number of subjects in period 1	Synflorix Vaccine Group
Started	230
Completed	226
Not completed	4
Consent withdrawn by subject	1
Adverse event, non-fatal	2
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Synflorix Vaccine Group
Reporting group description:	
Subjects receiving 3 doses of 10Pn-PD-DiT (Synflorix) vaccine co-administered with 3 doses of DTPa-HBV-IPV/Hib (Infanrix hexa) vaccine at 2, 4 and 6 months of age, and co-administered with 2 doses of HRV (Rotarix) vaccine at 2 and 4 months of age. 10Pn-PD-DIT and DTPa-HBV-IPV/Hib vaccines were administered intramuscularly in the thigh, on the right and left side, respectively. HRV vaccine was administered orally.	

Reporting group values	Synflorix Vaccine Group	Total	
Number of subjects	230	230	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	230	230	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: weeks			
arithmetic mean	8.2		
standard deviation	± 1.63	-	
Gender categorical Units: Subjects			
Female	123	123	
Male	107	107	

End points

End points reporting groups

Reporting group title	Synflorix Vaccine Group

Reporting group description:

Subjects receiving 3 doses of 10Pn-PD-DiT (Synflorix) vaccine co-administered with 3 doses of DTPa-HBV-IPV/Hib (Infanrix hexa) vaccine at 2, 4 and 6 months of age, and co-administered with 2 doses of HRV (Rotarix) vaccine at 2 and 4 months of age. 10Pn-PD-DIT and DTPa-HBV-IPV/Hib vaccines were administered intramuscularly in the thigh, on the right and left side, respectively. HRV vaccine was administered orally.

Subject analysis set title	10Pn-001 Group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This group consisted in a pooling of the subjects receiving the 10Pn vaccine in study 10PN-PD-DIT-001 (105553) (EuDRA CT number: 2005-003300-11). These subjects received in this 10PN-PD-DIT-001 study a 3-dose primary vaccination course of 10Pn vaccine at 2, 3 and 4 months of age (3 different lots)co-administered with DTPa-HBV-IPV/Hib (Infanrix hexa), except for the second dose in France which was co-administered with Infanrix-IPV/Hib™ vaccine. The number of subjects in this subject analysis set is in total 1107 subjects, 230 being a placeholder value.

Primary: Antibody concentrations against pneumococcal vaccine serotypes

End point title	Antibody concentrations against pneumococcal vaccine serotypes[1]

End point description:

Concentrations were expressed as geometric mean concentration (GMC). The vaccine pneumococcal serotypes assessed include 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F.

End point type	Primary

End point timeframe:

One month after the administration of the 3rd vaccine dose i.e. Month 5

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Synflorix Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	219			
Units: microgram per milliliter				
geometric mean (confidence interval 95%)				
Anti-1 antibody (N=219)	2.13 (1.94 to 2.34)			
Anti-4 antibody (N=218)	3.04 (2.77 to 3.34)			
Anti-5 antibody (N=218)	3.24 (2.97 to 3.53)			
Anti-6B antibody (N=218)	1.32 (1.14 to 1.54)			
Anti-7F antibody (N=218)	3.72 (3.4 to 4.07)			
Anti-9V antibody (N=218)	3.71 (3.37 to 4.09)			
Anti-14 antibody (N=218)	5.27 (4.66 to 5.96)			
Anti-18C antibody (N=219)	6.05 (5.3 to 6.89)			

Anti-19F antibody (N=219) Anti-23F antibody (N=218)	5.49 (4.88 to 6.17) 2 (1.7 to 2.35)			

Statistical analyses

No statistical analyses for this end point

Primary: Antibody concentrations against Protein D

End point title	Antibody concentrations against Protein D[2]

End point description:

Concentrations were given as geometric mean concentration (GMC) expressed as enzyme-linked immuno-sorbent assay (ELISA) units per milliliter.

End point type	Primary

End point timeframe:

One month after the administration of the 3rd vaccine dose i.e. Month 5

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Synflorix Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	219			
Units: ELISA units per milliliter				
geometric mean (confidence interval 95%)				
Anti-Protein D antibody	2923.2 (2588.6 to 3301.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Comparison of 10PN-PD-DIT-001 study vs 10PN-PD-DIT-029 study as regards Anti-Pneumococcal Vaccine Serotype Antibody Concentrations

End point title	Comparison of 10PN-PD-DIT-001 study vs 10PN-PD-DIT-029 study as regards Anti-Pneumococcal Vaccine Serotype Antibody Concentrations

End point description:

Antibodies assessed for this comparison endpoint were antibodies against the vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (ANTI-1, -4, -5, -6B, -7F, -9V, -14, -18C, -19F and -23F). The seropositivity cut-off of the assay was an antibody concentration ≥ 0.05 µg/mL. Studies compared as regards results for antibody concentrations against 10Pn pneumococcal vaccine serotypes were studies 10PN-PD-DIT-029 (this study) and 10PN-PD-DIT-001 (105553) (EuDRA CT number: 2005-003300-11) via a comparison of 10Pn-001 Group over Synflorix Vaccine Group.

End point type	Primary

End point timeframe:

One month after the administration of the 3rd vaccine dose, i.e. at Month 5

End point values	Synflorix Vaccine Group	10Pn-001 Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	219	1107		
Units: µg/mL				
number (not applicable)				
Anti-1 (N=219;1100)	2.13	1.05		
Anti-4 (N=218;1106)	3.04	1.45		
Anti-5 (N=218;1104)	3.24	1.7		
Anti-6B (N=218;1100)	1.32	0.33		
Anti-7F (N=218;1107)	3.72	1.72		
Anti-9V (N=218,1103)	3.71	1.32		
Anti-14 (N=218,1100)	5.27	2.9		
Anti-18C (N=219,1102)	6.05	1.66		
Anti-19F (N=219,1104)	5.49	1.84		
Anti-23F (N=218,1102)	2	0.53		

Statistical analyses

Statistical analysis title	10PN-PD-DIT-001 over -029 Anti-1 GMC ratio

Statistical analysis description:

One month after the administration of the 3rd vaccine dose, i.e. at Month 5, ratios of geometric mean concentrations (GMCs), by enzyme-linked immunosorbent assay (ELISA), of 10Pn-001 Group over Synflorix Vaccine Group were calculated for each of the 10 pneumococcal serotypes and for protein D (PD), using an ANOVA model. This statistical analysis section concerns Anti-1 pneumococcal antibodies.

Comparison groups	Synflorix Vaccine Group v 10Pn-001 Group
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	GMC ratio (see above)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.55

Notes:

[3] - Comparability to the 10PN-PD-DIT-001 study in terms of non-inferiority was demonstrated if the upper limit of the 2-sided 95% confidence interval (CI) on the GMC ratios (GMCs from study 10PN-PD-DIT-001 over GMCs of current 10PN-PD-DIT-029 study) was below a limit of 2-fold for all of the 10 vaccine pneumococcal serotypes and for protein D (PD).

Statistical analysis title	10PN-PD-DIT-001 over -029 Anti-4 GMC ratio

Statistical analysis description:

One month after the administration of the 3rd vaccine dose, i.e. at Month 5, ratios of geometric mean concentrations (GMCs), by enzyme-linked immunosorbent assay (ELISA), of 10Pn-001 Group over

Synflorix Vaccine Group were calculated for each of the 10 pneumococcal serotypes and for protein D (PD), using an ANOVA model. This statistical analysis section concerns Anti-4 pneumococcal antibodies.

Comparison groups	Synflorix Vaccine Group v 10Pn-001 Group
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	GMC ratio (see above)
Point estimate	0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.54

Notes:

[4] - Comparability to the 10PN-PD-DIT-001 study in terms of non-inferiority was demonstrated if the upper limit of the 2-sided 95% confidence interval (CI) on the GMC ratios (GMCs from study 10PN-PD-DIT-001 over GMCs of current 10PN-PD-DIT-029 study) was below a limit of 2-fold for all of the 10 vaccine pneumococcal serotypes and for protein D (PD).

Statistical analysis title	10PN-PD-DIT-001 over -029 Anti-5 GMC ratio

Statistical analysis description:

One month after the administration of the 3rd vaccine dose, i.e. at Month 5, ratios of geometric mean concentrations (GMCs), by enzyme-linked immunosorbent assay (ELISA), of 10Pn-001 Group over Synflorix Vaccine Group were calculated for each of the 10 pneumococcal serotypes and for protein D (PD), using an ANOVA model. This statistical analysis section concerns Anti-5 pneumococcal antibodies.

Comparison groups	Synflorix Vaccine Group v 10Pn-001 Group
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	GMC ratio (see above)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.59

Notes:

[5] - Comparability to the 10PN-PD-DIT-001 study in terms of non-inferiority was demonstrated if the upper limit of the 2-sided 95% confidence interval (CI) on the GMC ratios (GMCs from study 10PN-PD-DIT-001 over GMCs of current 10PN-PD-DIT-029 study) was below a limit of 2-fold for all of the 10 vaccine pneumococcal serotypes and for protein D (PD).

Statistical analysis title	10PN-PD-DIT-001 over -029 Anti-6B GMC ratio

Statistical analysis description:

One month after the administration of the 3rd vaccine dose, i.e. at Month 5, ratios of geometric mean concentrations (GMCs), by enzyme-linked immunosorbent assay (ELISA), of 10Pn-001 Group over Synflorix Vaccine Group were calculated for each of the 10 pneumococcal serotypes and for protein D (PD), using an ANOVA model. This statistical analysis section concerns Anti-6B pneumococcal antibodies.

Comparison groups	Synflorix Vaccine Group v 10Pn-001 Group

Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	GMC ratio (see above)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	0.3

Notes:

[6] - Comparability to the 10PN-PD-DIT-001 study in terms of non-inferiority was demonstrated if the upper limit of the 2-sided 95% confidence interval (CI) on the GMC ratios (GMCs from study 10PN-PD-DIT-001 over GMCs of current 10PN-PD-DIT-029 study) was below a limit of 2-fold for all of the 10 vaccine pneumococcal serotypes and for protein D (PD).

Statistical analysis title	10PN-PD-DIT-001 over -029 Anti-7F GMC ratio

Statistical analysis description:

One month after the administration of the 3rd vaccine dose, i.e. at Month 5, ratios of geometric mean concentrations (GMCs), by enzyme-linked immunosorbent assay (ELISA), of 10Pn-001 Group over Synflorix Vaccine Group were calculated for each of the 10 pneumococcal serotypes and for protein D (PD), using an ANOVA model. This statistical analysis section concerns Anti-7F pneumococcal antibodies.

Comparison groups	Synflorix Vaccine Group v 10Pn-001 Group
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	GMC ratio (see above)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.52

Notes:

[7] - Comparability to the 10PN-PD-DIT-001 study in terms of non-inferiority was demonstrated if the upper limit of the 2-sided 95% confidence interval (CI) on the GMC ratios (GMCs from study 10PN-PD-DIT-001 over GMCs of current 10PN-PD-DIT-029 study) was below a limit of 2-fold for all of the 10 vaccine pneumococcal serotypes and for protein D (PD).

Statistical analysis title	10PN-PD-DIT-001 over -029 Anti-9V GMC ratio

Statistical analysis description:

One month after the administration of the 3rd vaccine dose, i.e. at Month 5, ratios of geometric mean concentrations (GMCs), by enzyme-linked immunosorbent assay (ELISA), of 10Pn-001 Group over Synflorix Vaccine Group were calculated for each of the 10 pneumococcal serotypes and for protein D (PD), using an ANOVA model. This statistical analysis section concerns Anti-9V pneumococcal antibodies.

Comparison groups	Synflorix Vaccine Group v 10Pn-001 Group
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	GMC ratio (see above)
Point estimate	0.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	0.4

Notes:

[8] - Comparability to the 10PN-PD-DIT-001 study in terms of non-inferiority was demonstrated if the upper limit of the 2-sided 95% confidence interval (CI) on the GMC ratios (GMCs from study 10PN-PD-DIT-001 over GMCs of current 10PN-PD-DIT-029 study) was below a limit of 2-fold for all of the 10 vaccine pneumococcal serotypes and for protein D (PD).

Statistical analysis title	10PN-PD-DIT-001 over -029 Anti-14 GMC ratio

Statistical analysis description:

One month after the administration of the 3rd vaccine dose, i.e. at Month 5, ratios of geometric mean concentrations (GMCs), by enzyme-linked immunosorbent assay (ELISA), of 10Pn-001 Group over Synflorix Vaccine Group were calculated for each of the 10 pneumococcal serotypes and for protein D (PD), using an ANOVA model. This statistical analysis section concerns Anti-14 pneumococcal antibodies.

Comparison groups	Synflorix Vaccine Group v 10Pn-001 Group
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Parameter estimate	GMC ratio (see above)
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.63

Notes:

[9] - Comparability to the 10PN-PD-DIT-001 study in terms of non-inferiority was demonstrated if the upper limit of the 2-sided 95% confidence interval (CI) on the GMC ratios (GMCs from study 10PN-PD-DIT-001 over GMCs of current 10PN-PD-DIT-029 study) was below a limit of 2-fold for all of the 10 vaccine pneumococcal serotypes and for protein D (PD).

Statistical analysis title	10PN-PD-DIT-001 over -029 Anti-18C GMC ratio

Statistical analysis description:

One month after the administration of the 3rd vaccine dose, i.e. at Month 5, ratios of geometric mean concentrations (GMCs), by enzyme-linked immunosorbent assay (ELISA), of 10Pn-001 Group over Synflorix Vaccine Group were calculated for each of the 10 pneumococcal serotypes and for protein D (PD), using an ANOVA model. This statistical analysis section concerns Anti-18C pneumococcal antibodies.

Comparison groups	Synflorix Vaccine Group v 10Pn-001 Group
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	GMC ratio (see above)
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	0.32

Notes:

[10] - Comparability to the 10PN-PD-DIT-001 study in terms of non-inferiority was demonstrated if the upper limit of the 2-sided 95% confidence interval (CI) on the GMC ratios (GMCs from study 10PN-PD-DIT-001 over GMCs of current 10PN-PD-DIT-029 study) was below a limit of 2-fold for all of the 10 vaccine pneumococcal serotypes and for protein D (PD).

Statistical analysis title	10PN-PD-DIT-001 over -029 Anti-19F GMC ratio

Statistical analysis description:

One month after the administration of the 3rd vaccine dose, i.e. at Month 5, ratios of geometric mean concentrations (GMCs), by enzyme-linked immunosorbent assay (ELISA), of 10Pn-001 Group over Synflorix Vaccine Group were calculated for each of the 10 pneumococcal serotypes and for protein D (PD), using an ANOVA model. This statistical analysis section concerns Anti-19F pneumococcal antibodies.

Comparison groups	Synflorix Vaccine Group v 10Pn-001 Group
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
Parameter estimate	GMC ratio (see above)
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	0.4

Notes:

[11] - Comparability to the 10PN-PD-DIT-001 study in terms of non-inferiority was demonstrated if the upper limit of the 2-sided 95% confidence interval (CI) on the GMC ratios (GMCs from study 10PN-PD-DIT-001 over GMCs of current 10PN-PD-DIT-029 study) was below a limit of 2-fold for all of the 10 vaccine pneumococcal serotypes and for protein D (PD).

Statistical analysis title	10PN-PD-DIT-001 over -029 Anti-23F GMC ratio

Statistical analysis description:

One month after the administration of the 3rd vaccine dose, i.e. at Month 5, ratios of geometric mean concentrations (GMCs), by enzyme-linked immunosorbent assay (ELISA), of 10Pn-001 Group over Synflorix Vaccine Group were calculated for each of the 10 pneumococcal serotypes and for protein D (PD), using an ANOVA model. This statistical analysis section concerns Anti-23F pneumococcal antibodies.

Comparison groups	Synflorix Vaccine Group v 10Pn-001 Group
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
Parameter estimate	GMC ratio (see above)
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.32

Notes:

[12] - Comparability to the 10PN-PD-DIT-001 study in terms of non-inferiority was demonstrated if the upper limit of the 2-sided 95% confidence interval (CI) on the GMC ratios (GMCs from study 10PN-PD-DIT-001 over GMCs of current 10PN-PD-DIT-029 study) was below a limit of 2-fold for all of the 10 vaccine pneumococcal serotypes and for protein D (PD).

Primary: Comparison of 10PN-PD-DIT-001 study vs 10PN-PD-DIT-029 study as regards Anti-protein D (anti-PD) antibody concentrations

End point title	Comparison of 10PN-PD-DIT-001 study vs 10PN-PD-DIT-029 study as regards Anti-protein D (anti-PD) antibody concentrations

End point description:

Antibodies assessed for this comparison endpoint were antibodies against protein D (anti-PD). The seropositivity cut-off of the assay was an antibody concentration ≥ 100 enzyme-linked immunosorbent assay (ELISA) units per millilitre (EL.U/mL). Studies compared as regards results for Anti-PD antibody concentrations were studies 10PN-PD-DIT-029 (this study) and 10PN-PD-DIT-001 (105553) (EuDRA CT number: 2005-003300-11) via a comparison of 10Pn-001 Group over Synflorix Vaccine Group.

End point type	Primary

End point timeframe:

One month after the administration of the 3rd vaccine dose, i.e. at Month 5

End point values	Synflorix Vaccine Group	10Pn-001 Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	219	1095		
Units: EL.U/mL				
number (not applicable)				
Anti-PD	2923.2	1529.9		

Statistical analyses

Statistical analysis title	10PN-PD-DIT-001 over -029 Anti-PD GMC ratio

Statistical analysis description:

One month after the administration of the 3rd vaccine dose, i.e. at Month 5, ratios of geometric mean concentrations (GMCs), by enzyme-linked immunosorbent assay (ELISA), of 10Pn-001 Group over Synflorix Vaccine Group were calculated for each of the 10 pneumococcal serotypes and for protein D (PD), using an ANOVA model. This statistical analysis section concerns Anti-PD antibodies.

Comparison groups	Synflorix Vaccine Group v 10Pn-001 Group
Number of subjects included in analysis	1314
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
Parameter estimate	GMC ratio (see above)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.6

Notes:

[13] - Comparability to the 10PN-PD-DIT-001 study in terms of non-inferiority was demonstrated if the upper limit of the 2-sided 95% confidence interval (CI) on the GMC ratios (GMCs from study 10PN-PD-DIT-001 over GMCs of current 10PN-PD-DIT-029 study) was below a limit of 2-fold for all of the 10 vaccine pneumococcal serotypes and for protein D (PD).

Secondary: Opsonophagocytic titer against pneumococcal vaccine serotypes

End point title	Opsonophagocytic titer against pneumococcal vaccine serotypes

End point description:

The results were presented as the geometric mean dilution of serum (opsonic titer) able to sustain 50% killing of live pneumococci under the assay conditions. The vaccine pneumococcal serotypes assessed include 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F.

End point type	Secondary

End point timeframe:

One month after the administration of the 3rd vaccine dose i.e. Month 5

End point values	Synflorix Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: titer				
geometric mean (confidence interval 95%)				
Opsono-1 titer (N=97)	94.1 (68.2 to 130)			
Opsono-4 titer (N=97)	670.8 (516.1 to 871.7)			
Opsono-5 titer (N=94)	148.8 (120.6 to 183.6)			
Opsono-6B titer (N=96)	345.4 (205.5 to 580.4)			
Opsono-7F titer (N=96)	4435.4 (3635.9 to 5410.7)			
Opsono-9V titer (N=96)	1186.1 (955.9 to 1471.7)			
Opsono-14 titer (N=94)	1168.3 (907.4 to 1504.2)			
Opsono-18C titer (N=94)	222.9 (157.9 to 314.9)			
Opsono-19F titer (N=92)	589.2 (441.9 to 785.5)			
Opsono-23F titer (N=95)	1876.3 (1325.4 to 2656)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-pneumococcal vaccine serotypes antibody concentrations greater than or equal to 0.2 microgram per milliliter

End point title	Number of subjects with anti-pneumococcal vaccine serotypes antibody concentrations greater than or equal to 0.2 microgram per milliliter

End point description:

The vaccine pneumococcal serotypes assessed include 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F.

End point type	Secondary

End point timeframe:

One month after the administration of the 3rd vaccine dose i.e. Month 5

End point values	Synflorix Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	219			
Units: Subjects				
Anti-1 antibody (N=219)	219			
Anti-4 antibody (N=218)	218			
Anti-5 antibody (N=218)	218			
Anti-6B antibody (N=218)	203			
Anti-7F antibody (N=218)	218			
Anti-9V antibody (N=218)	218			
Anti-14 antibody (N=218)	216			
Anti-18C antibody (N=219)	218			
Anti-19F antibody (N=219)	217			
Anti-23F antibody (N=218)	207			

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody concentrations against pneumococcal cross-reactive serotypes

End point title	Antibody concentrations against pneumococcal cross-reactive serotypes

End point description:

Antibody concentrations were expressed as Geometric Mean Concentrations against pneumococcal cross-reactive serotypes 6A and 19A.

End point type	Secondary

End point timeframe:

One month after the administration of the 3rd vaccine dose i.e. Month 5

End point values	Synflorix Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	219			
Units: microgram per milliliter				
geometric mean (confidence interval 95%)				
Anti-6A antibody	0.28 (0.24 to 0.34)			
Anti-19A antibody	0.26 (0.22 to 0.31)			

Statistical analyses

No statistical analyses for this end point

Secondary: Opsonophagocytic titer against pneumococcal cross-reactive serotypes

End point title	Opsonophagocytic titer against pneumococcal cross-reactive serotypes

End point description:

The results were presented as the geometric mean dilution of serum (opsonic titer) able to sustain 50% killing of live pneumococci under the assay conditions. The cross-reactive pneumococcal serotypes assessed include 6A and 19A.

End point type	Secondary

End point timeframe:

One month after the administration of the 3rd vaccine dose i.e. Month 5

End point values	Synflorix Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	91			
Units: titer				
geometric mean (confidence interval 95%)				
Opsono-6A titer (N=91)	159.2 (98.8 to 256.4)			
Opsono-19A titer (N=81)	11.6 (7.3 to 18.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects seropositive against vaccine pneumococcal serotypes

End point title	Number of subjects seropositive against vaccine pneumococcal serotypes

End point description:

Seropositivity was defined as anti-pneumococcal antibody concentration greater than or equal to 0.05 microgram per milliliter. The vaccine pneumococcal serotypes assessed include 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F.

End point type	Secondary

End point timeframe:

One month after the administration of the 3rd vaccine dose i.e. Month 5

End point values	Synflorix Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	219			
Units: Subjects				
Anti-1 antibody (N=219)	219			
Anti-4 antibody (N=218)	218			
Anti-5 antibody (N=218)	218			

Anti-6B antibody (N=218)	212			
Anti-7F antibody (N=218)	218			
Anti-9V antibody (N=218)	218			
Anti-14 antibody (N=218)	218			
Anti-18C antibody (N=219)	218			
Anti-19F antibody (N=219)	219			
Anti-23F antibody (N=218)	212			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects seropositive for opsonic titer against vaccine pneumococcal serotypes

End point title	Number of subjects seropositive for opsonic titer against vaccine pneumococcal serotypes

End point description:

Seropositivity was defined as an opsonic titer greater than or equal to 8. The vaccine pneumococcal serotypes assessed include 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F.

End point type	Secondary

End point timeframe:

One month after the administration of the 3rd vaccine dose i.e. Month 5

End point values	Synflorix Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: Subjects				
Opsono-1 titer (N=97)	83			
Opsono-4 titer (N=97)	93			
Opsono-5 titer (N=94)	93			
Opsono-6B titer (N=96)	76			
Opsono-7F titer (N=96)	96			
Opsono-9V titer (N=96)	96			
Opsono-14 titer (N=94)	93			
Opsono-18C titer (N=94)	91			
Opsono-19F titer (N=92)	90			
Opsono-23F titer (N=95)	90			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects seropositive against cross-reactive pneumococcal serotypes

End point title	Number of subjects seropositive against cross-reactive pneumococcal serotypes

End point description:

Seropositivity was defined as anti-pneumococcal antibody concentration greater than or equal to 0.05 microgram per milliliter. The cross-reactive pneumococcal serotypes assessed include 6A and 19A.

End point type	Secondary

End point timeframe:

One month after the administration of the 3rd vaccine dose i.e. Month 5

End point values	Synflorix Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	219			
Units: Subjects				
Anti-6A antibody	203			
Anti-19A antibody	198			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects seropositive for opsonic titer against cross-reactive pneumococcal serotypes

End point title	Number of subjects seropositive for opsonic titer against cross-reactive pneumococcal serotypes

End point description:

Seropositivity was defined as anti-pneumococcal antibody opsonic titer greater than or equal to 8. The vaccine pneumococcal cross-reactive serotypes assessed include 6A and 19A.

End point type	Secondary

End point timeframe:

One month after the administration of the 3rd vaccine dose i.e. Month 5

End point values	Synflorix Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	91			
Units: Subjects				
Opsono-6A titer (N=91)	69			
Opsono-19A titer (N=81)	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects seropositive for anti-Protein D antibodies

End point title	Number of subjects seropositive for anti-Protein D antibodies

End point description:

Seropositivity was defined as antibody concentration greater than or equal to 100 Enzyme-Linked Immuno Sorbent Assay (ELISA) units per milliliter.

End point type	Secondary

End point timeframe:

One month after the administration of the 3rd vaccine dose i.e. Month 5

End point values	Synflorix Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	219			
Units: Subjects				
Anti-PD antibody	219			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any and grade 3 solicited local Adverse Events (AEs)

End point title	Number of subjects reporting any and grade 3 solicited local Adverse Events (AEs)

End point description:

Grade 3 redness and swelling was > 30 millimeter (mm) and grade 3 pain was subjects crying when limb was moved/spontaneously painful. Any was occurrence of any local symptom regardless of grade and whatever the number of injections.

End point type	Secondary

End point timeframe:

Within 4 days following any vaccine dose

End point values	Synflorix Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	230			
Units: Subjects				
Any pain	196			
Grade 3 pain	80			
Any redness	91			
Grade 3 redness	0			
Any swelling	178			
Grade 3 swelling	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any, grade 3 and related solicited general AEs

End point title	Number of subjects reporting any, grade 3 and related solicited general AEs

End point description:

Any fever was defined as axillary temperature ≥ 37.5 degree centigrade (°C), grade 3 fever was axillary temperature > 39.5°C. Grade 3 drowsiness, irritability, and loss of appetite was general symptom which prevented normal everyday activities. Grade 3 diarrhea was ≥ 6 looser than normal stools/day and Grade 3 vomiting was ≥ 3 episodes of vomiting/day. Related was solicited general symptom considered by the investigator to have a causal relationship to study vaccination.

End point type	Secondary

End point timeframe:

Within 4 days following any vaccine dose

End point values	Synflorix Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	230			
Units: Subjects				
Any diarrhea	55			
Grade 3 diarrhea	5			
Related diarrhea	55			
Any drowsiness	156			
Grade 3 drowsiness	7			
Related drowsiness	153			
Any fever	147			
Grade 3 fever	0			
Related fever	147			
Any irritability	198			
Grade 3 irritability	21			
Related irritability	196			
Any loss of appetite	113			
Grade 3 loss of appetite	1			
Related loss of appetite	111			
Any vomiting	56			
Grade 3 vomiting	7			
Related vomiting	56			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any unsolicited AEs

End point title	Number of subjects reporting any unsolicited AEs

End point description:

Unsolicited AE covers any AE reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms.

End point type	Secondary

End point timeframe:

Within 31 days after any vaccine dose

End point values	Synflorix Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	230			
Units: Subjects				
Any AE(s)	174			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any serious adverse events (SAEs)

End point title	Number of subjects reporting any serious adverse events (SAEs)

End point description:

SAEs assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization, result in disability/incapacity or are a congenital anomaly/birth defect in the offspring of a study subject.

End point type	Secondary

End point timeframe:

Entire study period, from Day 0 up to Month 5

End point values	Synflorix Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	230			
Units: Subjects				
Any SAE(s)	15			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events: Entire study period, from Day 0 up to Month 5. Systematically assessed frequent adverse events (AEs) and non-systematically assessed frequent AEs: During the 4- (Days 0-3) and 31-day (Days0-30) follow-up periods post vaccination,

Adverse event reporting additional description:

The occurrence of reported AEs (all/related) was not available and is encoded as equal to the number of subjects affected.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Synflorix vaccine Group

Reporting group description:

Subjects receiving 10Pn-PD-DiT (Synflorix) vaccine co-administered with DTPa-HBV-IPV/Hib (Infanrix hexa) vaccine at 2-4-6 months of age, and co-administered with HRV (Rotarix) vaccine at 2-4 months of age. 10Pn-PD-DIT and DTPa-HBV-IPV/Hib vaccines were administered intramuscularly in the thigh, on the right and left side, respectively. HRV vaccine was administered orally.

Serious adverse events	Synflorix vaccine Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 230 (6.52%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Convulsion			
subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			
subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	6 / 230 (2.61%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 1		
Bronchiolitis			
subjects affected / exposed	4 / 230 (1.74%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	2 / 230 (0.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis			
subjects affected / exposed	2 / 230 (0.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Herpangina			
subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laryngitis			
subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngitis			
subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pneumonia viral			
subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 230 (0.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Synflorix vaccine Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	198 / 230 (86.09%)		
General disorders and administration site conditions			
Pain (solicited AE)			
alternative assessment type: Systematic			
subjects affected / exposed	196 / 230 (85.22%)		
occurrences (all)	196		
Redness (solicited AE)			
alternative assessment type: Systematic			
subjects affected / exposed	91 / 230 (39.57%)		
occurrences (all)	91		
Swelling (solicited AE)			
alternative assessment type: Systematic			
subjects affected / exposed	178 / 230 (77.39%)		
occurrences (all)	178		
Diarrhea (solicited AE)			
alternative assessment type: Systematic			
subjects affected / exposed	55 / 230 (23.91%)		
occurrences (all)	55		
Drowsiness (solicited AE)			
alternative assessment type: Systematic			

subjects affected / exposed	156 / 230 (67.83%)		
occurrences (all)	156		
Fever (solicited AE)			
alternative assessment type: Systematic			
subjects affected / exposed	147 / 230 (63.91%)		
occurrences (all)	147		
Irritability (solicited AE)			
alternative assessment type: Systematic			
subjects affected / exposed	198 / 230 (86.09%)		
occurrences (all)	198		
Loss of appetite (solicited AE)			
alternative assessment type: Systematic			
subjects affected / exposed	113 / 230 (49.13%)		
occurrences (all)	113		
Vomiting (solicited AE)			
alternative assessment type: Systematic			
subjects affected / exposed	56 / 230 (24.35%)		
occurrences (all)	56		
Eye disorders			
Conjunctivitis (unsolicited AE)			
subjects affected / exposed	21 / 230 (9.13%)		
occurrences (all)	21		
Gastrointestinal disorders			
Diarrhea (unsolicited AE)			
subjects affected / exposed	14 / 230 (6.09%)		
occurrences (all)	14		
Respiratory, thoracic and mediastinal disorders			
Cough (unsolicited AE)			
subjects affected / exposed	17 / 230 (7.39%)		
occurrences (all)	17		
Infections and infestations			
Nasopharyngitis (unsolicited AE)			
subjects affected / exposed	123 / 230 (53.48%)		
occurrences (all)	123		
Pharyngitis (unsolicited AE)			

subjects affected / exposed	37 / 230 (16.09%)		
occurrences (all)	37		
Gastroenteritis (unsolicited AE)			
subjects affected / exposed	16 / 230 (6.96%)		
occurrences (all)	16		
Laryngitis (unsolicited AE)			
subjects affected / exposed	13 / 230 (5.65%)		
occurrences (all)	13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 March 2007	This amendment is made in order to update specific study information; because of an updated protocol template (version 12.4); and in general to facilitate reading of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported