Clinical trial results:
A phase III, multi-centre, double-blind, randomised study to assess the non-inferiority of a commercial lot of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate (10Pn-PD-DiT) vaccine compared to a clinical phase III vaccine lot, when given as a three-dose primary immunization course.

Summary

EudraCT number	2014-000101-12
Trial protocol	Outside EU/EEA
Global end of trial date	02 November 2009

Results information

Result version number	v1
This version publication date	05 April 2016
First version publication date	27 June 2015

Trial information

Trial identification

Sponsor protocol code	111654

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00808444
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	27 May 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 November 2009
Global end of trial reached?	Yes
Global end of trial date	02 November 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the immunogenicity of the commercial lot to the phase III clinical lot of GSK Biologicals' 10-valent pneumococcal conjugate vaccine (10Pn-PD-DiT), one month following a 3-dose primary vaccination course.

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. Subjects were followed-up for one month (minimum 30 days) following administration of the last dose of study vaccines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 January 2009
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	Malaysia: 168
Country: Number of subjects enrolled	Singapore: 298
Worldwide total number of subjects	466
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)	466
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: -

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Synflorix Clinical Lot & Infanrix Group

Arm description:

Subjects received 3 doses of the clinical lot of Synflorix TM (GSK1024850A) intramuscularly in the right thigh at 2-3-5 months of age (= study month 0, 1, 3) co-administered with a DTPa-combined vaccine (Infanrix hexa TM (at 2, 3 and 5 months of age in Malaysia or 2 and 5 months of age in Singapore) or Infanrix-IPV/Hib TM (at 3 months of age in Singapore)) intramuscularly in the left thigh and Rotarix TM orally at 2-3 months of age (= study month 0, 1).

Arm type	Experimental
Investigational medicinal product name	Pneumococcal conjugate vaccine GSK1024850A (different lots)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection, 3 doses.

Investigational medicinal product name	Infanrix hexa
Investigational medicinal product code	
Other name	DTPa-combined vaccine
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection, 3 doses in Malaysia and 2 doses in Singapore.

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

Dosage and administration details:

Intramuscular injection, only at 3 months of age in Singapore.

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

Dosage and administration details:

Oral, 2 doses.

Arm title	Synflorix Commercial Lot Infanrix Group

Arm description:

Subjects received 3 doses of the commercial lot of Synflorix TM (GSK1024850A) intramuscularly in the right thigh at 2-3-5 months of age (= study month 0, 1, 3) co-administered with a DTPa-combined vaccine (Infanrix hexa TM (at 2, 3 or 5 months of age in Malaysia or 2 and 5 months in Singapore) or Infanrix-IPV/Hib TM (at 3 months of age in Singapore)) intramuscularly in the left thigh and Rotarix TM orally at 2-3 months of age (= study month 0, 1).

Arm type	Experimental
Investigational medicinal product name	Pneumococcal conjugate vaccine GSK1024850A (different lots)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection, 3 doses.

Investigational medicinal product name	Infanrix hexa
Investigational medicinal product code	
Other name	DTPa-combined vaccine
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection, 3 doses in Malaysia and 2 doses in Singapore.

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

Dosage and administration details:

Intramuscular injection, only at 3 months of age in Singapore.

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

Dosage and administration details:

Oral, 2 doses.

Number of subjects in period 1	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group
Started	233	233
Completed	232	232
Not completed	1	1
Consent withdrawn by subject	1	-

Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Synflorix Clinical Lot & Infanrix Group
Reporting group description:	
Subjects received 3 doses of the clinical lot of Synflorix TM (GSK1024850A) intramuscularly in the right thigh at 2-3-5 months of age (= study month 0, 1, 3) co-administered with a DTPa-combined vaccine (Infanrix hexa TM (at 2, 3 and 5 months of age in Malaysia or 2 and 5 months of age in Singapore) or Infanrix-IPV/Hib TM (at 3 months of age in Singapore)) intramuscularly in the left thigh and Rotarix TM orally at 2-3 months of age (= study month 0, 1).	
Reporting group title	Synflorix Commercial Lot Infanrix Group
Reporting group description:	
Subjects received 3 doses of the commercial lot of Synflorix TM (GSK1024850A) intramuscularly in the right thigh at 2-3-5 months of age (= study month 0, 1, 3) co-administered with a DTPa-combined vaccine (Infanrix hexa TM (at 2, 3 or 5 months of age in Malaysia or 2 and 5 months in Singapore) or Infanrix-IPV/Hib TM (at 3 months of age in Singapore)) intramuscularly in the left thigh and Rotarix TM orally at 2-3 months of age (= study month 0, 1).	

Reporting group values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group	Total
Number of subjects	233	233	466
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: weeks			
arithmetic mean	7.3	7.2	
standard deviation	± 1.35	± 1.3	-
Gender categorical Units: Subjects			
Female	113	104	217
Male	120	129	249

End points

End points reporting groups

Reporting group title	Synflorix Clinical Lot & Infanrix Group

Reporting group description:

Subjects received 3 doses of the clinical lot of Synflorix TM (GSK1024850A) intramuscularly in the right thigh at 2-3-5 months of age (= study month 0, 1, 3) co-administered with a DTPa-combined vaccine (Infanrix hexa TM (at 2, 3 and 5 months of age in Malaysia or 2 and 5 months of age in Singapore) or Infanrix-IPV/Hib TM (at 3 months of age in Singapore)) intramuscularly in the left thigh and Rotarix TM orally at 2-3 months of age (= study month 0, 1).

Reporting group title	Synflorix Commercial Lot Infanrix Group

Reporting group description:

Subjects received 3 doses of the commercial lot of Synflorix TM (GSK1024850A) intramuscularly in the right thigh at 2-3-5 months of age (= study month 0, 1, 3) co-administered with a DTPa-combined vaccine (Infanrix hexa TM (at 2, 3 or 5 months of age in Malaysia or 2 and 5 months in Singapore) or Infanrix-IPV/Hib TM (at 3 months of age in Singapore)) intramuscularly in the left thigh and Rotarix TM orally at 2-3 months of age (= study month 0, 1).

Primary: Concentrations of antibodies against vaccine components of the pneumococcal vaccine

End point title	Concentrations of antibodies against vaccine components of the pneumococcal vaccine

End point description:

Concentrations are given as Geometric Mean Concentrations (GMCs) in microgram per milliliter (µg/mL). Vaccine pneumococcal serotypes assessed included 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.Pneumococcal serotype specific total imunoglobuline G (IgG) antibodies were measured by 22F-inhibition Enzyme-linked immunosorbent assay (ELISA). The cut-off of the assay was 0.05 µg/mL.

End point type	Primary

End point timeframe:

One month after primary immunization (month 4)

End point values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	218		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-1 (N=219; 218)	2.67 (2.46 to 2.91)	2.46 (2.25 to 2.69)		
Anti-4 (N=219; 218)	3.95 (3.59 to 4.36)	3.14 (2.84 to 3.47)		
Anti-5 (N=219; 218)	4.34 (3.95 to 4.76)	3.59 (3.29 to 3.92)		
Anti-6B (N=219; 218)	1.31 (1.16 to 1.48)	1.23 (1.07 to 1.41)		
Anti-7 (N= 218; 217)	3.1 (2.83 to 3.39)	3.2 (2.92 to 3.51)		
Anti-9V (N=219; 218)	3.34 (3.03 to 3.69)	3.14 (2.83 to 3.49)		

Anti-14 (N=219; 218)	5.13 (4.54 to 5.79)	4.74 (4.23 to 5.32)		
Anti-18C (N=219; 218)	5 (4.4 to 5.69)	5.15 (4.43 to 5.97)		
Anti-19F (N=219; 218)	6.69 (6.04 to 7.41)	6.96 (6.26 to 7.73)		
Anti-23F (N=219; 218)	1.98 (1.76 to 2.23)	1.68 (1.49 to 1.9)		

Statistical analyses

Statistical analysis title	Immune response non-inferiority–serotype Anti-1

Statistical analysis description:

To compare the immunogenicity of the commercial lot to the phase III clinical lot of GSK1024850A vaccine, one month following a 3-dose primary vaccination course.

Comparison groups	Synflorix Clinical Lot & Infanrix Group v Synflorix Commercial Lot Infanrix Group
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	GMC adjusted ratio
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.23

Notes:

[1] - Comparability between the commercial lot and the phase III clinical lot in terms of non-inferiority was demonstrated if the upper limit of the two-sided 95% confidence intervals (95% CIs) on the adjusted (for country) geometric mean concentration (GMC) ratios [adjusted GMC of the phase III clinical lot over the adjusted GMC of the commercial lot] was below a limit of 2-fold for antibodies against all vaccine pneumococcal serotypes and protein D (PD) measured by ELISA.

Statistical analysis title	Immune response non-inferiority–serotype Anti-4

Statistical analysis description:

To compare the immunogenicity of the commercial lot to the phase III clinical lot of GSK1024850A vaccine, one month following a 3-dose primary vaccination course.

Comparison groups	Synflorix Clinical Lot & Infanrix Group v Synflorix Commercial Lot Infanrix Group
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	GMC ajusted ratio
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	1.45

Notes:

[2] - Comparability between the commercial lot and the phase III clinical lot in terms of non-inferiority was demonstrated if the upper limit of the two-sided 95% confidence intervals (95% CIs) on the adjusted (for country) geometric mean concentration (GMC) ratios [adjusted GMC of the phase III

clinical lot over the adjusted GMC of the commercial lot] was below a limit of 2-fold for antibodies against all vaccine pneumococcal serotypes and protein D (PD) measured by ELISA.

Statistical analysis title	Immune response non-inferiority–serotype Anti-5

Statistical analysis description:

To compare the immunogenicity of the commercial lot to the phase III clinical lot of GSK1024850A vaccine, one month following a 3-dose primary vaccination course.

Comparison groups	Synflorix Clinical Lot & Infanrix Group v Synflorix Commercial Lot Infanrix Group
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	GMC adjusted ratio
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	1.37

Notes:

[3] - Comparability between the commercial lot and the phase III clinical lot in terms of non-inferiority was demonstrated if the upper limit of the two-sided 95% confidence intervals (95% CIs) on the adjusted (for country) geometric mean concentration (GMC) ratios [adjusted GMC of the phase III clinical lot over the adjusted GMC of the commercial lot] was below a limit of 2-fold for antibodies against all vaccine pneumococcal serotypes and protein D (PD) measured by ELISA.

Statistical analysis title	Immune response non-inferiority–serotype Anti-6B

Statistical analysis description:

To compare the immunogenicity of the commercial lot to the phase III clinical lot of GSK1024850A vaccine, one month following a 3-dose primary vaccination course.

Comparison groups	Synflorix Clinical Lot & Infanrix Group v Synflorix Commercial Lot Infanrix Group
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	GMC adjusted ratio
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.28

Notes:

[4] - Comparability between the commercial lot and the phase III clinical lot in terms of non-inferiority was demonstrated if the upper limit of the two-sided 95% confidence intervals (95% CIs) on the adjusted (for country) geometric mean concentration (GMC) ratios [adjusted GMC of the phase III clinical lot over the adjusted GMC of the commercial lot] was below a limit of 2-fold for antibodies against all vaccine pneumococcal serotypes and protein D (PD) measured by ELISA.

Statistical analysis title	Immune response non-inferiority–serotype Anti-7F

Statistical analysis description:

To compare the immunogenicity of the commercial lot to the phase III clinical lot of GSK1024850A vaccine, one month following a 3-dose primary vaccination course.

Comparison groups	Synflorix Clinical Lot & Infanrix Group v Synflorix Commercial Lot Infanrix Group

Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	GMC adjusted ratio
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.1

Notes:

[5] - Comparability between the commercial lot and the phase III clinical lot in terms of non-inferiority was demonstrated if the upper limit of the two-sided 95% confidence intervals (95% CIs) on the adjusted (for country) geometric mean concentration (GMC) ratios [adjusted GMC of the phase III clinical lot over the adjusted GMC of the commercial lot] was below a limit of 2-fold for antibodies against all vaccine pneumococcal serotypes and protein D (PD) measured by ELISA.

Statistical analysis title	Immune response non-inferiority–serotype Anti-9V

Statistical analysis description:

To compare the immunogenicity of the commercial lot to the phase III clinical lot of GSK1024850A vaccine, one month following a 3-dose primary vaccination course.

Comparison groups	Synflorix Commercial Lot Infanrix Group v Synflorix Clinical Lot & Infanrix Group
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	GMC adjusted ratio
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.23

Notes:

[6] - Comparability between the commercial lot and the phase III clinical lot in terms of non-inferiority was demonstrated if the upper limit of the two-sided 95% confidence intervals (95% CIs) on the adjusted (for country) geometric mean concentration (GMC) ratios [adjusted GMC of the phase III clinical lot over the adjusted GMC of the commercial lot] was below a limit of 2-fold for antibodies against all vaccine pneumococcal serotypes and protein D (PD) measured by ELISA.

Statistical analysis title	Immune response non-inferiority–serotype Anti-14

Statistical analysis description:

To compare the immunogenicity of the commercial lot to the phase III clinical lot of GSK1024850A vaccine, one month following a 3-dose primary vaccination course.

Comparison groups	Synflorix Clinical Lot & Infanrix Group v Synflorix Commercial Lot Infanrix Group
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	GMC adjusted ratio
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.27

Notes:

[7] - Comparability between the commercial lot and the phase III clinical lot in terms of non-inferiority was demonstrated if the upper limit of the two-sided 95% confidence intervals (95% CIs) on the adjusted (for country) geometric mean concentration (GMC) ratios [adjusted GMC of the phase III clinical lot over the adjusted GMC of the commercial lot] was below a limit of 2-fold for antibodies against all vaccine pneumococcal serotypes and protein D (PD) measured by ELISA.

Statistical analysis title	Immune response non-inferiority–serotype Anti-18C

Statistical analysis description:

To compare the immunogenicity of the commercial lot to the phase III clinical lot of GSK1024850A vaccine, one month following a 3-dose primary vaccination course.

Comparison groups	Synflorix Clinical Lot & Infanrix Group v Synflorix Commercial Lot Infanrix Group
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	GMC adjusted ratio
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.18

Notes:

[8] - Comparability between the commercial lot and the phase III clinical lot in terms of non-inferiority was demonstrated if the upper limit of the two-sided 95% confidence intervals (95% CIs) on the adjusted (for country) geometric mean concentration (GMC) ratios [adjusted GMC of the phase III clinical lot over the adjusted GMC of the commercial lot] was below a limit of 2-fold for antibodies against all vaccine pneumococcal serotypes and protein D (PD) measured by ELISA.

Statistical analysis title	Immune response non-inferiority–serotype Anti-19F

Statistical analysis description:

To compare the immunogenicity of the commercial lot to the phase III clinical lot of GSK1024850A vaccine, one month following a 3-dose primary vaccination course.

Comparison groups	Synflorix Clinical Lot & Infanrix Group v Synflorix Commercial Lot Infanrix Group
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Parameter estimate	GMC adjusted ratio
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.11

Notes:

[9] - Comparability between the commercial lot and the phase III clinical lot in terms of non-inferiority was demonstrated if the upper limit of the two-sided 95% confidence intervals (95% CIs) on the adjusted (for country) geometric mean concentration (GMC) ratios [adjusted GMC of the phase III clinical lot over the adjusted GMC of the commercial lot] was below a limit of 2-fold for antibodies against all vaccine pneumococcal serotypes and protein D (PD) measured by ELISA.

Statistical analysis title	Immune response non-inferiority–serotype Anti-23F

Statistical analysis description:

To compare the immunogenicity of the commercial lot to the phase III clinical lot of GSK1024850A vaccine, one month following a 3-dose primary vaccination course.

Comparison groups	Synflorix Clinical Lot & Infanrix Group v Synflorix Commercial Lot Infanrix Group
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	GMC adjusted ratio
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.4

Notes:

[10] - Comparability between the commercial lot and the phase III clinical lot in terms of non-inferiority was demonstrated if the upper limit of the two-sided 95% confidence intervals (95% CIs) on the adjusted (for country) geometric mean concentration (GMC) ratios [adjusted GMC of the phase III clinical lot over the adjusted GMC of the commercial lot] was below a limit of 2-fold for antibodies against all vaccine pneumococcal serotypes and protein D (PD) measured by ELISA.

Primary: Concentration of antibody against protein D (PD)

End point title	Concentration of antibody against protein D (PD)

End point description:

Concentration was expressed as GMC in GSK's 22F enzyme-linked-immunosorbent assay (ELISA) units per milliliter (EL.U/mL). The cut-off of the assay is 100 EL.U/mL.

End point type	Primary

End point timeframe:

One month after primary immunization (month 4)

End point values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	218		
Units: EL.U/mL				
geometric mean (confidence interval 95%)	2543.6 (2319.4 to 2789.4)	1869.8 (1671.2 to 2091.9)		

Statistical analyses

Statistical analysis title	Immune response non-inferiority-Anti-PD

Statistical analysis description:

To compare the immunogenicity of the commercial lot to the phase III clinical lot of GSK1024850A vaccine, one month following a 3-dose primary vaccination course.

Comparison groups	Synflorix Clinical Lot & Infanrix Group v Synflorix Commercial Lot Infanrix Group

Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
Parameter estimate	GMC adjusted ratio
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	1.58

Notes:

[11] - Comparability between the commercial lot and the phase III clinical lot in terms of non-inferiority was demonstrated if the upper limit of the two-sided 95% confidence intervals (95% CIs) on the adjusted (for country) geometric mean concentration (GMC) ratios [adjusted GMC of the phase III clinical lot over the adjusted GMC of the commercial lot] was below a limit of 2-fold for antibodies against all vaccine pneumococcal serotypes and protein D (PD) measured by ELISA.

Secondary: Number of subjects with anti-pneumococcal vaccine serotype antibody concentrations equal to or above 0.20 µg/mL

End point title	Number of subjects with anti-pneumococcal vaccine serotype antibody concentrations equal to or above 0.20 µg/mL

End point description:

Vaccine pneumococcal serotypes included 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.

End point type	Secondary

End point timeframe:

One month after primary immunization (month 4)

End point values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	218		
Units: Subjects				
Anti-1 (N= 219; 218)	219	218		
Anti-4 (N= 219; 218)	219	218		
Anti-5 (N=219; 218)	218	218		
Anti-6B (N=219; 218)	211	204		
Anti-7F (N=218; 217)	218	217		
Anti-9V (N=219; 218)	219	218		
Anti-14 (N=219; 218)	218	218		
Anti-18C (N=219; 218)	219	217		
Anti-19F (N=219; 218)	218	217		
Anti-23F (N=219; 218)	215	212		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-pneumococcal cross-reactive serotype

concentrations equal to or above 0.20 µg/mL	
End point title	Number of subjects with anti-pneumococcal cross-reactive serotype concentrations equal to or above 0.20 µg/mL

End point description:

Anti-pneumococcal cross-reactive serotypes were 6A and 19A.

End point type	Secondary

End point timeframe:

One month after primary immunization (month 4)

End point values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	218		
Units: Subjects				
Anti-6A	152	132		
Anti-19A	135	119		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with opsonophagocytic activity against vaccine pneumococcal serotypes

End point title	Number of subjects with opsonophagocytic activity against vaccine pneumococcal serotypes

End point description:

Vaccine pneumococcal serotypes included 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F. Opsonophagocytic activity was defined as the dilution of serum (opsonic titer) able to sustain 50% killing of live pneumococci under the assay conditions. The cut-off of the assay was an opsonic titer equal to or greater than 8.

End point type	Secondary

End point timeframe:

One month after primary immunization (month 4)

End point values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	210		
Units: Subjects				
Opsono-1 (N=209; 210)	185	189		
Opsono-4 (N=207; 207)	207	203		
Opsono-5 (N=207; 210)	204	203		
Opsono-6B (N=205; 206)	196	191		
Opsono-7F (N=206; 208)	206	208		

Opsono-9V (N=207; 208)	207	208		
Opsono-14 (N=209; 208)	208	207		
Opsono-18C (N=204; 206)	202	199		
Opsono-19F (N=206; 206)	202	200		
Opsono-23F (N=209; 207)	207	206		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with opsonophagocytic activity against cross-reactive pneumococcal serotypes

End point title	Number of subjects with opsonophagocytic activity against cross-reactive pneumococcal serotypes

End point description:

Cross-reactive pneumococcal serotypes were 6A and 19A. Opsonophagocytic activity was defined as the dilution of serum (opsonic titer) able to sustain 50% killing of live pneumococci under the assay conditions. The cut-off of the assay was an opsonic titer equal to or greater than 8.

End point type	Secondary

End point timeframe:

One month after primary immunization (month 4)

End point values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	200		
Units: Subjects				
Opsono-6A (N=197; 200)	173	171		
Opsono-19A (N=197; 199)	83	75		

Statistical analyses

No statistical analyses for this end point

Secondary: Opsonophagocytic titers of cross-reactive pneumococcal serotypes

End point title	Opsonophagocytic titers of cross-reactive pneumococcal serotypes

End point description:

Opsonophagocytic titers were expressed as GMTs. Cross-reactive pneumococcal serotypes included 6A and 19A. Seropositivity status, defined as Opsonophagocytic activity against pneumococcal serotypes ≥ 8.

End point type	Secondary

End point timeframe:

One month after primary immunization (month 4)

End point values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	200		
Units: Titer				
geometric mean (confidence interval 95%)				
Opsono-6A (N=197;200)	230.8 (180.3 to 295.4)	173.7 (133.9 to 225.3)		
Opsono-19A (N=197;199)	18.1 (13.7 to 23.8)	15.1 (11.5 to 19.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Poliovirus types 1, 2 and 3 titers

End point title	Poliovirus types 1, 2 and 3 titers

End point description:

Titers were given as Geometric Mean Titers (GMTs).Seroprotection status, defined as Anti-polio type 1, Anti-polio type 2 and Anti-polio type 3 antibody titers ≥ 8

End point type	Secondary

End point timeframe:

One month after primary immunization (month 4)

End point values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	93		
Units: Titer				
geometric mean (confidence interval 95%)				
Anti-Polio 1 (N=99; 93)	313.8 (250.4 to 393.3)	328.7 (253.1 to 427)		
Anti-Polio 2 (N=98; 93)	278.7 (225.4 to 344.7)	229.1 (176.9 to 296.6)		
Anti-Polio 3 (N=97; 93)	408.8 (330.1 to 506.4)	449.4 (351.9 to 573.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against diphteria toxoid (DT) and tetanus toxoid (TT)

End point title	Concentrations of antibodies against diphteria toxoid (DT) and tetanus toxoid (TT)

End point description:

Concentrations were defined as GMCs in international units per milliter (IU/mL). Seroprotection status, defined as anti-diphtheria toxoid or anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/mL

End point type	Secondary

End point timeframe:

One month after primary immunization (month 4)

End point values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	107		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-DT	3.317 (2.895 to 3.8)	3.353 (2.991 to 3.759)		
Anti-TT	4.897 (4.358 to 5.502)	4.476 (4.013 to 4.992)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of antibody against hepatitis B surface antigen (HBs) by Enzyme Linked ImmunoSorbent Assay (ELISA).

End point title	Concentration of antibody against hepatitis B surface antigen (HBs) by Enzyme Linked ImmunoSorbent Assay (ELISA).

End point description:

Concentration was given as GMC in milli international units per milliliter (mIU/mL).Seroprotection status, defined as Anti-HBs antibody concentrations >= 10 mIU/mL. As a decrease in the specificity of the anti-HB ELISA assay had been observed in some studies for low levels of antibody (10-100 mIU/mL), the table shows results following partial or complete reanalysis.

End point type	Secondary

End point timeframe:

One month after primary immunization (month 4)

End point values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	97		
Units: mIU/mL				
geometric mean (confidence interval 95%)	1521.2 (1129.7 to 2048.4)	2114.1 (1658.5 to 2694.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of antibody against rotavirus immunoglobulin A (IgA)

End point title	Concentration of antibody against rotavirus immunoglobulin A (IgA)

End point description:

Concentration was expressed as GMC in units per milliliter (U/mL). Seroprotection status, defined as Anti-rotavirus IgA antibody concentration >= 20 U/mL.

End point type	Secondary

End point timeframe:

3 months after primary immunization (month 4)

End point values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: U/mL				
geometric mean (confidence interval 95%)	141.1 (103 to 193.4)	114.8 (85 to 155.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of serious adverse events

End point title	Occurrence of serious adverse events

End point description:

SAEs assessed include medical occurrences that result in death, is 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:

Following vaccination and throughout the entire study period (Month 0 to Month 4)

End point values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	233		
Units: Subjects	18	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Opsonophagocytic titers of vaccine pneumococcal serotypes

End point title	Opsonophagocytic titers of vaccine pneumococcal serotypes

End point description:

Titers are presented as Geometric Mean Titers (GMTs). Pneumococcal serotypes included 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. Seropositivity status, defined as Opsonophagocytic activity against pneumococcal serotypes ≥ 8.

End point type	Secondary

End point timeframe:

One month after primary immunization (month 4)

End point values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	210		
Units: Titer				
geometric mean (confidence interval 95%)				
Opsono-1 (N=209;210)	128.9 (102.7 to 161.7)	122.1 (98.3 to 151.7)		
Opsono-4 (N=207;207)	698.3 (619.6 to 786.9)	609.3 (519.6 to 714.3)		
Opsono-5 (N=207;210)	127.9 (109 to 149.9)	98.6 (83 to 117.1)		
Opsono-6B (N=205;206)	870.7 (710.2 to 1067.6)	619.2 (483.4 to 793.2)		
Opsono-7F (N=206;208)	3905.8 (3420.2 to 4460.4)	3585.7 (3119.8 to 4121.2)		
Opsono-9V (N=207;208)	1800 (1596.6 to 2029.3)	1851.3 (1612.3 to 2125.8)		
Opsono-14 (N=209;208)	1521 (1313.3 to 1761.6)	1485.8 (1280.5 to 1724)		
Opsono-18C (N=204;206)	533.5 (461.8 to 616.4)	383.9 (319.3 to 461.5)		

Opsono-19F (N=206;206)	689.6 (581.1 to 818.2)	573.5 (477.2 to 689.3)		
Opsono-23F (N=209;207)	2716.7 (2316.3 to 3186.3)	2379.5 (2043.4 to 2770.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited local and general symptoms.

End point title	Number of subjects with solicited local and general symptoms.

End point description:

Solicited local symptoms were pain, redness and swelling. Solicited general symptoms were drowsiness, fever, irritability, loss of appetite, diarrhoea and vomiting.

End point type	Secondary

End point timeframe:

Within 4 days (day 0-3) after vaccination

End point values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	233		
Units: Subjects				
Pain	162	157		
Redness	149	142		
Swelling	133	124		
Drowsiness	151	136		
Fever	193	175		
Irritability	168	171		
Loss of appetite	127	121		
Diarrhoea	53	54		
Vomiting	44	46		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN)

End point title	Concentrations of antibodies against pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN)

End point description:

Concentrations are expressed as GMCs in EL.U/mL. Seropositivity status, defined as anti-PT, anti-FHA, anti-PRN antibody concentrations ≥ 5 EL.U/mL.

End point type	Secondary

End point timeframe:

One month after primary immunization (month 4)

End point values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	107		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-PT (N=109; 107)	46.5 (41.1 to 52.6)	45.4 (39.8 to 51.7)		
Anti-FHA (N=107; 107)	179.2 (157.5 to 203.9)	186.2 (165.5 to 209.5)		
Anti-PRN (N=109; 107)	142.1 (123.2 to 164)	128.3 (110.9 to 148.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of antibody against polyribosyl-ribitol phosphate (PRP)

End point title	Concentration of antibody against polyribosyl-ribitol phosphate (PRP)

End point description:

Concentrain was expressed as GMC in µg/mL. Seroprotection status, defined as anti-PRP antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL

End point type	Secondary

End point timeframe:

One month after primary immunization (month 4)

End point values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	108		
Units: µg/mL				
geometric mean (confidence interval 95%)	9.745 (7.807 to 12.164)	6.387 (5.051 to 8.078)		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of unsolicited adverse events

End point title	Occurrence of unsolicited adverse events

End point description:

An AE is 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.

End point type	Secondary

End point timeframe:

Within 31 days (Days 0-30) after vaccination

End point values	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot Infanrix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	233		
Units: Subjects	88	96		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Frequent AEs were assessed during the 4-day (Days 0-3) follow-up period after vaccination for solicited AEs and 31-day (Days 0-30) follow-up period for unsolicited AEs. SAEs were assessed from month 0 until study end (month 4).

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	13.0

Reporting groups

Reporting group title	Synflorix Clinical Lot & Infanrix Group

Reporting group description:

Subjects received 3 doses of the clinical lot of Synflorix TM (GSK1024850A) intramuscularly in the right thigh at 2-3-5 months of age (= study month 0, 1, 3) co-administered with a DTPa-combined vaccine (Infanrix hexa TM (at 2, 3 and 5 months of age in Malaysia or 2 and 5 months of age in Singapore) or Infanrix-IPV/Hib TM (at 3 months of age in Singapore)) intramuscularly in the left thigh and Rotarix TM orally at 2-3 months of age (= study month 0, 1).

Reporting group title	Synflorix Commercial Lot & Infanrix Group

Reporting group description:

Subjects received 3 doses of the commercial lot of Synflorix TM (GSK1024850A) intramuscularly in the lright thigh at 2-3-5 months of age (= study month 0, 1, 3) co-administered with a DTPa-combined vaccine (Infanrix hexa TM (at 2, 3 or 5 months of age in Malaysia or 2 and 5 months in Singapore) or Infanrix-IPV/Hib TM (at 3 months of age in Singapore)) intramuscularly in the left thigh and Rotarix TM orally at 2-3 months of age (= study month 0, 1).

Serious adverse events	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot & Infanrix Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 233 (7.73%)	7 / 233 (3.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	2 / 233 (0.86%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Spinal muscular atrophy			

subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Kawasaki's disease			
subjects affected / exposed	1 / 233 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Vith nerve parlysis			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	5 / 233 (2.15%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	3 / 233 (1.29%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	4 / 233 (1.72%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	2 / 233 (0.86%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 233 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis tuberculous			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			

subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Synflorix Clinical Lot & Infanrix Group	Synflorix Commercial Lot & Infanrix Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	193 / 233 (82.83%)	175 / 233 (75.11%)	
General disorders and administration site conditions			
Pain			
alternative assessment type: Systematic			
subjects affected / exposed	162 / 233 (69.53%)	157 / 233 (67.38%)	
occurrences (all)	162	157	
Redness			
alternative assessment type: Systematic			
subjects affected / exposed	149 / 233 (63.95%)	142 / 233 (60.94%)	
occurrences (all)	149	142	
Swelling			
alternative assessment type: Systematic			

subjects affected / exposed	133 / 233 (57.08%)	124 / 233 (53.22%)	
occurrences (all)	133	124	
Drowsiness			
alternative assessment type: Systematic			
subjects affected / exposed	151 / 233 (64.81%)	136 / 233 (58.37%)	
occurrences (all)	151	136	
Fever			
alternative assessment type: Systematic			
subjects affected / exposed	193 / 233 (82.83%)	175 / 233 (75.11%)	
occurrences (all)	193	175	
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	168 / 233 (72.10%)	171 / 233 (73.39%)	
occurrences (all)	168	171	
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	53 / 233 (22.75%)	54 / 233 (23.18%)	
occurrences (all)	53	54	
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	44 / 233 (18.88%)	46 / 233 (19.74%)	
occurrences (all)	44	46	
Loss of appetite			
alternative assessment type: Systematic			
subjects affected / exposed	127 / 233 (54.51%)	121 / 233 (51.93%)	
occurrences (all)	127	121	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	33 / 233 (14.16%)	40 / 233 (17.17%)	
occurrences (all)	33	40	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported