



Clinical trial results:

A phase IIIb randomized, open, controlled study to assess the effect of prophylactic antipyretic treatment on the rate of febrile reactions following concomitant administration of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine with GSK Biologicals' Infanrix hexa vaccine in children at 3, 4 and 5 months of age and GSK Biologicals' Rotarix vaccine at 3 and 4 months of age.

Summary

EudraCT number	2006-000559-16
Trial protocol	CZ
Global end of trial date	10 April 2007

Results information

Result version number	v1
This version publication date	08 March 2016
First version publication date	28 March 2015

Trial information

Trial identification

Sponsor protocol code	107017
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00370318
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, 044 2089-904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, 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	26 July 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 April 2007
Global end of trial reached?	Yes
Global end of trial date	10 April 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the percentage reduction in febrile reactions (rectal temperature $>$ or $=$ 38.0°C) when prophylactic antipyretic treatment is administered compared to no prophylactic antipyretic treatment, after primary vaccination with GSK Biologicals' 10-valent pneumococcal conjugate vaccine and routine DTPa-HBV-IPV/Hib (Infanrix hexa) vaccination in children at 3, 4 and 5 months of age and oral live attenuated HRV (Rotarix) vaccination in children at 3 and 4 months of age.

Protection of trial subjects:

All subjects were supervised for 30 min after vaccination/product administration with appropriate medical treatment readily available. Vaccines/products were administered by qualified and trained personnel. Vaccines/products were administered only to eligible subjects that had no contraindications to any components of the vaccines/products. Subjects were followed-up for 6 months after the last vaccination/product administration (Safety Follow-Up (FU) Phase). Adverse events specifically checked for while assessing the subjects' safety were acute disease at the time of vaccination (acute disease being defined the presence of a mild, moderate or severe illness with or without fever defined as rectal temperature $>$ 37.5°C ; any fever \geq 40.5°C (rectal temperature) or \geq 40.0°C (oral/axillary/tympanic temperature) within 48 hours of vaccination, collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination, persistent, inconsolable crying occurring within 48 hours of vaccination and lasting 3 hours, seizures with or without fever occurring within 3 days of vaccination and gastroenteritis (GE) within 7 days preceding the study vaccine administration (i.e. diarrhoea with or without vomiting).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 September 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czech Republic: 459
Worldwide total number of subjects	459
EEA total number of subjects	459

Notes:

Subjects enrolled per age group

In utero	0
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Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	459
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:

This study included an Active Phase, up to 3 months post the first study vaccination and an Safety Follow-Up Phase of up to 6 months after the last study vaccination. Withdrawal information on subjects was collected up to the end of the Active Phase, up to Month 3.

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	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	10Pn-PD-DiT/ Paracetamol Group

Arm description:

Subjects were vaccinated with a 3-dose course administered at 3, 4 and 5 months of age (Study Months 0, 1 and 2) of GSK Biologicals' pneumococcal conjugate vaccine GSK1024850A (also referred to as 10Pn-PD-DiT or 10Pn vaccine) co-administered with Infanrix™ hexa (also referred to as DTPa-HBV-IPV/Hib) and with prophylactic antipyretic treatment (rectal paracetamol or acetaminophen) under the form of suppositories of CALPOL 80 or 125, depending on the subjects' body weight. In addition, subjects also received 2 doses of HRV vaccine (Rotarix™) and of at 3 and 4 months of age (Study Months 0 and 1).

Arm type	Experimental
Investigational medicinal product name	10-valent Streptococcus pneumoniae conjugate vaccine
Investigational medicinal product code	
Other name	10Pn, 10Pn-PD-DiT, GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine, Synflorix™, GlaxoSmithKline (GSK) Biologicals' 1024850A vaccine,
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Three doses of the vaccine were administered intramuscularly, into the right thigh at 3, 4 and 5 months of age (Study Months 0, 1 and 2).

Investigational medicinal product name	Rotarix™
Investigational medicinal product code	
Other name	HRV, GSK Biologicals' oral live attenuated human rotavirus vaccine.
Pharmaceutical forms	Powder and solvent for oral suspension
Routes of administration	Oral use

Dosage and administration details:

2 doses of the vaccine were administered orally at 3 and 4 months of age (Study Months 0 and 1).

Investigational medicinal product name	Infanrix™ Hexa
Investigational medicinal product code	
Other name	DTPa-IPV-HBV/Hib, Infanrix Hexa GSK Biologicals' diphtheria-tetanus-acellular pertussis, hepatitis B virus-inactivated poliovirus and Haemophilus influenzae typ
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3 doses of the vaccine were administered intramuscularly in the left thigh at 3, 4 and 5 months of age (Study Months 0, 1 and 2).

Investigational medicinal product name	CALPOL 80
Investigational medicinal product code	
Other name	Paracetamol 80 mg; Acetaminophen
Pharmaceutical forms	Suppository
Routes of administration	Rectal use

Dosage and administration details:

In subjects weighing 4.5 to < 7 kg: 3 doses administered rectally at 3, 4 and 5 months of age (Study Months 0, 1 and 2).

Investigational medicinal product name	CALPOL 125
Investigational medicinal product code	
Other name	Paracetamol 125 mg; Acetaminophen
Pharmaceutical forms	Suppository
Routes of administration	Rectal use

Dosage and administration details:

In subjects weighing ≥ 7 kg: 3 doses administered rectally at 3, 4 and 5 months of age (Study Months 0, 1 and 2).

Arm title	10Pn-PD-DiT Group
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Arm description:

Subjects were vaccinated with a 3-dose course administered at 3, 4 and 5 months of age (Study Months 0, 1 and 2) of GSK Biologicals' pneumococcal conjugate vaccine GSK1024850A (also referred to as 10Pn-PD-DiT or 10Pn vaccine) co-administered with Infanrix™ hexa (also referred to as DTPa-HBV-IPV/Hib). Subjects also received 2 doses of HRV vaccine (Rotarix™) without prophylactic antipyretic treatment at 3 and 4 months of age (Study Months 0 and 1).

Arm type	Experimental
Investigational medicinal product name	10-valent Streptococcus pneumoniae conjugate vaccine
Investigational medicinal product code	
Other name	10Pn, 10Pn-PD-DiT, GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine, Synflorix™, GlaxoSmithKline (GSK) Biologicals' 1024850A vaccine,
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Three doses of the vaccine were administered intramuscularly, into the right thigh at 3, 4 and 5 months of age (Study Months 0, 1 and 2).

Investigational medicinal product name	Rotarix™
Investigational medicinal product code	
Other name	HRV, GSK Biologicals' oral live attenuated human rotavirus vaccine.
Pharmaceutical forms	Powder and solvent for oral suspension
Routes of administration	Oral use

Dosage and administration details:

2 doses of the vaccine were administered orally at 3 and 4 months of age (Study Months 0 and 1).

Investigational medicinal product name	Infanrix™ Hexa
Investigational medicinal product code	
Other name	DTPa-IPV-HBV/Hib, Infanrix Hexa GSK Biologicals' diphtheria-tetanus-acellular pertussis, hepatitis B virus-inactivated poliovirus and Haemophilus influenzae typ
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3 doses of the vaccine were administered intramuscularly in the left thigh at 3, 4 and 5 months of age (Study Months 0, 1 and 2).

Number of subjects in period 1	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group
Started	226	233
Completed	224	232
Not completed	2	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	-
Migrated/moved from study area	-	1

Baseline characteristics

Reporting groups

Reporting group title	10Pn-PD-DiT/ Paracetamol Group
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Reporting group description:

Subjects were vaccinated with a 3-dose course administered at 3, 4 and 5 months of age (Study Months 0, 1 and 2) of GSK Biologicals' pneumococcal conjugate vaccine GSK1024850A (also referred to as 10Pn-PD-DiT or 10Pn vaccine) co-administered with Infanrix™ hexa (also referred to as DTPa-HBV-IPV/Hib) and with prophylactic antipyretic treatment (rectal paracetamol or acetaminophen) under the form of suppositories of CALPOL 80 or 125, depending on the subjects' body weight . In addition, subjects also received 2 doses of HRV vaccine (Rotarix™) and of at 3 and 4 months of age (Study Months 0 and 1).

Reporting group title	10Pn-PD-DiT Group
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Reporting group description:

Subjects were vaccinated with a 3-dose course administered at 3, 4 and 5 months of age (Study Months 0, 1 and 2) of GSK Biologicals' pneumococcal conjugate vaccine GSK1024850A (also referred to as 10Pn-PD-DiT or 10Pn vaccine) co-administered with Infanrix™ hexa (also referred to as DTPa-HBV-IPV/Hib). Subjects also received 2 doses of HRV vaccine (Rotarix™) without prophylactic antipyretic treatment at 3 and 4 months of age (Study Months 0 and 1).

Reporting group values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group	Total
Number of subjects	226	233	459
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	12.2	12.3	
standard deviation	± 2.06	± 2.21	-
Gender categorical Units: Subjects			
Female	114	109	223
Male	112	124	236

End points

End points reporting groups

Reporting group title	10Pn-PD-DiT/ Paracetamol Group
Reporting group description: Subjects were vaccinated with a 3-dose course administered at 3, 4 and 5 months of age (Study Months 0, 1 and 2) of GSK Biologicals' pneumococcal conjugate vaccine GSK1024850A (also referred to as 10Pn-PD-DiT or 10Pn vaccine) co-administered with Infanrix™ hexa (also referred to as DTPa-HBV-IPV/Hib) and with prophylactic antipyretic treatment (rectal paracetamol or acetaminophen) under the form of suppositories of CALPOL 80 or 125, depending on the subjects' body weight . In addition, subjects also received 2 doses of HRV vaccine (Rotarix™) and of at 3 and 4 months of age (Study Months 0 and 1).	
Reporting group title	10Pn-PD-DiT Group
Reporting group description: Subjects were vaccinated with a 3-dose course administered at 3, 4 and 5 months of age (Study Months 0, 1 and 2) of GSK Biologicals' pneumococcal conjugate vaccine GSK1024850A (also referred to as 10Pn-PD-DiT or 10Pn vaccine) co-administered with Infanrix™ hexa (also referred to as DTPa-HBV-IPV/Hib). Subjects also received 2 doses of HRV vaccine (Rotarix™) without prophylactic antipyretic treatment at 3 and 4 months of age (Study Months 0 and 1).	

Primary: Number of subjects reported with core fever (rectal temperature) ≥ 38.0 degrees Celsius ($^{\circ}\text{C}$)

End point title	Number of subjects reported with core fever (rectal temperature) ≥ 38.0 degrees Celsius ($^{\circ}\text{C}$)
End point description:	
End point type	Primary
End point timeframe: Within 4 days (Day 0-3) after each vaccination, across doses	

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	233		
Units: Subjects				
Fever $\geq 38.0^{\circ}\text{C}$	94	154		

Statistical analyses

Statistical analysis title	Difference between groups in percentage
Statistical analysis description: Analysis aimed at demonstrating the superiority in terms of post-immunization core fever $\geq 38.0^{\circ}\text{C}$ of 10Pn-PD-DiT vaccine when co-administered with paracetamol compared to the 10Pn-PD-DiT vaccine when administered without such co-administration. Towards this analysis, standardized asymptotic 95% confidence interval (CI) for the groups difference [10Pn-PD-DiT/Paracetamol Group minus 10Pn-PD-DiT Group] in percentages of subjects reported with core fever $\geq 38.0^{\circ}\text{C}$ was computed.	
Comparison groups	10Pn-PD-DiT/ Paracetamol Group v 10Pn-PD-DiT Group

Number of subjects included in analysis	459
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
Parameter estimate	Difference in percentage
Point estimate	24.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.49
upper limit	33.11

Notes:

[1] - Superiority was demonstrated if the lower limit (LL) computed standardized asymptotic 95% CI was above 0%

Secondary: Number of subjects reported with core fever (rectal temperature) > 39.0°C

End point title	Number of subjects reported with core fever (rectal temperature) > 39.0°C
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End point description:

End point type	Secondary
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End point timeframe:

Within 4 days (Day 0-3) after at least one vaccination, across doses

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	233		
Units: Subjects				
Fever (rectal temperature) > 39.0°C	4	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reported with any and Grade 3 solicited local symptoms

End point title	Number of subjects reported with any and Grade 3 solicited local symptoms
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End point description:

Solicited local symptoms assessed were pain, redness and swelling. Any was defined as any occurrence of the specified symptom regardless of intensity. Grade 3 pain was defined as cried when limb was moved/spontaneously painful. Grade 3 redness/swelling was defined as redness/swelling > 30 millimetres from injection site.

End point type	Secondary
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End point timeframe:

Within 4 days after each vaccination, across doses

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	233		
Units: Subjects				
Any pain	69	101		
Grade 3 pain	2	10		
Any redness	134	143		
Grade 3 redness	6	10		
Any swelling	89	102		
Grade 3 swelling	18	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reported with any and Grade 3 solicited general symptoms

End point title	Number of subjects reported with any and Grade 3 solicited general symptoms
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End point description:

Solicited general symptoms assessed were diarrhea, drowsiness, fever (rectal temperature $\geq 38.5^{\circ}\text{C}$), irritability, loss of appetite and vomiting. Any was defined as any occurrence of the specified symptom regardless of intensity and relation to vaccination. Any for diarrhea was defined as 3 looser than normal stools/day and any for vomiting was defined as one episode of vomiting/day. Grade 3 diarrhea was defined as 6 or more looser stools/day. Grade 3 drowsiness was defined as drowsiness that prevented normal activity. Grade 3 fever was defined as rectal temperature $>40.0^{\circ}\text{C}$. Grade 3 irritability was defined as crying that could not be comforted/ prevented normal activity. Grade 3 loss of appetite was defined as not eating at all. Grade 3 vomiting was defined as 3 or more episodes of vomiting/day.

End point type	Secondary
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End point timeframe:

Within 4 days after each vaccination, across doses

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	233		
Units: Subjects				
Any diarrhea	34	31		
Grade 3 diarrhea	8	5		
Any drowsiness	137	155		
Grade 3 drowsiness	0	5		

Any fever (rectal temperature $\geq 38.0^{\circ}\text{C}$)	94	154		
Grade 3 fever (rectal temperature $> 40.0^{\circ}\text{C}$)	4	17		
Any irritability	139	166		
Grade 3 irritability	2	8		
Any loss of appetite	49	68		
Grade 3 loss of appetite	0	0		
Any vomiting	30	15		
Grade 3 vomiting	6	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reported with unsolicited adverse events (AEs)

End point title	Number of subjects reported with unsolicited adverse events (AEs)
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End point description:

End point type	Secondary
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End point timeframe:

Within 31 days (Day 0-30) after each vaccination, across doses

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	233		
Units: Subjects				
Subject(s) with AE(s)	100	114		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reported with serious adverse events (SAEs) during the Active Phase of the study

End point title	Number of subjects reported with serious adverse events (SAEs) during the Active Phase of the study
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End point description:

End point type	Secondary
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End point timeframe:

During the Active Phase of the study, from Month 0 to Month 3)

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	233		
Units: Subjects				
Subject(s) with SAE(s)	8	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reported with serious adverse events (SAEs) throughout the entire study

End point title	Number of subjects reported with serious adverse events (SAEs) throughout the entire study
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End point description:

End point type	Secondary
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End point timeframe:

During the entire study period, from Month 0 to Month 8, up to 6 months after the last study vaccine dose

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	233		
Units: Subjects				
Subject(s) with SAE(s)	20	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with antibody concentrations against 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) ≥ 0.2 µg/mL

End point title	Number of subjects with antibody concentrations against 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) ≥ 0.2 µg/mL
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End point description:

Anti-1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody concentrations were measured by 22F-inhibition Enzyme-Linked ImmunoSorbent Assay (ELISA). Seroprotection and seropositivity cut-offs for the assay were ≥ 0.20 and $0.05 \mu\text{g/mL}$, respectively.

End point type	Secondary
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End point timeframe:

At Month 3 (M3), one month after Dose 3 of pneumococcal vaccination.

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	227		
Units: Subjects				
Anti-1 $\geq 0.2 \mu\text{g/mL}$, at M3 (N=207; 226)	202	224		
Anti-4 $\geq 0.2 \mu\text{g/mL}$, at M3 (N=206; 226)	205	225		
Anti-5 $\geq 0.2 \mu\text{g/mL}$, at M3 (N=207; 227)	206	226		
Anti-6B $\geq 0.2 \mu\text{g/mL}$, at M3 (N=206; 225)	128	170		
Anti-7F $\geq 0.2 \mu\text{g/mL}$, at M3 (N=208; 227)	206	226		
Anti-9V $\geq 0.2 \mu\text{g/mL}$, at M3 (N=204; 225)	200	222		
Anti-14 $\geq 0.2 \mu\text{g/mL}$, at M3 (N=207; 225)	206	224		
Anti-18C $\geq 0.2 \mu\text{g/mL}$, at M3 (N=208; 227)	199	226		
Anti-19F $\geq 0.2 \mu\text{g/mL}$, at M3 (N=208; 227)	203	227		
Anti-23F $\geq 0.2 \mu\text{g/mL}$, at M3 (N=204; 225)	164	196		

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody concentrations against 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)

End point title	Antibody concentrations against 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)
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End point description:

Anti-1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody concentrations were measured by 22F-inhibition Enzyme-Linked ImmunoSorbent Assay (ELISA). Seropositivity cut-off for the assay was $\geq 0.05 \mu\text{g/mL}$.

End point type	Secondary
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End point timeframe:

At Month 3 (M3), one month after Dose 3 of pneumococcal vaccination.

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	227		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-1, M3, (N=207; 226)	0.92 (0.83 to 1.03)	1.45 (1.31 to 1.61)		
Anti-4, M3, (N=206; 226)	1.33 (1.18 to 1.5)	2.13 (1.91 to 2.37)		
Anti-5, M3, (N=207; 227)	1.42 (1.28 to 1.58)	2.04 (1.85 to 2.25)		
Anti-6B, M3, (N=206; 225)	0.26 (0.22 to 0.31)	0.46 (0.38 to 0.54)		
Anti-7F, M3, (N=208; 227)	1.57 (1.43 to 1.72)	2.16 (1.96 to 2.37)		
Anti-9V, M3, (N=204; 225)	1.03 (0.92 to 1.15)	1.48 (1.34 to 1.64)		
Anti-14, M3, (N=207; 225)	2.3 (2.05 to 2.58)	3.57 (3.16 to 4.03)		
Anti-18C, M3, (N=208; 227)	1.19 (1.03 to 1.38)	2.65 (2.37 to 2.98)		
Anti-19F, M3, (N=208; 227)	3.46 (3.01 to 3.98)	5.59 (4.99 to 6.26)		
Anti-23F, M3, (N=204; 225)	0.49 (0.42 to 0.59)	0.76 (0.64 to 0.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Opsonophagocytic activity (OPA) titers against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F

End point title	Opsonophagocytic activity (OPA) titers against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F
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End point description:

OPA titers against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (Opsono-1, -4, -5, -6B, -7F, -9V, -14, -18C, -19F and -23F) were calculated, expressed as geometric mean titers (GMTs) and tabulated. The seropositivity cut-off for the assay was ≥ 8 .

End point type	Secondary
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End point timeframe:

At Month 3 (M3), one month after Dose 3 of pneumococcal vaccination

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	176		
Units: Titers				
geometric mean (confidence interval 95%)				
Opsono-1 (N=164;176)	10.3 (8.3 to 12.8)	23.7 (18.2 to 31)		
Opsono-4 (N=163;175)	788.3 (691.8 to 898.4)	744.6 (649.2 to 854.2)		
Opsono-5 (N=159;171)	32.2 (25.9 to 40)	72.5 (59.9 to 87.7)		
Opsono-6B (N=157;162)	386.7 (270 to 554)	684.8 (523.9 to 895.3)		
Opsono-7F (N=158;170)	2458.2 (2096 to 2883)	2345.3 (1970.7 to 2791.2)		
Opsono-9V (N=154;169)	1658.1 (1438.3 to 1911.4)	1230.3 (1026.8 to 1474)		
Opsono-14 (N=160;175)	897.6 (753.2 to 1069.6)	1161.6 (985 to 1369.8)		
Opsono-18C (N=157;170)	135 (106.6 to 171)	202.2 (170.4 to 240)		
Opsono-19F (N=155;165)	244.6 (187.4 to 319.4)	369.5 (295.6 to 461.9)		
Opsono-23F (N=160;170)	1163.6 (885.4 to 1529.2)	1497.2 (1215 to 1845.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody concentrations against pneumococcal serotypes 6A and 19A (Anti-6A and 19A)

End point title	Antibody concentrations against pneumococcal serotypes 6A and 19A (Anti-6A and 19A)
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End point description:

Anti-6A and 19A antibody concentrations were measured by 22F-inhibition Enzyme-Linked ImmunoSorbent Assay (ELISA).

End point type	Secondary
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End point timeframe:

At Month 3 (M3), one month after Dose 3 of pneumococcal vaccination.

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	224		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-6A (N=204;224)	0.07 (0.06 to 0.08)	0.12 (0.1 to 0.15)		
Anti-19A (N=205;223)	0.12 (0.1 to 0.14)	0.19 (0.17 to 0.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Opsonophagocytic activity (OPA) titers against pneumococcal cross-reactive serotypes 6A and 19A

End point title	Opsonophagocytic activity (OPA) titers against pneumococcal cross-reactive serotypes 6A and 19A
End point description: OPA titers against pneumococcal serotypes 6A and 19A (Opsono-6A and 19A) were calculated, expressed as geometric mean titers (GMTs) and tabulated. The seropositivity cut-off for the assay was ≥ 8.	
End point type	Secondary
End point timeframe: At Month 3 (M3), one month after Dose 3 of pneumococcal vaccination	

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	172		
Units: Titers				
geometric mean (confidence interval 95%)				
Opsono-6A (N=153;165)	49.3 (34.8 to 69.9)	61.4 (43.7 to 86.1)		
Opsono-19A (N=160;172)	6.3 (5.2 to 7.8)	7.9 (6.3 to 10)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Concentrations of antibodies against protein D (Anti-PD)
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End point description:

The seropositivity cut-off for the assay was ≥ 100 Enzyme-Linked ImmunoSorbent Assay (ELISA). units per millilitre.

End point type	Secondary
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End point timeframe:

At Month 3 (M3), one month after Dose 3 of pneumococcal vaccination.

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	222		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-PD	985.4 (872.9 to 1112.4)	1599.1 (1434.6 to 1782.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with antibody concentrations against 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) ≥ 0.05 $\mu\text{g/mL}$

End point title	Number of subjects with antibody concentrations against 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) ≥ 0.05 $\mu\text{g/mL}$
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End point description:

Anti-1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody concentrations were measured by 22F-inhibition Enzyme-Linked ImmunoSorbent Assay (ELISA). Seropositivity cut-off for the assay was ≥ 0.05 $\mu\text{g/mL}$.

End point type	Secondary
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End point timeframe:

At Month 3 (M3), one month after Dose 3 of pneumococcal vaccination.

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	227		
Units: Subjects				
Anti-1 (N=207; 226)	207	226		
Anti-4 (N=206; 226)	205	226		
Anti-5 (N=207; 227)	207	227		
Anti-6B (N=206; 225)	179	209		

Anti-7F (N=208; 227)	208	227		
Anti-9V (N=204; 225)	204	225		
Anti-14 (N=207; 225)	207	225		
Anti-18C (N=208; 227)	204	227		
Anti-19F (N=208; 227)	208	227		
Anti-23F (N=204; 225)	192	212		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with opsonophagocytic activity titers against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (Opsono-1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) ≥ 8

End point title	Number of subjects with opsonophagocytic activity titers against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (Opsono-1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) ≥ 8
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End point description:

The seropositivity cut-off of the assay was ≥ 8 .

End point type	Secondary
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End point timeframe:

At Month 3 (M3), one month after Dose 3 of pneumococcal vaccination.

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	175		
Units: Subjects				
Opsono-1 ≥ 8 (N=164;176)	57	97		
Opsono-4 ≥ 8 (N=163;175)	163	175		
Opsono-5 ≥ 8 (N=159;171)	127	159		
Opsono-6B ≥ 8 (N=157;162)	129	151		
Opsono-7F ≥ 8 (N=158;170)	158	169		
Opsono-9V ≥ 8 (N=154;169)	154	168		
Opsono-14 ≥ 8 (N=160;175)	158	174		
Opsono-18C ≥ 8 (N=157;170)	144	167		
Opsono-19F ≥ 8 (N=155;165)	142	156		
Opsono-23F ≥ 8 (N=160;170)	150	166		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with antibody concentrations against pneumococcal

serotypes 6A and 19A (Anti-6A and 19A) \geq 0.05 μ g/mL

End point title	Number of subjects with antibody concentrations against pneumococcal serotypes 6A and 19A (Anti-6A and 19A) \geq 0.05 μ g/mL
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End point description:

Anti-6A and 19A antibody concentrations were measured by 22F-inhibition Enzyme-Linked ImmunoSorbent Assay (ELISA).

End point type	Secondary
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End point timeframe:

At Month 3 (M3), one month after Dose 3 of pneumococcal vaccination.

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	224		
Units: Subjects				
Anti-6A, (N=204;224)	120	162		
Anti-19A (N=205;223)	164	193		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with opsonophagocytic activity (OPA) titers against pneumococcal cross-reactive serotypes 6A and 19A (Opsono-6A and 19A) \geq 8

End point title	Number of subjects with opsonophagocytic activity (OPA) titers against pneumococcal cross-reactive serotypes 6A and 19A (Opsono-6A and 19A) \geq 8
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End point description:

The seropositivity cut-off of the assay was \geq 8.

End point type	Secondary
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End point timeframe:

At Month 3 (M3), one month after Dose 3 of pneumococcal vaccination.

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	172		
Units: Subjects				
Opsono-6A, (N=153;165)	92	107		
Opsono-19A, (N=160;172)	19	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with concentrations of antibodies against protein D (Anti-PD) \geq 100 Enzyme-Linked ImmunoSorbent Assay (ELISA) units per millilitre (EL.U/mL)

End point title	Number of subjects with concentrations of antibodies against protein D (Anti-PD) \geq 100 Enzyme-Linked ImmunoSorbent Assay (ELISA) units per millilitre (EL.U/mL)
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End point description:

End point type	Secondary
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End point timeframe:

At Month 3 (M3), one month after Dose 3 of pneumococcal vaccination.

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	222		
Units: Subjects				
Anti-PD	205	222		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against diphtheria and tetanus toxoids (anti-D and T)

End point title	Concentrations of antibodies against diphtheria and tetanus toxoids (anti-D and T)
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End point description:

The seroprotection cut-off for the assay was \geq 0.1 IU/mL.

End point type	Secondary
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End point timeframe:

At Month 3 (M3), one month after Dose 3 of Infanrix™ hexa vaccine.

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	225		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-D	2.67 (2.417 to 2.95)	3.561 (3.294 to 3.849)		
Anti-T	1.639 (1.474 to 1.822)	2.669 (2.434 to 2.927)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-polyribosyl-ribitol phosphate (anti-PRP) antibody concentrations

End point title	Anti-polyribosyl-ribitol phosphate (anti-PRP) antibody concentrations
End point description: The seroprotection cut-off for the assay was $\geq 0.15 \mu\text{g/mL}$.	
End point type	Secondary
End point timeframe: At Month 3 (M3), one month after Dose 3 of Infanrix™ hexa vaccine.	

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	224		
Units: $\mu\text{g/mL}$				
geometric mean (confidence interval 95%)				
Anti-PRP	2.278 (1.883 to 2.755)	4.264 (3.673 to 4.951)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-pertussis toxoid (anti-PT), anti-filamentous haemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) antibody concentrations

End point title	Anti-pertussis toxoid (anti-PT), anti-filamentous haemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) antibody concentrations
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End point description:

The seropositivity cut-off for the assay was ≥ 5 Enzyme-Linked ImmunoSorbent Assay (ELISA) units per

milliliter (EL.U/mL).

End point type	Secondary
End point timeframe:	
At Month 3 (M3), one month after Dose 3 of Infanrix™ hexa vaccine.	

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	225		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-PT (N=205;224)	39.3 (36.5 to 42.3)	42.3 (39.2 to 45.7)		
Anti-FHA (N=204;224)	148 (134.5 to 162.8)	166.2 (151.9 to 181.8)		
Anti-PRN (N=206;225)	59 (52.1 to 66.8)	78 (70.5 to 86.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-hepatitis B surface antigen (anti-HBs) antibody concentrations

End point title	Anti-hepatitis B surface antigen (anti-HBs) antibody concentrations
End point description:	
The seroprotection cut-off for the assay was ≥ 10 mIU/mL.	
End point type	Secondary
End point timeframe:	
At Month 3 (M3), one month after Dose 3 of Infanrix™ hexa vaccine.	

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	66		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-HBs	254.2 (171.6 to 376.6)	306.6 (218.6 to 430.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-polio types 1, 2 and 3 titers

End point title	Anti-polio types 1, 2 and 3 titers
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End point description:

The seroprotection cut-off for the assay was ≥ 8 .

End point type	Secondary
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End point timeframe:

At Month 3 (M3), one month after Dose 3 of Infanrix™ hexa vaccine.

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	25		
Units: Titers				
geometric mean (confidence interval 95%)				
Anti-Polio 1 (N=20;25)	215.3 (135.4 to 342.1)	142.7 (78.7 to 258.8)		
Anti-Polio 2 (N=19;23)	171.7 (91.1 to 323.7)	108.6 (59.8 to 197.3)		
Anti-Polio 3 (N=17;23)	409.1 (222.2 to 753.4)	284.3 (165.9 to 487.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U/mL

End point title	Number of subjects with anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U/mL
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End point description:

The seropositivity cut-off for the assay was ≥ 5 Enzyme-Linked ImmunoSorbent Assay (ELISA) units per milliliter (EL.U/mL).

End point type	Secondary
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End point timeframe:

At Month 3 (M3), one month after Dose 3 of Infanrix™ hexa vaccine.

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	225		
Units: Subjects				
Anti-PT (N=205;224)	205	224		
Anti-FHA (N=204;224)	204	224		
Anti-PRN (N=206;225)	205	224		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL.

End point title	Number of subjects with anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL.
End point description:	The seroprotection cut-off for the assay was ≥ 0.1 IU/mL.
End point type	Secondary
End point timeframe:	At Month 3 (M3), one month after Dose 3 of Infanrix™ hexa vaccine.

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	225		
Units: Subjects				
Anti-D	206	225		
Anti-T	206	225		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-PRP antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL.

End point title	Number of subjects with anti-PRP antibody concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL.
End point description:	The seroprotection cut-offs for the assay were ≥ 0.15 µg/mL and ≥ 1.0 µg/mL.
End point type	Secondary
End point timeframe:	At Month 3 (M3), one month after Dose 3 of Infanrix™ hexa vaccine.

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	224		
Units: Subjects				
Anti-PRP ≥ 0.15 $\mu\text{g/mL}$	199	224		
Anti-PRP ≥ 1.0 $\mu\text{g/mL}$	153	205		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-HBs antibody concentrations ≥ 10 mIU/mL.

End point title	Number of subjects with anti-HBs antibody concentrations ≥ 10 mIU/mL.
End point description: The seroprotection cut-off for the assay was ≥ 10 mIU/mL.	
End point type	Secondary
End point timeframe: At Month 3 (M3), one month after Dose 3 of Infanrix™ hexa vaccine.	

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	66		
Units: Subjects				
Anti-HBs	48	64		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-polio type 1, 2 and 3 titers ≥ 8

End point title	Number of subjects with anti-polio type 1, 2 and 3 titers ≥ 8
End point description: The seroprotection cut-off for the assay was ≥ 8 .	
End point type	Secondary
End point timeframe: At Month 3 (M3), one month after Dose 3 of Infanrix™ hexa vaccine.	

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	25		
Units: Subjects				
Anti-Polio 1 (N=20;25)	20	25		
Anti-Polio 2 (N=19;23)	19	23		
Anti-Polio 3 (N=17;23)	17	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of vaccine responders as regards antibodies against pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)

End point title	Number of vaccine responders as regards antibodies against pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)
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End point description:

A vaccine responder to PT/FHA/PRN was defined as a subject with the appearance of antibodies against PT/FHA/PRN in subjects who were initially seronegative for anti-PT/FHA/PRN antibodies (i.e., subjects with anti-PT/FHA/PRN antibody concentrations < 5 EL.U/mL), or at least the maintenance of pre-vaccination antibody concentrations in subjects who were initially seropositive (i.e., subjects with anti-PT/FHA/PRN antibody concentrations ≥ 5 EL.U/mL).

End point type	Secondary
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End point timeframe:

At Month 3 (M3), one month after Dose 3 of Infanrix™ hexa vaccine

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	221		
Units: Subjects				
Anti-PT (N=196;213)	194	207		
Anti-FHA (N=197;216)	192	213		
Anti-PRN (N=201;221)	185	211		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-rotavirus (anti-RV) Immunoglobulin A (IgA) antibody concentrations

End point title	Anti-rotavirus (anti-RV) Immunoglobulin A (IgA) antibody concentrations
End point description: The seropositivity cut-off for the assay was ≥ 20 U/mL.	
End point type	Secondary
End point timeframe: At Month 3 (M3), 2 months after Dose 2 of Rotarix™ vaccine.	

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	210		
Units: U/mL				
geometric mean (confidence interval 95%)				
Anti-RV IgA	162.7 (126.6 to 208.9)	187.9 (149.4 to 236.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-RV IgA antibody concentrations ≥ 20 U/mL

End point title	Number of subjects with anti-RV IgA antibody concentrations ≥ 20 U/mL
End point description: The seropositivity cut-off for the assay was ≥ 20 U/mL.	
End point type	Secondary
End point timeframe: At Month 3 (M3), 2 months after Dose 2 of Rotarix™ vaccine.	

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	210		
Units: Subjects				
Anti-RV IgA	156	179		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroconverted subjects as regards anti-RV IgA antibodies

End point title	Number of seroconverted subjects as regards anti-RV IgA antibodies
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End point description:

A seroconverted subject as regards anti-RV IgA antibodies was defined as a subject with the appearance of anti-RV IgA antibody concentrations ≥ 20 U/mL in subjects initially seronegative for anti-RV IgA antibodies (i.e. subjects with anti-RV IgA antibodies concentrations < 20 U/mL).

End point type	Secondary
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End point timeframe:

At Month 3 (M3), 2 months after Dose 2 of Rotarix™ vaccine.

End point values	10Pn-PD-DiT/ Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	193		
Units: Subjects				
Anti-R IgA	142	163		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited symptoms: 4-day follow-up periods after vaccination (Days 0- 3), across doses; Unsolicited AEs: 31-day follow-up periods after vaccination (Days 0-30), across doses; SAEs: Entire study period (Months 0-8).

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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Reporting groups

Reporting group title	10Pn-PD-DiT/Paracetamol Group
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Reporting group description:

Subjects were vaccinated with a 3-dose course administered at 3, 4 and 5 months of age (Study Months 0, 1 and 2) of GSK Biologicals' pneumococcal conjugate vaccine GSK1024850A (also referred to as 10Pn-PD-DiT or 10Pn vaccine) co-administered with Infanrix™ hexa (also referred to as DTPa-HBV-IPV/Hib) and with prophylactic antipyretic treatment (rectal paracetamol or acetaminophen) under the form of suppositories of CALPOL 80 or 125, depending on the subjects' body weight . In addition, subjects also received 2 doses of HRV vaccine (Rotarix™) and of at 3 and 4 months of age (Study Months 0 and 1).

Reporting group title	10Pn-PD-DiT Group
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Reporting group description:

Subjects were vaccinated with a 3-dose course administered at 3, 4 and 5 months of age (Study Months 0, 1 and 2) of GSK Biologicals' pneumococcal conjugate vaccine GSK1024850A (also referred to as 10Pn-PD-DiT or 10Pn vaccine) co-administered with Infanrix™ hexa (also referred to as DTPa-HBV-IPV/Hib). Subjects also received 2 doses of HRV vaccine (Rotarix™) without prophylactic antipyretic treatment at 3 and 4 months of age (Study Months 0 and 1).

Serious adverse events	10Pn-PD-DiT/Paracetamol Group	10Pn-PD-DiT Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 226 (8.85%)	17 / 233 (7.30%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	2 / 226 (0.88%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental exposure			

subjects affected / exposed	0 / 226 (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	
Concussion			
subjects affected / exposed	0 / 226 (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	
Contusion			
subjects affected / exposed	0 / 226 (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	
Thermal burn			
subjects affected / exposed	0 / 226 (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	
Wound			
subjects affected / exposed	1 / 226 (0.44%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 226 (0.44%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 226 (0.44%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Milk allergy			
subjects affected / exposed	1 / 226 (0.44%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	0 / 226 (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 haemorrhage			
subjects affected / exposed	0 / 226 (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, thoracic and mediastinal disorders			
Bronchitis chronic			
subjects affected / exposed	1 / 226 (0.44%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychomotor retardation			
subjects affected / exposed	1 / 226 (0.44%)	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			
Bronchitis			
subjects affected / exposed	4 / 226 (1.77%)	4 / 233 (1.72%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exanthema subitum			
subjects affected / exposed	1 / 226 (0.44%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 226 (0.44%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			

subjects affected / exposed	1 / 226 (0.44%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 226 (0.44%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	1 / 226 (0.44%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis viral			
subjects affected / exposed	1 / 226 (0.44%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 226 (0.44%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	1 / 226 (0.44%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 226 (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	
Tonsillitis			
subjects affected / exposed	1 / 226 (0.44%)	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 infection			

subjects affected / exposed	1 / 226 (0.44%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Weight gain poor			
subjects affected / exposed	1 / 226 (0.44%)	2 / 233 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 226 (0.44%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	10Pn-PD-DiT/Paracetamol Group	10Pn-PD-DiT Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	139 / 226 (61.50%)	166 / 233 (71.24%)	
General disorders and administration site conditions			
Pain			
alternative assessment type: Systematic			
subjects affected / exposed	69 / 226 (30.53%)	101 / 233 (43.35%)	
occurrences (all)	69	101	
Redness			
alternative assessment type: Systematic			
subjects affected / exposed	134 / 226 (59.29%)	143 / 233 (61.37%)	
occurrences (all)	134	143	
Swelling			
alternative assessment type: Systematic			
subjects affected / exposed	89 / 226 (39.38%)	102 / 233 (43.78%)	
occurrences (all)	89	102	
Diarrhea			
alternative assessment type: Systematic			

subjects affected / exposed	34 / 226 (15.04%)	31 / 233 (13.30%)	
occurrences (all)	34	31	
Drowsiness			
alternative assessment type: Systematic			
subjects affected / exposed	137 / 226 (60.62%)	155 / 233 (66.52%)	
occurrences (all)	137	155	
Fever (rectal temperature $\geq 38.0^{\circ}$ C)			
alternative assessment type: Systematic			
subjects affected / exposed	94 / 226 (41.59%)	154 / 233 (66.09%)	
occurrences (all)	94	154	
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	139 / 226 (61.50%)	166 / 233 (71.24%)	
occurrences (all)	139	166	
Loss of appetite			
alternative assessment type: Systematic			
subjects affected / exposed	49 / 226 (21.68%)	68 / 233 (29.18%)	
occurrences (all)	49	68	
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	30 / 226 (13.27%)	15 / 233 (6.44%)	
occurrences (all)	30	15	
Infections and infestations			
Bronchitis			
subjects affected / exposed	15 / 226 (6.64%)	20 / 233 (8.58%)	
occurrences (all)	15	20	
Nasopharyngitis			
subjects affected / exposed	15 / 226 (6.64%)	19 / 233 (8.15%)	
occurrences (all)	15	19	
Pharyngitis			
subjects affected / exposed	18 / 226 (7.96%)	16 / 233 (6.87%)	
occurrences (all)	18	16	
Rhinitis			

subjects affected / exposed	10 / 226 (4.42%)	14 / 233 (6.01%)	
occurrences (all)	10	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 July 2006	The protocol was amended on 20-July-2006 (Amendment 1). This Amendment 1 was written in response to comments given by the Czech Republic Ethics Committee (changes concerned the exclusion criteria and contra-indication sections). Furthermore, the post-licensure surveillance of Prevenar™ in the United States had shown a decrease and an increase in invasive pneumococcal disease caused by the cross-reactive vaccine serotypes 6A and 19A, respectively. Therefore it was of interest to document the immune responses (ELISA and OPA) to these cross-reactive vaccine serotypes.
23 November 2006	The protocol was amended on 23-November-2006 (Amendment 3). The Pneumococcal Otitis Efficacy Trial (POET) (GSK Biologicals' identifier 347414/010; Protocol & Results posting on GSK Clinical Trial Register: http://www.gsk-clinicalstudyregister.com/study/347414/010?study_ids=347414) using the experimental 11-valent PD-conjugate vaccine (11Pn-PD) demonstrated a statistically significant and clinically relevant protective effect of the 11Pn-PD vaccine on acute otitis media (AOM). To provide a basis for the AOM efficacy of the 10Pn-PD-DiT vaccine, an immunological comparison between the 10Pn-PD-DiT vaccine and the 11Pn-PD vaccine tested in the POET trial based on a non-inferiority approach using OPA geometric mean titers (GMT) ratios and a clinical limit of 2.5, was included in the protocol. Furthermore to avoid confusion regarding the total number of enrolled subjects and the number of subjects in the randomized OPA subset, clarifications were added to the immunological read-outs table and the study design.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported