Clinical trial results:
A phase III long-term follow-up study to assess immunological memory induced following primary and booster vaccination with GSK Biologicals' 10-valent pneumococcal conjugate vaccine (10Pn-PD-DiT), through evaluation of early antibody responses after an additional dose of 10Pn-PD-DiT at 40-48 months of age, to evaluate in the fourth year of life, the immunogenicity and safety of a 2-dose catch-up immunization course with the 10Pn-PD-DiT vaccine and the impact of pneumococcal vaccination on nasopharyngeal carriage.

Summary

EudraCT number	2008-008104-41
Trial protocol	CZ
Global end of trial date	29 July 2011

Results information

Result version number	v2
This version publication date	03 August 2016
First version publication date	02 August 2015
Version creation reason	• Correction of full data set Data (typos) were corrected in section/ endpoint.

Trial information

Trial identification

Sponsor protocol code	112801

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00950833
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000673-PIP01-09
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	19 August 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 September 2010
Global end of trial reached?	Yes
Global end of trial date	29 July 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the immunological memory induced following primary vaccination in study 10PN-PD-DIT-010 (107017) and booster vaccination in study 10PN-PD-DIT-014 (107137) with the 10Pn-PD-DiT vaccine, through evaluation of early antibody responses after an additional dose of 10Pn-PD-DiT at 40-48 months of age, compared to the unprimed group.
Criteria for immune memory:
The immune memory will be demonstrated if the lower limit of the 95% CI around the GMC ratios (pooled primed groups over unprimed group) is higher than 1 for all 10 vaccine serotypes.

Protection of trial subjects:

The subjects were observed closely for at least 30 minutes following the administration of vaccine(s), with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 August 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	Czech Republic: 466
Worldwide total number of subjects	466
EEA total number of subjects	466

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)	0
Children (2-11 years)	466
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.

Pre-assignment period milestones

Number of subjects started	466
Number of subjects completed	443

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 18
Reason: Number of subjects	Vaccine not administered: 5

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 three primary vaccination doses of Synflorix™ with prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and a booster dose of Synflorix™ vaccine, co-administered with Infanrix™ hexa and with prophylactic antipyretic treatment (rectal paracetamol) in study 10PN-PD-DIT-014 BST-010 (107137) and received in this study an additional dose of Synflorix™ vaccine at Month 9 (40-48 months of age).

Arm type	Experimental
Investigational medicinal product name	10-valent pneumococcal 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:

One dose administered intramuscularly in the deltoid muscle at Month 9 (40-48 months of age).

Arm title	10Pn-PD-DiT Group

Arm description:

Subjects were vaccinated with three primary vaccination doses of Synflorix™ vaccine without prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), with a booster dose of Synflorix™ vaccine, co-administered with Infanrix™ hexa without prophylactic antipyretic treatment (rectal paracetamol) in study 10PN-PD-DIT-014 BST-010 (107137) and an additional dose of Synflorix™ vaccine in this study at Month 9 (40-48 months of age).

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:

One dose administered intramuscularly in the deltoid region at Month 9 (40-48 months of age).

Arm title	Unprimed Group

Arm description:

Subjects were not previously vaccinated with any pneumococcal vaccine. Age-matched subjects from the unprimed group of the 10PN-PD-DIT-014 study (107137), not previously vaccinated with any pneumococcal vaccine, received two doses of Synflorix™ vaccine: one at Month 9 (40-48 months of age) and one at Month 11 (42-50 months of age).

Arm type	Active comparator
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:

Two doses administered intramuscularly in the deltoid muscle at Month 9 (40-48 months of age) and Month 11 (42-50 months of age).

Number of subjects in period 1[1]	10Pn-PD-DiT/Paracetamol Group	10Pn-PD-DiT Group	Unprimed Group
Started	112	108	223
Completed	112	108	223

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 5 of the enrolled subjects were allocated subject numbers but did not receive vaccination, hence they were excluded from the study. Also, 18 subjects dropped out of the study prior to start and were eliminated from the Total vaccinated cohort.

Baseline characteristics

Reporting groups	
Reporting group title	10Pn-PD-DiT/Paracetamol Group

Reporting group description:

Subjects were vaccinated with three primary vaccination doses of Synflorix™ with prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and a booster dose of Synflorix™ vaccine, co-administered with Infanrix™ hexa and with prophylactic antipyretic treatment (rectal paracetamol) in study 10PN-PD-DIT-014 BST-010 (107137) and received in this study an additional dose of Synflorix™ vaccine at Month 9 (40-48 months of age).

Reporting group title	10Pn-PD-DiT Group

Reporting group description:

Subjects were vaccinated with three primary vaccination doses of Synflorix™ vaccine without prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), with a booster dose of Synflorix™ vaccine, co-administered with Infanrix™ hexa without prophylactic antipyretic treatment (rectal paracetamol) in study 10PN-PD-DIT-014 BST-010 (107137) and an additional dose of Synflorix™ vaccine in this study at Month 9 (40-48 months of age).

Reporting group title	Unprimed Group

Reporting group description:

Subjects were not previously vaccinated with any pneumococcal vaccine. Age-matched subjects from the unprimed group of the 10PN-PD-DIT-014 study (107137), not previously vaccinated with any pneumococcal vaccine, received two doses of Synflorix™ vaccine: one at Month 9 (40-48 months of age) and one at Month 11 (42-50 months of age).

Reporting group values	10Pn-PD-DiT/Paracetamol Group	10Pn-PD-DiT Group	Unprimed Group
Number of subjects	112	108	223
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: months			
arithmetic mean	39.2	39.1	37.7
standard deviation	± 1.53	± 1.54	± 3.36
Gender categorical Units: Subjects			
Female	60	48	99
Male	52	60	124

Reporting group values	Total		
Number of subjects	443		

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: months			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	207		
Male	236		

Subject analysis sets

Subject analysis set title	Pooled primed Group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

10PN-PD-DIT/Paracetamol and 10PN-PD-DIT Groups were pooled into Primed Group.

Reporting group values	Pooled primed Group		
Number of subjects	220		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: months			
arithmetic mean	39.15		
standard deviation	± 1.53		
Gender categorical Units: Subjects			
Female	108		
Male	112		

End points

End points reporting groups

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

Reporting group description:

Subjects were vaccinated with three primary vaccination doses of Synflorix™ with prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and a booster dose of Synflorix™ vaccine, co-administered with Infanrix™ hexa and with prophylactic antipyretic treatment (rectal paracetamol) in study 10PN-PD-DIT-014 BST-010 (107137) and received in this study an additional dose of Synflorix™ vaccine at Month 9 (40-48 months of age).

Reporting group title	10Pn-PD-DiT Group

Reporting group description:

Subjects were vaccinated with three primary vaccination doses of Synflorix™ vaccine without prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), with a booster dose of Synflorix™ vaccine, co-administered with Infanrix™ hexa without prophylactic antipyretic treatment (rectal paracetamol) in study 10PN-PD-DIT-014 BST-010 (107137) and an additional dose of Synflorix™ vaccine in this study at Month 9 (40-48 months of age).

Reporting group title	Unprimed Group

Reporting group description:

Subjects were not previously vaccinated with any pneumococcal vaccine. Age-matched subjects from the unprimed group of the 10PN-PD-DIT-014 study (107137), not previously vaccinated with any pneumococcal vaccine, received two doses of Synflorix™ vaccine: one at Month 9 (40-48 months of age) and one at Month 11 (42-50 months of age).

Subject analysis set title	Pooled primed Group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

10PN-PD-DIT/Paracetamol and 10PN-PD-DIT Groups were pooled into Primed Group.

Primary: 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).[1]

End point description:

Seropositivity status, defined as anti-pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody concentrations ≥ 0.05 microgram per millilitre (µg/mL).

End point type	Primary

End point timeframe:

At 7-10 days after the single/first dose of 10-valent pneumococcal conjugate vaccine.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the pooled primed group that included the subjects in the remaining baseline groups.

End point values	Unprimed Group	Pooled primed Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	204	215		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-1 (N=204;215)	1.24 (1.07 to 1.42)	7.63 (6.57 to 8.86)		
Anti-4 (N=204;215)	4.52 (3.96 to 5.17)	12.95 (11.37 to 14.75)		

Anti-5 (N=202;215)	0.72 (0.63 to 0.84)	9.76 (8.44 to 11.29)		
Anti-6B (N=203;215)	0.27 (0.22 to 0.33)	7.67 (6.7 to 8.78)		
Anti-7F (N=204;215)	1.37 (1.19 to 1.58)	6.51 (5.69 to 7.46)		
Anti-9V (N=202;213)	0.69 (0.58 to 0.83)	9.75 (8.46 to 11.24)		
Anti-14 (N=204;214)	1.01 (0.8 to 1.27)	23.07 (20.03 to 26.57)		
Anti-18C (N=204;214)	3.25 (2.71 to 3.9)	32.54 (28.15 to 37.61)		
Anti-19F (N=204;214)	4.31 (3.59 to 5.17)	39.84 (34.12 to 46.51)		
Anti-23F (N=204;215)	0.25 (0.2 to 0.32)	9.24 (7.86 to 10.86)		

Statistical analyses

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

Statistical analysis description:

To demonstrate the immunological memory induced following primary vaccination in study 10PN-PD-DIT-010 (107017) and booster vaccination in study 10PN-PD-DIT-014 (107137) with the 10Pn-PD-DiT vaccine, through evaluation of early antibody responses after an additional dose of 10Pn-PD-DiT vaccine at 40-48 months of age, compared to the Unprimed Group.

Comparison groups	Unprimed Group v Pooled primed Group
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	GMC ratio
Point estimate	6.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.03
upper limit	7.58

Notes:

[2] - The immune memory would be demonstrated if the lower limit of the 95% confidence interval (CI) around the geometric mean concentration (GMC) ratios (Pooled Primed Group over Unprimed Group) was higher than 1 for all 10 vaccine serotypes.

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

Statistical analysis description:

To demonstrate the immunological memory induced following primary vaccination in study 10PN-PD-DIT-010 (107017) and booster vaccination in study 10PN-PD-DIT-014 (107137) with the 10Pn-PD-DiT vaccine, through evaluation of early antibody responses after an additional dose of 10Pn-PD-DiT vaccine at 40-48 months of age, compared to the Unprimed Group.

Comparison groups	Unprimed Group v Pooled primed Group
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	GMC ratio
Point estimate	2.86

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.38
upper limit	3.45

Notes:

[3] - The immune memory would be demonstrated if the lower limit of the 95% confidence interval (CI) around the geometric mean concentration (GMC) ratios (Pooled Primed Group over Unprimed Group) was higher than 1 for all 10 vaccine serotypes.

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

Statistical analysis description:

To demonstrate the immunological memory induced following primary vaccination in study 10PN-PD-DIT-010 (107017) and booster vaccination in study 10PN-PD-DIT-014 (107137) with the 10Pn-PD-DiT vaccine, through evaluation of early antibody responses after an additional dose of 10Pn-PD-DiT vaccine at 40-48 months of age, compared to the Unprimed Group.

Comparison groups	Unprimed Group v Pooled primed Group
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	GMC ratio
Point estimate	13.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.96
upper limit	16.55

Notes:

[4] - The immune memory would be demonstrated if the lower limit of the 95% confidence interval (CI) around the geometric mean concentration (GMC) ratios (Pooled Primed Group over Unprimed Group) was higher than 1 for all 10 vaccine serotypes.

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

Statistical analysis description:

To demonstrate the immunological memory induced following primary vaccination in study 10PN-PD-DIT-010 (107017) and booster vaccination in study 10PN-PD-DIT-014 (107137) with the 10Pn-PD-DiT vaccine, through evaluation of early antibody responses after an additional dose of 10Pn-PD-DiT vaccine at 40-48 months of age, compared to the Unprimed Group.

Comparison groups	Unprimed Group v Pooled primed Group
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	GMC ratio
Point estimate	28.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.54
upper limit	36.81

Notes:

[5] - The immune memory would be demonstrated if the lower limit of the 95% confidence interval (CI) around the geometric mean concentration (GMC) ratios (Pooled Primed Group over Unprimed Group) was higher than 1 for all 10 vaccine serotypes.

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

Statistical analysis description:

To demonstrate the immunological memory induced following primary vaccination in study 10PN-PD-DIT-010 (107017) and booster vaccination in study 10PN-PD-DIT-014 (107137) with the 10Pn-PD-DiT vaccine, through evaluation of early antibody responses after an additional dose of 10Pn-PD-DiT vaccine at 40-48 months of age, compared to the Unprimed Group.

Comparison groups	Unprimed Group v Pooled primed Group
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	GMC ratio
Point estimate	4.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.9
upper limit	5.78

Notes:

[6] - The immune memory would be demonstrated if the lower limit of the 95% confidence interval (CI) around the geometric mean concentration (GMC) ratios (Pooled Primed Group over Unprimed Group) was higher than 1 for all 10 vaccine serotypes.

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

Statistical analysis description:

To demonstrate the immunological memory induced following primary vaccination in study 10PN-PD-DIT-010 (107017) and booster vaccination in study 10PN-PD-DIT-014 (107137) with the 10Pn-PD-DiT vaccine, through evaluation of early antibody responses after an additional dose of 10Pn-PD-DiT vaccine at 40-48 months of age, compared to the Unprimed Group.

Comparison groups	Unprimed Group v Pooled primed Group
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	GMC ratio
Point estimate	14.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.21
upper limit	17.75

Notes:

[7] - The immune memory would be demonstrated if the lower limit of the 95% confidence interval (CI) around the geometric mean concentration (GMC) ratios (Pooled Primed Group over Unprimed Group) was higher than 1 for all 10 vaccine serotypes.

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

Statistical analysis description:

To demonstrate the immunological memory induced following primary vaccination in study 10PN-PD-DIT-010 (107017) and booster vaccination in study 10PN-PD-DIT-014 (107137) with the 10Pn-PD-DiT vaccine, through evaluation of early antibody responses after an additional dose of 10Pn-PD-DiT vaccine at 40-48 months of age, compared to the Unprimed Group.

Comparison groups	Unprimed Group v Pooled primed Group

Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	GMC ratio
Point estimate	22.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.51
upper limit	30

Notes:

[8] - The immune memory would be demonstrated if the lower limit of the 95% confidence interval (CI) around the geometric mean concentration (GMC) ratios (Pooled Primed Group over Unprimed Group) was higher than 1 for all 10 vaccine serotypes.

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

Statistical analysis description:

To demonstrate the immunological memory induced following primary vaccination in study 10PN-PD-DIT-010 (107017) and booster vaccination in study 10PN-PD-DIT-014 (107137) with the 10Pn-PD-DiT vaccine, through evaluation of early antibody responses after an additional dose of 10Pn-PD-DiT vaccine at 40-48 months of age, compared to the Unprimed Group.

Comparison groups	Unprimed Group v Pooled primed Group
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Parameter estimate	GMC ratio
Point estimate	10.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.95
upper limit	12.61

Notes:

[9] - The immune memory would be demonstrated if the lower limit of the 95% confidence interval (CI) around the geometric mean concentration (GMC) ratios (Pooled Primed Group over Unprimed Group) was higher than 1 for all 10 vaccine serotypes.

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

Statistical analysis description:

To demonstrate the immunological memory induced following primary vaccination in study 10PN-PD-DIT-010 (107017) and booster vaccination in study 10PN-PD-DIT-014 (107137) with the 10Pn-PD-DiT vaccine, through evaluation of early antibody responses after an additional dose of 10Pn-PD-DiT vaccine at 40-48 months of age, compared to the Unprimed Group.

Comparison groups	Unprimed Group v Pooled primed Group
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	GMC ratio
Point estimate	9.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.29
upper limit	11.74

Notes:

[10] - The immune memory would be demonstrated if the lower limit of the 95% confidence interval (CI) around the geometric mean concentration (GMC) ratios (Pooled Primed Group over Unprimed Group) was higher than 1 for all 10 vaccine serotypes.

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

Statistical analysis description:

To demonstrate the immunological memory induced following primary vaccination in study 10PN-PD-DIT-010 (107017) and booster vaccination in study 10PN-PD-DIT-014 (107137) with the 10Pn-PD-DiT vaccine, through evaluation of early antibody responses after an additional dose of 10Pn-PD-DiT vaccine at 40-48 months of age, compared to the Unprimed Group.

Comparison groups	Unprimed Group v Pooled primed Group
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
Parameter estimate	GMC ratio
Point estimate	36.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.59
upper limit	48.34

Notes:

[11] - The immune memory would be demonstrated if the lower limit of the 95% confidence interval (CI) around the geometric mean concentration (GMC) ratios (Pooled Primed Group over Unprimed Group) was higher than 1 for all 10 vaccine serotypes.

Secondary: Anti-1, anti-4, anti-5, anti-6B, anti-7F, anti-9V, anti-14, anti-18C, anti 19F and anti 23-F antibody concentrations.

End point title	Anti-1, anti-4, anti-5, anti-6B, anti-7F, anti-9V, anti-14, anti-18C, anti 19F and anti 23-F antibody concentrations.[12]

End point description:

Seropositivity status, defined as anti-pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody concentrations ≥ 0.05 microgram per millilitre (µg/mL).

End point type	Secondary

End point timeframe:

Prior to the single/first dose of 10-valent pneumococcal conjugate vaccine.

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the pooled primed group that included the subjects in the remaining baseline groups.

End point values	Unprimed Group	Pooled primed Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	209	215		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-1 (N=208;215)	0.09 (0.08 to 0.11)	0.27 (0.23 to 0.33)		
Anti-4 (N=206;213)	0.05 (0.04 to 0.06)	0.2 (0.17 to 0.23)		
Anti-5 (N=208;212)	0.1 (0.09 to 0.11)	0.41 (0.36 to 0.47)		

Anti-6B (N=202;212)	0.1 (0.08 to 0.12)	0.8 (0.61 to 1.05)		
Anti-7F (N=209;215)	0.06 (0.05 to 0.07)	0.48 (0.41 to 0.56)		
Anti-9V (N=203;211)	0.07 (0.06 to 0.09)	0.5 (0.41 to 0.61)		
Anti-14 (N=203;213)	0.28 (0.22 to 0.36)	1.21 (0.97 to 1.5)		
Anti-18C (N=205;215)	0.09 (0.07 to 0.11)	0.65 (0.54 to 0.79)		
Anti-19F (N=208;215)	0.44 (0.32 to 0.59)	2.35 (1.75 to 3.15)		
Anti-23F (N=207;215)	0.08 (0.07 to 0.1)	0.96 (0.72 to 1.29)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Opsonophagocytic activity (OPA) titres against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.[13]

End point description:

Seropositivity status, defined as Opsonophagocytic activity against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F ≥ 8.

End point type	Secondary

End point timeframe:

Prior to (PRE) and 7-10 days after (POST) the single/first dose of 10-valent pneumococcal conjugate vaccine.

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the pooled primed group that included the subjects in the remaining baseline groups.

End point values	Unprimed Group	Pooled primed Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	191	199		
Units: Titres				
geometric mean (confidence interval 95%)				
Opsono-1, PRE (N=191;199)	5.4 (4.7 to 6.2)	10.2 (8 to 12.9)		
Opsono-1, POST (N=182;194)	632 (524.4 to 761.7)	3106.5 (2670 to 3614.5)		
Opsono-4, PRE (N=174;189)	9.1 (6.8 to 12.1)	18.1 (13.1 to 24.9)		
Opsono-4, POST (N=187;195)	13109.9 (11080.6 to 15510.7)	27273.3 (22682.9 to 32792.6)		
Opsono-5, PRE (N=185;199)	4 (4 to 4.1)	8.9 (7.6 to 10.5)		
Opsono-5, POST (N=182;194)	145.8 (111.7 to 190.3)	1020 (874 to 1190.2)		

Opsono-6B, PRE (N=173;183)	46.7 (29.8 to 73.3)	163.5 (108.5 to 246.4)		
Opsono-6B, POST (N=184;192)	1472.2 (1053.2 to 2057.8)	5789.5 (4637.3 to 7227.9)		
Opsono-7F, PRE (N=167;187)	973.4 (798.5 to 1186.6)	1112.3 (951.4 to 1300.4)		
Opsono-7F, POST (N=186;191)	13647.4 (11801.9 to 15781.3)	19988.9 (16834.5 to 23734.2)		
Opsono-9V, PRE (N=156;171)	268.2 (192.2 to 374.3)	481.8 (394.6 to 588.1)		
Opsono-9V, POST (N=186;194)	14668.8 (12476.1 to 17247)	17952.5 (14699.2 to 21925.7)		
Opsono-14, PRE (N=166;184)	145.3 (97.5 to 216.6)	267.6 (196.9 to 363.8)		
Opsono-14, POST (N=187;195)	4454.3 (3921.1 to 5059.9)	16256.8 (13573 to 19471.4)		
Opsono-18C, PRE (N=169;186)	5.7 (4.7 to 7)	14.2 (10.6 to 19.2)		
Opsono-18C, POST (N=180;188)	9092.2 (7381.2 to 11199.9)	7413.8 (6072.3 to 9051.6)		
Opsono-19F, PRE (N=186;192)	12.9 (9.6 to 17.2)	79.5 (55.4 to 113.9)		
Opsono-19F, POST (N=190;192)	902.5 (659.2 to 1235.6)	6271.1 (4814.8 to 8168)		
Opsono-23F, PRE (N=166;189)	220.6 (132 to 368.7)	462.7 (292.9 to 730.9)		
Opsono-23F, POST (N=189;197)	5776.5 (4686.8 to 7119.5)	15613.5 (12386.9 to 19680.6)		

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).[14]

End point description:

Seropositivity status, defined as anti-pneumococcal cross-reactive serotype 6A and 19A antibody concentrations ≥ 0.05 microgram per millilitre (µg/mL).

End point type	Secondary

End point timeframe:

Prior to and 7-10 days after the single/first dose of 10-valent pneumococcal conjugate vaccine.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the pooled primed group that included the subjects in the remaining baseline groups.

End point values	Unprimed Group	Pooled primed Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	207	215		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-6A, PRE (N=207;214)	0.11 (0.09 to 0.13)	0.39 (0.3 to 0.5)		
Anti-6A, PI (N=203;215)	0.2 (0.17 to 0.25)	2.4 (2.01 to 2.85)		
Anti-19A, PRE (N=207;215)	0.22 (0.18 to 0.28)	0.52 (0.41 to 0.67)		
Anti-19A, PI (N=203;214)	0.65 (0.52 to 0.82)	6.75 (5.41 to 8.41)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Opsonophagocytic activity (OPA) titres against pneumococcal cross-reactive serotypes 6A and 19A.[15]

End point description:

Seropositivity status, defined as Opsonophagocytic activity against pneumococcal cross-reactive serotypes 6A and 19A ≥ 8.

End point type	Secondary

End point timeframe:

Prior to and 7-10 days after the single/first dose of 10-valent pneumococcal conjugate vaccine.

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the pooled primed group that included the subjects in the remaining baseline groups.

End point values	Unprimed Group	Pooled primed Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	183	191		
Units: Titres				
geometric mean (confidence interval 95%)				
Opsono-6A, PRE (N=167;178)	49 (32.4 to 74)	95.2 (65.3 to 138.7)		
Opsono-6A, PI (N=180;191)	863.3 (619.3 to 1203.4)	2408.4 (1815.7 to 3194.5)		
Opsono-19A, PRE (N=183;190)	10.3 (7.9 to 13.4)	15.9 (11.7 to 21.6)		
Opsono-19A, PI (N=175;191)	880.5 (622.7 to 1245)	2104.9 (1560.9 to 2838.7)		

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).[16]

End point description:

Seropositivity status, defined as anti-PD antibody concentrations ≥ 100 ELISA units per millilitre (EL.U/mL).

End point type	Secondary

End point timeframe:

Prior to and 7-10 days after the single/first dose of 10-valent pneumococcal conjugate vaccine.

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the pooled primed group that included the subjects in the remaining baseline groups.

End point values	Unprimed Group	Pooled primed Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	204	215		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-PD, PRE (N=198;210)	105.6 (93.8 to 119)	464.2 (401.6 to 536.5)		
Anti-PD, PI (N=204;215)	374.3 (315.1 to 444.6)	2673.7 (2359.1 to 3030.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Memory B-cell detection for serotype specific polysaccharides (PS) (polysaccharides 1, 5, 6B, 18C, 19F, 23F and C).

End point title	Memory B-cell detection for serotype specific polysaccharides (PS) (polysaccharides 1, 5, 6B, 18C, 19F, 23F and C).

End point description:

Descriptive statistics about subjects with B-cell detection for serotype specific polysaccharides were tabulated for a subset of subjects from each group. The results are expressed as the frequencies of antigen-specific memory B-cells within the total memory B-cell population.

End point type	Secondary

End point timeframe:

Prior to (PRE) and 7-10 days (POST) after the single/first dose of 10-valent pneumococcal conjugate

vaccine.

End point values	10Pn-PD-DiT/Paracetamol Group	10Pn-PD-DiT Group	Unprimed Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	107	210	
Units: Memory B-cells				
arithmetic mean (standard deviation)				
1 PS, PRE (N=23;22;47)	288.6 (± 352.5)	269.5 (± 432.2)	254.8 (± 368.4)	
5 PS, PRE (N=26;27;42)	139.4 (± 214.7)	141.9 (± 232.4)	81.5 (± 109.2)	
6B PS, PRE (N=20;22;44)	372 (± 545.5)	327.2 (± 554.4)	639.9 (± 846.5)	
18C PS, PRE (N=26;26;42)	537.7 (± 641.8)	530.9 (± 693.8)	135.2 (± 200.6)	
19F PS, PRE (N=20;22;44)	169.7 (± 415.3)	149.1 (± 194.4)	164.5 (± 343.4)	
23F PS, PRE (N=23;22;45)	112.6 (± 176.1)	285 (± 484.3)	185.6 (± 270.1)	
C-PS, PRE (N=70;71;133)	475.9 (± 682.3)	462.5 (± 704.5)	469.9 (± 639.2)	
1 PS, POST (N=23;23;43)	1488.8 (± 1584.2)	1017.4 (± 1309.9)	755.9 (± 1017.4)	
5 PS, POST (N=28;23;37)	233.5 (± 235.7)	406.6 (± 447.8)	152.6 (± 231)	
6B PS, POST (N=16;24;42)	629.1 (± 773.2)	1265.8 (± 1738.6)	526 (± 648.6)	
18C PS, POST (N=28;23;36)	3839 (± 5960.5)	8308.4 (± 7166.9)	2053.8 (± 2122.2)	
19F PS, POST (N=16;23;42)	1056.7 (± 1334)	1092.4 (± 1724.3)	708.2 (± 1609.4)	
23F PS, POST (N=23;23;43)	579.8 (± 632.5)	1123.7 (± 2095.4)	327.9 (± 470.5)	
C-PS, POST (N=67;70;123)	679.2 (± 885.8)	915.5 (± 1191.3)	762.6 (± 1039.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-1, anti-4, anti-5, anti-6B, anti-7F, anti-9V, anti-14, anti-18C, anti 19F and anti 23F antibody concentrations.

End point title	Anti-1, anti-4, anti-5, anti-6B, anti-7F, anti-9V, anti-14, anti-18C, anti 19F and anti 23F antibody concentrations.[17]

End point description:

Seropositivity status, defined as anti-pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody concentrations ≥ 0.05 microgram per millilitre (µg/mL).

End point type	Secondary

End point timeframe:

1 month after vaccination with the second dose of 10-valent pneumococcal conjugate vaccine (Month 12).

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was based on the unprimed group only.

End point values	Unprimed Group			
Subject group type	Reporting group			
Number of subjects analysed	209			
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-1 (N=209)	2.33 (2.13 to 2.54)			
Anti-4 (N=209)	6.26 (5.73 to 6.84)			
Anti-5 (N=209)	2.69 (2.44 to 2.96)			
Anti-6B (N=209)	0.84 (0.73 to 0.97)			
Anti-7F (N=208)	3.63 (3.33 to 3.95)			
Anti-9V (N=209)	1.73 (1.56 to 1.93)			
Anti-14 (N=209)	5.21 (4.6 to 5.89)			
Anti-18C (N=209)	13.59 (11.91 to 15.51)			
Anti-19F (N=209)	11.83 (10.35 to 13.52)			
Anti-23F (N=209)	0.99 (0.86 to 1.15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Opsono-1, opsono-4, opsono-5, opsono-6B, opsono-7F, opsono-9V, opsoo-14, opsono-18C, opsono-19F and opsono-23F titres.

End point title	Opsono-1, opsono-4, opsono-5, opsono-6B, opsono-7F, opsono-9V, opsoo-14, opsono-18C, opsono-19F and opsono-23F titres.[18]

End point description:

Seropositivity status, defined as Opsonophagocytic activity against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F ≥ 8.

End point type	Secondary

End point timeframe:

1 month after vaccination with the second dose of 10-valent pneumococcal conjugate vaccine (Month 12).

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was based on the unprimed group only.

End point values	Unprimed Group			
Subject group type	Reporting group			
Number of subjects analysed	201			
Units: Titres				
geometric mean (confidence interval 95%)				
Opsono-1 (N=201)	125.6 (105 to 150.1)			
Opsono-4 (N=200)	2451.2 (2203.6 to 2726.8)			
Opsono-5 (N=198)	57.2 (47.3 to 69.1)			
Opsono-6B (N=196)	1345 (1066.8 to 1695.7)			
Opsono-7F (N=198)	6527.2 (5836.5 to 7299.6)			
Opsono-9V (N=197)	6091.6 (5328.7 to 6963.8)			
Opsono-14 (N=197)	4544.9 (4030.2 to 5125.4)			
Opsono-18C (N=196)	3827.5 (3367.5 to 4350.4)			
Opsono-19F (N=201)	1251 (1045.6 to 1496.8)			
Opsono-23F (N=198)	4629.1 (3890.6 to 5507.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-6A and anti-19A antibody concentrations.

End point title	Anti-6A and anti-19A antibody concentrations.[19]

End point description:

Seropositivity status, defined as anti-pneumococcal cross-reactive serotype 6A and 19A antibody concentrations ≥ 0.05 microgram per millilitre (µg/mL).

End point type	Secondary

End point timeframe:

1 month after vaccination with the second dose of 10-valent pneumococcal conjugate vaccine (Month 12).

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the unprimed group only.

End point values	Unprimed Group			
Subject group type	Reporting group			
Number of subjects analysed	209			
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-6A	0.51 (0.43 to 0.6)			
Anti-19A	1.99 (1.68 to 2.36)			

Statistical analyses

No statistical analyses for this end point

Secondary: Opsono-6A and opsono-19A titres.

End point title	Opsono-6A and opsono-19A titres.[20]

End point description:

Seropositivity status, defined as Opsonophagocytic activity against pneumococcal cross-reactive serotypes 6A and 19A ≥ 8.

End point type	Secondary

End point timeframe:

1 month after vaccination with the second dose of 10-valent pneumococcal conjugate vaccine (Month 12).

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the unprimed group only.

End point values	Unprimed Group			
Subject group type	Reporting group			
Number of subjects analysed	196			
Units: Titres				
geometric mean (confidence interval 95%)				
Opsono-6A (N=193)	918.6 (742.7 to 1136.1)			
Opsono-19A (N=196)	597.6 (467.2 to 764.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-PD antibody concentrations.

End point title	Anti-PD antibody concentrations.[21]

End point description:

Seropositivity status, defined as anti-PD antibody concentrations ≥ 100 ELISA units per millilitre (EL.U/mL).

End point type	Secondary

End point timeframe:

1 month after vaccination with the second dose of 10-valent pneumococcal conjugate vaccine (Month 12).

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the unprimed group only.

End point values	Unprimed Group			
Subject group type	Reporting group			
Number of subjects analysed	209			
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-PD	785.9 (695.7 to 887.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Rabbit complement-mediated Serum Bactericidal Activity titres against Neisseria meningitidis serogroup A (rSBA-MenA), rSBA-MenC, rSBA-MenW-135 and rSBA-MenY.

End point title	Rabbit complement-mediated Serum Bactericidal Activity titres against Neisseria meningitidis serogroup A (rSBA-MenA), rSBA-MenC, rSBA-MenW-135 and rSBA-MenY.[22]

End point description:

Seropositivity status, defined as anti-rSBA titres ≥ 8.

End point type	Secondary

End point timeframe:

25-36 months post-vaccination in previous 10PN-PD-DIT-014 (107137) study

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the unprimed group only.

End point values	Unprimed Group			
Subject group type	Reporting group			
Number of subjects analysed	83			
Units: Titres				
geometric mean (confidence interval 95%)				
rSBA-MenA (N=66)	325.5 (243.9 to 434.5)			

rSBA-MenC (N=80)	63.6 (41.2 to 98)			
rSBA-MenY (N=83)	372.2 (270 to 513)			
rSBA-MenW-135 (N=83)	247.6 (190.7 to 321.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reported with any and grade 3 solicited local symptoms in the primed groups.

End point title	Number of subjects reported with any and grade 3 solicited local symptoms in the primed groups.[23]

End point description:

Solicited local symptoms assessed include pain, redness and swelling. Grade 3 pain was defined as crying when limb was moved/spontaneously painful. Grade 3 swelling/redness was defined as swelling/redness larger than (>) 30 millimetres (mm). "Any" is defined as incidence of the specified symptom regardless of intensity.

End point type	Secondary

End point timeframe:

During the 4-day (Days 0-3) post-vaccination period.

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the primed baseline groups.

End point values	10Pn-PD-DiT/Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	108		
Units: Subjects				
Any pain	75	67		
Grade 3 pain	7	5		
Any redness	58	60		
Grade 3 redness	13	12		
Any swelling	43	41		
Grade 3 swelling	11	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reported with any and grade 3 solicited local symptoms in the unprimed group.

End point title	Number of subjects reported with any and grade 3 solicited local symptoms in the unprimed group.[24]

End point description:

Solicited local symptoms assessed include pain, redness and swelling. Grade 3 pain was defined as crying when limb was moved/spontaneously painful. Grade 3 swelling/redness was defined as swelling/redness larger than (>) 30 millimetres (mm). "Any" is defined as incidence of the specified symptom regardless of intensity.

End point type	Secondary

End point timeframe:

During the 4-day (Days 0-3) post-vaccination period.

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the unprimed group only.

End point values	Unprimed Group			
Subject group type	Reporting group			
Number of subjects analysed	223			
Units: Subjects				
Any pain, D1 (N=223)	150			
Grade 3 pain, D1 (N=223)	13			
Any redness, D1 (N=223)	102			
Grade 3 redness, D1 (N=223)	23			
Any swelling, D1 (N=223)	78			
Grade 3 swelling, D1 (N=223)	14			
Any pain, D2 (N=222)	121			
Grade 3 pain, D2 (N=222)	12			
Any redness, D2 (N=222)	93			
Grade 3 redness, D2 (N=222)	12			
Any swelling, D2 (N=222)	65			
Grade 3 swelling, D2 (N=222)	3			
Any pain, Across (N=223)	167			
Grade 3 pain, Across (N=223)	23			
Any redness, Across (N=223)	127			
Grade 3 redness, Across (N=223)	29			
Any swelling, Across (N=223)	101			
Grade 3 swelling, Across (N=223)	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reported with any, grade 3 and related solicited general symptoms in the primed groups.

End point title	Number of subjects reported with any, grade 3 and related solicited general symptoms in the primed groups.[25]

End point description:

Solicited general symptoms assessed include drowsiness, fever (defined as axilliary temperature ≥ 37.5 °C), irritability, and loss of appetite. Grade 3 drowsiness = drowsiness which prevented normal activities. Grade 3 fever was defined as fever (axilliary temperature) above (>) 39.5 degree Celsius (°C). Grade 3 irritability = crying that could not be comforted/preventing normal activity. Grade 3 loss of appetite = not eating at all. "Any" is defined as incidence of the specified symptom regardless of intensity or relationship to study vaccination.

End point type	Secondary

End point timeframe:

During the 4-day (Days 0-3) post-vaccination period.

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the primed baseline groups.

End point values	10Pn-PD-DiT/Paracetamol Group	10Pn-PD-DiT Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	108		
Units: Subjects				
Any drowsiness	41	34		
Related drowsiness	0	0		
Grade 3 drowsiness	26	26		
Any Irritability	33	26		
Related Irritability	1	0		
Grade 3 Irritability	21	16		
Any loss of appetite	23	15		
Related loss of appetite	1	1		
Grade 3 loss of appetite	13	10		
Any fever (Axillary/37.5°C)	12	8		
Grade 3 fever (Axillary/39.5°C)	0	1		
Related fever	10	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reported with any, grade 3 and related solicited general symptoms in the unprimed group.

End point title	Number of subjects reported with any, grade 3 and related solicited general symptoms in the unprimed group.[26]

End point description:

Solicited general symptoms assessed include drowsiness, fever (defined as axilliary temperature ≥ 37.5 °C), irritability, and loss of appetite. Grade 3 drowsiness = drowsiness which prevented normal activities. Grade 3 fever was defined as fever (axilliary temperature) above (>) 39.5 degree Celsius (°C). Grade 3 irritability = crying that could not be comforted/preventing normal activity. Grade 3 loss of appetite = not eating at all. "Any" is defined as incidence of the specified symptom regardless of intensity or relationship to study vaccination.

End point type	Secondary

End point timeframe:

During the 4-day (Days 0-3) post-vaccination period.

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the unprimed group only.

End point values	Unprimed Group			
Subject group type	Reporting group			
Number of subjects analysed	223			
Units: Subjects				
Any drowsiness, D1 (N=223)	79			
Grade 3 drowsiness, D1 (N=223)	1			
Related drowsiness, D1 (N=223)	56			
Any Irritability, D1 (N=223)	69			
Grade 3 Irritability, D1 (N=223)	2			
Related irritability, D1 (N=223)	49			
Any loss of appetite, D1 (N=223)	47			
Grade 3 loss of appetite, D1 (N=223)	5			
Related loss of appetite, D1 (N=223)	32			
Any fever (Axillary/37.5°C), D1 (N=223)	23			
Grade 3 fever (Axillary/39.5°C), D1 (N=223)	1			
Related fever, D1 (N=223)	15			
Any drowsiness, D2 (N=222)	60			
Grade 3 drowsiness, D2 (N=222)	1			
Related drowsiness, D2 (N=222)	43			
Any Irritability, D2 (N=222)	59			
Grade 3 Irritability, D2 (N=222)	1			
Related irritability, D2 (N=222)	44			
Any loss of appetite, D2 (N=222)	26			
Grade 3 loss of appetite, D2 (N=222)	1			
Related loss of appetite, D2 (N=222)	16			
Any fever (Axillary/37.5°C), D2 (N=222)	9			
Grade 3 fever (Axillary/39.5°C), D2 (N=222)	1			
Related fever, D2 (N=222)	5			
Any drowsiness, Across (N=223)	102			
Grade 3 drowsiness, Across (N=223)	2			
Related drowsiness, Across (N=223)	73			
Any Irritability, Across (N=223)	98			
Grade 3 Irritability, Across (N=223)	3			
Related irritability, Across (N=223)	74			
Any loss of appetite, Across (N=223)	61			
Grade 3 loss of appetite, Across (N=223)	6			
Related loss of appetite, Across (N=223)	42			
Any fever (Axillary/37.5°C), Across (N=223)	30			
Grade 3 fever (Axillary/39.5°C), Across (N=223)	2			
Related fever, Across (N=223)	19			

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).

End point description:

End point type	Secondary

End point timeframe:

Within 31 days after each vaccination.

End point values	10Pn-PD-DiT/Paracetamol Group	10Pn-PD-DiT Group	Unprimed Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	108	223	
Units: Subjects				
Any AE(s)	24	29	73	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reported with serious adverse events (SAEs).

End point title	Number of subjects reported with serious adverse events (SAEs).

End point description:

End point type	Secondary

End point timeframe:

During the entire study period.

End point values	10Pn-PD-DiT/Paracetamol Group	10Pn-PD-DiT Group	Unprimed Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	108	223	
Units: Subjects				
Any SAE(s)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of nasopharyngeal swabs with S.pneumoniae (vaccine serotypes).

End point title	Number of nasopharyngeal swabs with S.pneumoniae (vaccine serotypes).[27]

End point description:

End point type	Secondary

End point timeframe:

At 31-44 months of age and prior to the single/first dose of 10-valent pneumococcal conjugate vaccine at 40-48 months of age.

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the pooled primed group that included the subjects in the remaining baseline groups.

End point values	Unprimed Group	Pooled primed Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	210	216		
Units: Swabs				
31-44 months (N=210;216)	40	21		
40-48 months (N=208;212)	46	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of nasopharyngeal swabs with S.pneumoniae (cross-reactive serotypes).

End point title	Number of nasopharyngeal swabs with S.pneumoniae (cross-reactive serotypes).[28]

End point description:

End point type	Secondary

End point timeframe:

At 31-44 months of age and prior to the single/first dose of 10-valent pneumococcal conjugate vaccine at 40-48 months of age.

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the pooled primed group that included the subjects in the remaining baseline groups.

End point values	Unprimed Group	Pooled primed Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	210	216		
Units: Swabs				
31-44 months (N=210;216)	9	13		
40-48 months (N=208;212)	19	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of nasopharyngeal swabs with S.pneumoniae (non-vaccine and non-cross-reactive serotypes).

End point title	Number of nasopharyngeal swabs with S.pneumoniae (non-vaccine and non-cross-reactive serotypes).[29]

End point description:

End point type	Secondary

End point timeframe:

At 31-44 months of age and prior to the single/first dose of 10-valent pneumococcal conjugate vaccine at 40-48 months of age.

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the pooled primed group that included the subjects in the remaining baseline groups.

End point values	Unprimed Group	Pooled primed Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	210	216		
Units: Swabs				
31-44 months (N=210;216)	25	34		
40-48 months (N=208;212)	27	35		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of nasopharyngeal swabs with H. influenzae.

End point title	Number of nasopharyngeal swabs with H. influenzae.[30]

End point description:

End point type	Secondary

End point timeframe:

At 31-44 months of age and prior to the single/first dose of 10-valent pneumococcal conjugate vaccine at 40-48 months of age.

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the pooled primed group that included the subjects in the remaining baseline groups.

End point values	Unprimed Group	Pooled primed Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	210	216		
Units: Swabs				
31-44 months (N=210;216)	43	54		
40-48 months (N=208;212)	89	74		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with new acquisition of S. pneumoniae (vaccine serotypes) in nasopharyngeal swabs.

End point title	Number of subjects with new acquisition of S. pneumoniae (vaccine serotypes) in nasopharyngeal swabs.[31]

End point description:

End point type	Secondary

End point timeframe:

At 31-44 months of age and prior to the single/first dose of 10-valent pneumococcal conjugate vaccine at 40-48 months of age.

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the pooled primed group that included the subjects in the remaining baseline groups.

End point values	Unprimed Group	Pooled primed Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	210	216		
Units: Subjects				
31-44 months (N=210;216)	39	20		
40-48 months (N=208;212)	41	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with new acquisition of S. pneumoniae (cross-reactive serotypes) in nasopharyngeal swabs.

End point title	Number of subjects with new acquisition of S. pneumoniae

	(cross-reactive serotypes) in nasopharyngeal swabs.[32]

End point description:

End point type	Secondary

End point timeframe:

At 31-44 months of age and prior to the single/first dose of 10-valent pneumococcal conjugate vaccine at 40-48 months of age.

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the pooled primed group that included the subjects in the remaining baseline groups.

End point values	Unprimed Group	Pooled primed Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	210	216		
Units: Subjects				
31-44 months (N=210;216)	9	13		
40-48 months (N=208;212)	18	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with new acquisition of S. pneumoniae (non-vaccine and non-cross-reactive serotypes) in nasopharyngeal swabs.

End point title	Number of subjects with new acquisition of S. pneumoniae (non-vaccine and non-cross-reactive serotypes) in nasopharyngeal swabs.[33]

End point description:

End point type	Secondary

End point timeframe:

At 31-44 months of age and prior to the single/first dose of 10-valent pneumococcal conjugate vaccine at 40-48 months of age.

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the pooled primed group that included the subjects in the remaining baseline groups.

End point values	Unprimed Group	Pooled primed Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	210	216		
Units: Subjects				
31-44 months (N=210;216)	24	32		
40-48 months (N=208;212)	25	33		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with new acquisition of H. influenzae in nasopharyngeal swabs.

End point title	Number of subjects with new acquisition of H. influenzae in nasopharyngeal swabs.[34]

End point description:

End point type	Secondary

End point timeframe:

At 31-44 months of age and prior to the single/first dose of 10-valent pneumococcal conjugate vaccine at 40-48 months of age.

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This analysis was based on the pooled primed group that included the subjects in the remaining baseline groups.

End point values	Unprimed Group	Pooled primed Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	210	216		
Units: Subjects				
31-44 months (N=210;216)	35	49		
40-48 months (N=208;212)	70	50		

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: during the entire study period.

Adverse event reporting additional description:

Note: the occurrences (all) numbers were not calculated during the analysis: data entered are equal to the affected subject numbers.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

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

Reporting group description:

Subjects were vaccinated with three primary vaccination doses of Synflorix™ with prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and a booster dose of Synflorix™ vaccine, co-administered with Infanrix™ hexa and with prophylactic antipyretic treatment (rectal paracetamol) in study 10PN-PD-DIT-014 BST-010 (107137) and received in this study an additional dose of Synflorix™ vaccine at Month 9 (40-48 months of age).

Reporting group title	Unprimed Group

Reporting group description:

Subjects were not previously vaccinated with any pneumococcal vaccine. Age-matched subjects from the unprimed group of the 10PN-PD-DIT-014 study (107137), not previously vaccinated with any pneumococcal vaccine, received two doses of Synflorix™ vaccine: one at Month 9 (40-48 months of age) and one at Month 11 (42-50 months of age).

Reporting group title	10Pn-PD-DiT Group

Reporting group description:

Subjects were vaccinated with three primary vaccination doses of Synflorix™ vaccine without prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), with a booster dose of Synflorix™ vaccine, co-administered with Infanrix™ hexa without prophylactic antipyretic treatment (rectal paracetamol) in study 10PN-PD-DIT-014 BST-010 (107137) and an additional dose of Synflorix™ vaccine in this study at Month 9 (40-48 months of age).

Serious adverse events	10Pn-PD-DiT/ Paracetamol Group	Unprimed Group	10Pn-PD-DiT Group
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 112 (0.00%)	0 / 223 (0.00%)	0 / 108 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	10Pn-PD-DiT/ Paracetamol Group	Unprimed Group	10Pn-PD-DiT Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 112 (66.96%)	167 / 223 (74.89%)	67 / 108 (62.04%)
General disorders and administration site conditions			
Pain			
subjects affected / exposed	75 / 112 (66.96%)	167 / 223 (74.89%)	67 / 108 (62.04%)
occurrences (all)	75	167	67
Redness			
subjects affected / exposed	58 / 112 (51.79%)	127 / 223 (56.95%)	60 / 108 (55.56%)
occurrences (all)	58	127	60
Swelling			
subjects affected / exposed	43 / 112 (38.39%)	101 / 223 (45.29%)	41 / 108 (37.96%)
occurrences (all)	43	101	41
Drowsiness			
subjects affected / exposed	41 / 112 (36.61%)	102 / 223 (45.74%)	34 / 108 (31.48%)
occurrences (all)	41	102	34
Irritability			
subjects affected / exposed	33 / 112 (29.46%)	98 / 223 (43.95%)	26 / 108 (24.07%)
occurrences (all)	33	98	26
Loss of appetite			
subjects affected / exposed	23 / 112 (20.54%)	61 / 223 (27.35%)	15 / 108 (13.89%)
occurrences (all)	23	61	15
Fever/(Axillary ≥ 37.5°C)			
subjects affected / exposed	12 / 112 (10.71%)	30 / 223 (13.45%)	8 / 108 (7.41%)
occurrences (all)	12	30	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 March 2011	The primary objective of the current study is to demonstrate the immunological memory induced following primary vaccination in study 10PN-PD-DIT-010 (107017) and booster vaccination in study 10PN-PD-DIT-014 (107137) with the 10Pn-PD-DiT vaccine, through evaluation of early antibody responses after an additional dose of 10Pn-PD-DiT at 40-48 months of age. In addition, as secondary objective, the antibody persistence 25-36 months following vaccination with GSK Biologicals' MenACWYTT conjugate vaccine in study 10PN-PD-DIT-014 (107137) will be evaluated in terms of the percentage of subjects with N. meningitidis serogroup A, C, W-135 and Y titers ≥ 8 as measured by a serum bactericidal assay using rabbit complement (rSBA). In addition, to support the data obtained by rSBA testing, antibody concentrations against meningococcal polysaccharides are planned to be assessed by ELISA. However, the sponsor has decided not to perform the ELISA testing against meningococcal polysaccharides for this study for the following reasons: ● the World Health Organization (WHO) considers SBA the primary means of assessing immune response to meningococcal conjugate vaccines [WHO, 2006; WHO, 1999] ● circulating bactericidal antibodies are more critical for persistent protection against meningococcal disease than antibodies against meningococcal polysaccharides [CDC, 2011; WHO, 2006]. Although antibody concentrations will not be determined by ELISA, all subjects will be informed of their antibody titers measured by rSBA when statistical analyses have been completed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported