Clinical trial results:
A phase III, open, controlled, multi-centric study to evaluate the immunogenicity, safety and reactogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine when administered to children aged between 2 to17 years who are at an increased risk of pneumococcal infection and to an age-matched control group of healthy children aged 24 to 59 months.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2011-006013-34
Trial protocol	Outside EU/EEA PL
Global end of trial date	29 June 2015

Results information

Result version number	v1
This version publication date	04 February 2016
First version publication date	04 February 2016

Trial information

Trial identification

Sponsor protocol code	115884

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01746108
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000673-PIP01-09
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	Interim
Date of interim/final analysis	01 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 June 2015
Global end of trial reached?	Yes
Global end of trial date	29 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the immunogenicity of GSK Biologicals' 10Pn-PD-DiT vaccine when administered to at-risk children aged between 2-17 years, either as a 2-dose catch-up vaccination in unprimed children or as a single dose in primed children.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 June 2013
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	Poland: 15
Country: Number of subjects enrolled	Russian Federation: 37
Worldwide total number of subjects	52
EEA total number of subjects	15

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)	35
Adolescents (12-17 years)	17
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

No Healthy primed subjects, aged 2-4 years (age-matched to the 2-4 years primed subjects in At risk group - see enrolment process for healthy subjects, as described for HE-Un-2-4Y Group; who had to receive 1 dose of 10Pn-PD-DiT because vaccinated with at least 1 dose of a pneumococcal conjugate vaccine before enrolment) were enrolled in the study.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	52
Number of subjects completed	52

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	AR-Pr-2-17Y Group

Arm description:

Primed subjects aged between 24 months and 17 years, who were at an increased risk of pneumococcal infection*, receiving 1 dose of 10Pn-PD-DiT vaccine: Primed groups included subjects who have been previously vaccinated with at least one dose of a pneumococcal conjugate vaccine, i.e. either Synflorix (10Pn-PD-DiT), Prevenar or Prevenar13 or with plain polysaccharide pneumococcal vaccine more than 2 years (24 months) and less than 5 years (60 months) before enrolment.
*An at-risk subject was a subject with Congenital or acquired asplenia such as anatomic, surgical or functional asplenia, or Splenic dysfunction [some degree of functional asplenia, such as sickle-cell disease and other hemoglobinopathies, Hodgkin disease, rheumatologic diseases, systemic lupus erythematous (SLE), chronic gastrointestinal disorders, liver disease, infiltrative disorders, vascular disorder etc.] or Complement deficiencies, e.g.C1-C4, C5-C9, properdin factor H or factor D.

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

Dosage and administration details:

Subjects received 1 dose of Synflorix™ vaccine (Month 0). Pneumococcal vaccine dose was administered intramuscularly into the non-dominant deltoid for Children ≥ 12 months of age if the muscle size is adequate or in the thigh for the other subjects.

Arm title	AR-Un-2-17Y Group

Arm description:

Unprimed subjects aged between 24 months and 17 years, who were at an increased risk of pneumococcal infection*, receiving 2 doses of 10Pn-PD-DiT vaccine: Unprimed groups included subjects who have not been previously vaccinated with any pneumococcal vaccine, i.e. either plain polysaccharide pneumococcal vaccine, Synflorix (10Pn-PD-DiT), Prevenar or Prevenar13.
* An at-risk subject was a subject with Congenital or acquired asplenia such as anatomic, surgical or functional asplenia, or Splenic dysfunction [some degree of functional asplenia, such as sickle-cell disease and other hemoglobinopathies, Hodgkin disease, rheumatologic diseases, systemic lupus

erythematous (SLE), chronic gastrointestinal disorders, liver disease, infiltrative disorders, vascular disorder etc.] or Complement deficiencies, e.g.C1-C4, C5-C9, properdin factor H or factor D.

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

Dosage and administration details:

Subjects received 2 doses of Synflorix™ vaccine (Month 0 and Month 2). Pneumococcal vaccine doses were administered intramuscularly into the non-dominant deltoid for Children ≥ 12 months of age if the muscle size is adequate or in the thigh for the other subjects.

Arm title	HE-Un-2-4Y Group

Arm description:

Healthy (HE) unprimed subjects, aged between 24 and 59 months of age (age-matched to the subjects aged 24-59 months in the At risk groups), receiving 2 doses of 10Pn-PD-DiT vaccine. Unprimed groups included subjects who have not been previously vaccinated with any pneumococcal vaccine, i.e. either plain polysaccharide pneumococcal vaccine, Synflorix (10Pn-PD-DiT), Prevenar or Prevenar13. For each enrolled at-risk subject aged between 24-59 months, a healthy subject of the same age expressed in years from the same country should be enrolled regardless of the priming status. In other words, a healthy subject could be enrolled only once if he/she could be matched with an unmatched at-risk subject of the same age and country.

Arm type	Active comparator
Investigational medicinal product name	Synflorix
Investigational medicinal product code	GSK1024850A
Other name	10Pn-PD-DiT, 10Pn
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received 2 doses of Synflorix™ vaccine (Month 0 and Month 2). Pneumococcal vaccine doses were administered intramuscularly into the non-dominant deltoid for Children ≥ 12 months of age if the muscle size is adequate or in the thigh for the other subjects.

Number of subjects in period 1	AR-Pr-2-17Y Group	AR-Un-2-17Y Group	HE-Un-2-4Y Group
Started	18	28	6
Completed	18	24	6
Not completed	0	4	0
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	-	1	-
Migrated /moved from study area	-	1	-
Lost to follow-up	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	AR-Pr-2-17Y Group

Reporting group description:

Primed subjects aged between 24 months and 17 years, who were at an increased risk of pneumococcal infection*, receiving 1 dose of 10Pn-PD-DiT vaccine: Primed groups included subjects who have been previously vaccinated with at least one dose of a pneumococcal conjugate vaccine, i.e. either Synflorix (10Pn-PD-DiT), Prevenar or Prevenar13 or with plain polysaccharide pneumococcal vaccine more than 2 years (24 months) and less than 5 years (60 months) before enrolment.
*An at-risk subject was a subject with Congenital or acquired asplenia such as anatomic, surgical or functional asplenia, or Splenic dysfunction [some degree of functional asplenia, such as sickle-cell disease and other hemoglobinopathies, Hodgkin disease, rheumatologic diseases, systemic lupus erythematous (SLE), chronic gastrointestinal disorders, liver disease, infiltrative disorders, vascular disorder etc.] or Complement deficiencies, e.g.C1-C4, C5-C9, properdin factor H or factor D.

Reporting group title	AR-Un-2-17Y Group

Reporting group description:

Unprimed subjects aged between 24 months and 17 years, who were at an increased risk of pneumococcal infection*, receiving 2 doses of 10Pn-PD-DiT vaccine: Unprimed groups included subjects who have not been previously vaccinated with any pneumococcal vaccine, i.e. either plain polysaccharide pneumococcal vaccine, Synflorix (10Pn-PD-DiT), Prevenar or Prevenar13.
* An at-risk subject was a subject with Congenital or acquired asplenia such as anatomic, surgical or functional asplenia, or Splenic dysfunction [some degree of functional asplenia, such as sickle-cell disease and other hemoglobinopathies, Hodgkin disease, rheumatologic diseases, systemic lupus erythematous (SLE), chronic gastrointestinal disorders, liver disease, infiltrative disorders, vascular disorder etc.] or Complement deficiencies, e.g.C1-C4, C5-C9, properdin factor H or factor D.

Reporting group title	HE-Un-2-4Y Group

Reporting group description:

Healthy (HE) unprimed subjects, aged between 24 and 59 months of age (age-matched to the subjects aged 24-59 months in the At risk groups), receiving 2 doses of 10Pn-PD-DiT vaccine. Unprimed groups included subjects who have not been previously vaccinated with any pneumococcal vaccine, i.e. either plain polysaccharide pneumococcal vaccine, Synflorix (10Pn-PD-DiT), Prevenar or Prevenar13. For each enrolled at-risk subject aged between 24-59 months, a healthy subject of the same age expressed in years from the same country should be enrolled regardless of the priming status. In other words, a healthy subject could be enrolled only once if he/she could be matched with an unmatched at-risk subject of the same age and country.

Reporting group values	AR-Pr-2-17Y Group	AR-Un-2-17Y Group	HE-Un-2-4Y Group
Number of subjects	18	28	6
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: years			
arithmetic mean	11.3	8.6	2.8
standard deviation	± 3.8	± 4.2	± 0.8
Gender categorical			
Units: Subjects			
Female	10	14	2
Male	8	14	4

Reporting group values	Total		
Number of subjects	52		
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: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	26		
Male	26		

End points

End points reporting groups

Reporting group title	AR-Pr-2-17Y Group

Reporting group description:

Primed subjects aged between 24 months and 17 years, who were at an increased risk of pneumococcal infection*, receiving 1 dose of 10Pn-PD-DiT vaccine: Primed groups included subjects who have been previously vaccinated with at least one dose of a pneumococcal conjugate vaccine, i.e. either Synflorix (10Pn-PD-DiT), Prevenar or Prevenar13 or with plain polysaccharide pneumococcal vaccine more than 2 years (24 months) and less than 5 years (60 months) before enrolment.
*An at-risk subject was a subject with Congenital or acquired asplenia such as anatomic, surgical or functional asplenia, or Splenic dysfunction [some degree of functional asplenia, such as sickle-cell disease and other hemoglobinopathies, Hodgkin disease, rheumatologic diseases, systemic lupus erythematous (SLE), chronic gastrointestinal disorders, liver disease, infiltrative disorders, vascular disorder etc.] or Complement deficiencies, e.g.C1-C4, C5-C9, properdin factor H or factor D.

Reporting group title	AR-Un-2-17Y Group

Reporting group description:

Unprimed subjects aged between 24 months and 17 years, who were at an increased risk of pneumococcal infection*, receiving 2 doses of 10Pn-PD-DiT vaccine: Unprimed groups included subjects who have not been previously vaccinated with any pneumococcal vaccine, i.e. either plain polysaccharide pneumococcal vaccine, Synflorix (10Pn-PD-DiT), Prevenar or Prevenar13.
* An at-risk subject was a subject with Congenital or acquired asplenia such as anatomic, surgical or functional asplenia, or Splenic dysfunction [some degree of functional asplenia, such as sickle-cell disease and other hemoglobinopathies, Hodgkin disease, rheumatologic diseases, systemic lupus erythematous (SLE), chronic gastrointestinal disorders, liver disease, infiltrative disorders, vascular disorder etc.] or Complement deficiencies, e.g.C1-C4, C5-C9, properdin factor H or factor D.

Reporting group title	HE-Un-2-4Y Group

Reporting group description:

Healthy (HE) unprimed subjects, aged between 24 and 59 months of age (age-matched to the subjects aged 24-59 months in the At risk groups), receiving 2 doses of 10Pn-PD-DiT vaccine. Unprimed groups included subjects who have not been previously vaccinated with any pneumococcal vaccine, i.e. either plain polysaccharide pneumococcal vaccine, Synflorix (10Pn-PD-DiT), Prevenar or Prevenar13. For each enrolled at-risk subject aged between 24-59 months, a healthy subject of the same age expressed in years from the same country should be enrolled regardless of the priming status. In other words, a healthy subject could be enrolled only once if he/she could be matched with an unmatched at-risk subject of the same age and country.

Subject analysis set title	AR-PR-2-4Y Group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

subset of the AR-PR-2-17Y Group including subjects aged between 24 and 59 months.

Subject analysis set title	AR-Un-2-4Y Group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

subset of the AR-UN-2-17Y Group including subjects aged between 24 and 59 months.

Subject analysis set title	AR-PR-5-17Y Group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

subset of the AR-PR-2-17Y Group including subjects aged between 5 and 17 years.

Subject analysis set title	AR- UN-5-17Y Group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

subset of the AR- UN-5-17Y Group including subjects aged between 5 and 17 years.

Primary: Concentrations of antibodies against Vaccine Pneumococcal Serotypes.

End point title	Concentrations of antibodies against Vaccine Pneumococcal Serotypes.[1]

End point description:

Antibodies assessed for this outcome measure were those against the vaccine pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (ANTI-1, -4, -5, -6A, -6B, -7F, -9V, -14, -18C, -19A, -19F and -23F). Antibody concentrations were measured by 22F enzyme-linked immunosorbent assay (ELISA), expressed as geometric mean concentrations (GMCs), in micrograms per millilitre (µg/mL). The seropositivity cut-off of the assay was an antibody concentration ≥ 0.05 µg/mL. Antibody concentrations < 0.05 µg/mL were given an arbitrary value of half the cut-off for the purpose of GMC calculation. Primary results are the results presented for the At-risk groups. Results were not available at the time of the posting and are entered as equal to "9" (placeholder values), the numbers of subjects in each group are entered as equal to the numbers of subjects who completed the study.

End point type	Primary

End point timeframe:

One month after Dose 1 (At Month 1 for primed subjects) or after Dose 2 (At Month 3 for unprimed subjects)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The intent of this endpoint was descriptive, no comparison of groups was performed

End point values	AR-Pr-2-17Y Group	AR-Un-2-17Y Group	HE-Un-2-4Y Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	24	6	
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-1	9 (9 to 9)	9 (9 to 9)	9 (9 to 9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any and severe (grade 3) solicited local Adverse Events (AEs) after dose 1 for subjects aged between 2 to 4 years.

End point title	Number of subjects with any and severe (grade 3) solicited local Adverse Events (AEs) after dose 1 for subjects aged between 2 to 4 years.[2]

End point description:

Solicited local AEs assessed were pain, redness and swelling. Any = incidence of any local symptom regardless of intensity grade. Grade 3 pain = cried when limb was moved/spontaneously painful. Grade 3 redness/swelling = redness/swelling above 30 millimetre. Primed subjects received one dose and Unprimed subjects received two doses.

End point type	Secondary

End point timeframe:

During the 4-day (Days 0-3) after dose 1

Notes:

[2] - 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: The endpoint concerns only subjects aged between 2 to 4 years (subset of the population).

End point values	HE-Un-2-4Y Group	AR-PR-2-4Y Group	AR-Un-2-4Y Group	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	6	1	5	
Units: Subjects				
Any pain Dose 1	5	1	2	
Grade 3 pain Dose 1	1	0	0	
Any redness Dose 1	6	1	2	
Grade 3 redness Dose 1	2	0	0	
Any swelling Dose 1	3	1	1	
Grade 3 Swelling Dose 1	1	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any and severe (grade 3) solicited local Adverse Events (AEs) after dose 2 for subjects aged between 2 to 4 years.

End point title	Number of subjects with any and severe (grade 3) solicited local Adverse Events (AEs) after dose 2 for subjects aged between 2 to 4 years.[3]

End point description:

Solicited local AEs assessed were pain, redness and swelling. Any = incidence of any local symptom regardless of intensity grade. Grade 3 pain = cried when limb was moved/spontaneously painful. Grade 3 redness/swelling = redness/swelling above 30 millimetre. Primed subjects received one dose and Unprimed subjects received two doses.

End point type	Secondary

End point timeframe:

During the 4-day (Days 0-3) after dose 2

Notes:

[3] - 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: Since all the groups didn't receive dose 2, there are no results to be analyzed for that timeframe for those groups. Moreover the endpoint concerns only subjects aged between 2 to 4 years.

End point values	HE-Un-2-4Y Group	AR-Un-2-4Y Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	6	2		
Units: Subjects				
Any pain Dose 2	3	1		
Grade 3 pain Dose 2	1	0		
Any redness Dose 2	4	0		
Grade 3 Redness Dose 2	0	0		
Any swelling Dose 2	1	1		
Grade 3 Swelling Dose 2	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any and severe (grade 3) solicited local Adverse Events (AEs) after dose 1 for subjects aged between 5 to 17 years.

End point title	Number of subjects with any and severe (grade 3) solicited local Adverse Events (AEs) after dose 1 for subjects aged between 5 to 17 years.

End point description:

Solicited local AEs assessed were pain, redness and swelling. Any = incidence of any local symptom regardless of intensity grade. Grade 3 pain =Significant pain at rest. Prevented normal every day activities. Grade 3 redness/swelling = redness/swelling above 50 millimetre. Primed subjects received one dose and Unprimed subjects received two doses.

End point type	Secondary

End point timeframe:

During the 4-day (Days 0-3) after dose 1

End point values	AR-PR-5-17Y Group	AR- UN-5-17Y Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	23		
Units: Subjects				
Any pain Dose 1	14	22		
Grade 3 pain Dose 1	0	4		
Any redness Dose 1	6	10		
Grade 3 redness Dose 1	0	0		
Any swelling Dose 1	4	6		
Grade 3 Swelling Dose 1	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any and severe (grade 3) solicited local Adverse Events (AEs) after dose 2 for subjects aged between 5 to 17 years.

End point title	Number of subjects with any and severe (grade 3) solicited local Adverse Events (AEs) after dose 2 for subjects aged between 5 to 17 years.

End point description:

Solicited local AEs assessed were pain, redness and swelling. Any = incidence of any local symptom regardless of intensity grade. Grade 3 pain = Significant pain at rest. Prevented normal every day activities. Grade 3 redness/swelling = redness/swelling above 50 millimetre. Primed subjects received one dose and Unprimed subjects received two doses.

End point type	Secondary

End point timeframe:

During the 4-day (Days 0-3) after dose 2

End point values	AR- UN-5-17Y Group			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Subjects				
Any pain Dose 2	16			
Grade 3 pain Dose 2	1			
Any redness Dose 2	7			
Grade 3 redness Dose 2	1			
Any swelling Dose 2	5			
Grade 3 Swelling Dose 2	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any, severe (grade 3) and related solicited general Adverse Events (AEs) after dose 1 for subjects aged between 2 to 4 years.

End point title	Number of subjects with any, severe (grade 3) and related solicited general Adverse Events (AEs) after dose 1 for subjects aged between 2 to 4 years.[4]

End point description:

General AEs = drowsiness, irritability, loss of appetite (loss of appet) and fever (axillary ≥ 37.5 degrees Celsius). Any= Incidence of any solicited general symptom regardless of intensity grade or relationship to vaccination. Grade 3: drowsiness = prevented normal activity; irritability = crying that could not be comforted/ prevented normal activity; loss of appetite = not eating at all; fever > 39.5°C. Related = symptom assessed by the investigator as related to the vaccination. Primed subjects received one dose and Unprimed subjects received two doses.

End point type	Secondary

End point timeframe:

During the 4-day (Days 0-3) after dose 1

Notes:

[4] - 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: The endpoint concerns only subjects aged between 2 to 4 years (subset of the population).

End point values	HE-Un-2-4Y Group	AR-PR-2-4Y Group	AR-Un-2-4Y Group	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	6	1	5	
Units: Subjects				
Any drowsiness Dose 1	1	1	0	
Grade 3 drowsiness Dose 1	0	0	0	
Related drowsiness Dose 1	1	1	0	
Any irritability Dose 1	3	1	1	
Grade 3 irritability Dose 1	0	0	0	
Related irritability Dose 1	3	1	1	
Any loss of appet Dose 1	4	1	2	
Grade 3 loss of appet. Dose 1	0	0	0	
Related loss of appet. Dose 1	3	1	1	
Any Fever Dose 1	1	0	1	
Grade 3 Fever Dose 1	0	0	0	

Related fever Dose 1	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any, severe (grade 3) and related solicited general Adverse Events (AEs) after dose 2 for subjects aged between 2 to 4 years.

End point title	Number of subjects with any, severe (grade 3) and related solicited general Adverse Events (AEs) after dose 2 for subjects aged between 2 to 4 years.[5]

End point description:

General AEs = drowsiness, irritability, loss of appetite (loss of appet) and fever (axillary ≥ 37.5 degrees Celsius). Any= Incidence of any solicited general symptom regardless of intensity grade or relationship to vaccination. Grade 3: drowsiness = prevented normal activity; irritability = crying that could not be comforted/ prevented normal activity; loss of appetite = not eating at all; fever > 39.5°C. Related = symptom assessed by the investigator as related to the vaccination. Primed subjects received one dose and Unprimed subjects received two doses.

End point type	Secondary

End point timeframe:

During the 4-day (Days 0-3) after dose 2

Notes:

[5] - 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: Since all the groups didn't receive dose 2, there are no results to be analyzed for that timeframe for those groups. Moreover the endpoint concerns only subjects aged between 2 to 4 years.

End point values	HE-Un-2-4Y Group	AR-Un-2-4Y Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	6	2		
Units: Subjects				
Any drowsiness Dose 2	1	1		
Grade 3 drowsiness Dose 2	0	0		
Related drowsiness Dose 2	1	1		
Any irritability Dose 2	1	1		
Grade 3 irritability Dose 2	0	0		
Related irritability Dose 2	1	1		
Any loss of appet Dose 2	2	1		
Grade 3 loss of appet. Dose 2	0	0		
Related loss of appet. Dose 2	2	1		
Any Fever Dose 2	0	1		
Grade 3 Fever Dose 2	0	0		
Related fever Dose 2	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any, severe (grade 3) and related solicited general Adverse Events (AEs) after dose 1 for subjects aged between 5 to 17 years..

End point title	Number of subjects with any, severe (grade 3) and related solicited general Adverse Events (AEs) after dose 1 for subjects aged between 5 to 17 years..

End point description:

General AEs = headache, fatigue, gastrointestinal symptoms (gastro symp) (nausea, vomiting, diarrhoea and/or abdominal pain) and fever (axillary ≥ 37.5 degrees Celsius). Any= Incidence of any solicited general symptom regardless of intensity grade or relationship to vaccination. Grade 3: headache, fatigue and gastrointestinal symptoms = symptoms that prevented normal activity; Fever > 39.5°C. Related = symptom assessed by the investigator as related to the vaccination. Primed subjects received one dose and Unprimed subjects received two doses.

End point type	Secondary

End point timeframe:

During the 4-day (Days 0-3) after dose 1

End point values	AR-PR-5-17Y Group	AR- UN-5-17Y Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	23		
Units: Subjects				
Any fatigue Dose 1	5	5		
Grade 3 fatigue Dose 1	0	0		
Related fatigue Dose 1	4	4		
Any gastro symp Dose 1	3	4		
Grade 3 gastro symp. Dose 1	0	0		
Related gastro symp. Dose 1	2	0		
Any headache Dose 1	5	6		
Grade 3 headache Dose 1	0	0		
Related headache Dose 1	5	6		
Any Fever Dose 1	0	2		
Grade 3 Fever Dose 1	0	0		
Related fever Dose 1	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any, severe (grade 3) and related solicited general Adverse Events (AEs) after dose 2 for subjects aged between 5 to 17 years.

End point title	Number of subjects with any, severe (grade 3) and related solicited general Adverse Events (AEs) after dose 2 for subjects aged between 5 to 17 years.

End point description:

General AEs = headache, fatigue, gastrointestinal symptoms (gastro symp) (nausea, vomiting, diarrhoea and/or abdominal pain) and fever (axillary ≥ 37.5 degrees Celsius). Any= Incidence of any solicited general symptom regardless of intensity grade or relationship to vaccination. Grade 3: headache, fatigue and gastrointestinal symptoms = symptoms that prevented normal activity; Fever >

39.5°C. Related = symptom assessed by the investigator as related to the vaccination. Primed subjects received one dose and Unprimed subjects received two doses.

End point type	Secondary

End point timeframe:

During the 4-day (Days 0-3) after dose 2

End point values	AR- UN-5-17Y Group			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Subjects				
Any fatigue Dose 2	7			
Grade 3 fatigue Dose 2	0			
Related fatigue Dose 2	6			
Any gastro symp Dose 2	2			
Grade 3 gastro symp. Dose 2	0			
Related gastro symp. Dose 2	0			
Any headache Dose 2	5			
Grade 3 headache Dose 2	0			
Related headache Dose 2	5			
Any Fever Dose 2	1			
Grade 3 Fever Dose 2	0			
Related fever Dose 2	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with unsolicited AEs.

End point title	Number of subjects with unsolicited AEs.

End point description:

An unsolicited adverse event is any adverse event (i.e. any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with use of a medicinal product, whether or not considered related to the medicinal product) reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms.

End point type	Secondary

End point timeframe:

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

End point values	AR-Pr-2-17Y Group	AR-Un-2-17Y Group	HE-Un-2-4Y Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	28	6	
Units: Subjects				
Any AE	2	14	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Serious Adverse Events (SAEs).

End point title	Number of subjects with Serious Adverse Events (SAEs).

End point description:

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

End point type	Secondary

End point timeframe:

From Dose 1 at Month 0 up to study end at Month 1 for primed subjects and at Month 3 for unprimed subjects.

End point values	AR-Pr-2-17Y Group	AR-Un-2-17Y Group	HE-Un-2-4Y Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	28	6	
Units: Subjects				
Any SAE	0	1	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs: from Month 0 up to Study end, Solicited and Unsolicited AEs: within the 31-day post- vaccination period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	AR-Pr-2-17Y

Reporting group description:

Primed subjects aged between 24 months and 17 years, who were at an increased risk of pneumococcal infection*, receiving 1 dose of 10Pn-PD-DiT vaccine: Primed groups included subjects who have been previously vaccinated with at least one dose of a pneumococcal conjugate vaccine, i.e. either Synflorix (10Pn-PD-DiT), Prevenar or Prevenar13 or with plain polysaccharide pneumococcal vaccine more than 2 years (24 months) and less than 5 years (60 months) before enrolment.
*An at-risk subject was a subject with Congenital or acquired asplenia such as anatomic, surgical or functional asplenia, or Splenic dysfunction [some degree of functional asplenia, such as sickle-cell disease and other hemoglobinopathies, Hodgkin disease, rheumatologic diseases, systemic lupus erythematous (SLE), chronic gastrointestinal disorders, liver disease, infiltrative disorders, vascular disorder etc.] or Complement deficiencies, e.g.C1-C4, C5-C9, properdin factor H or factor D.

Reporting group title	AR-Un-2-17Y

Reporting group description:

Unprimed subjects aged between 24 months and 17 years, who were at an increased risk of pneumococcal infection*, receiving 2 doses of 10Pn-PD-DiT vaccine: Unprimed groups included subjects who have not been previously vaccinated with any pneumococcal vaccine, i.e. either plain polysaccharide pneumococcal vaccine, Synflorix (10Pn-PD-DiT), Prevenar or Prevenar13.
* An at-risk subject was a subject with Congenital or acquired asplenia such as anatomic, surgical or functional asplenia, or Splenic dysfunction [some degree of functional asplenia, such as sickle-cell disease and other hemoglobinopathies, Hodgkin disease, rheumatologic diseases, systemic lupus erythematous (SLE), chronic gastrointestinal disorders, liver disease, infiltrative disorders, vascular disorder etc.] or Complement deficiencies, e.g.C1-C4, C5-C9, properdin factor H or factor D.

Reporting group title	HE-Un-2-4Y

Reporting group description:

Healthy (HE) unprimed subjects, aged between 24 and 59 months of age (age-matched to the subjects aged 24-59 months in the At risk groups), receiving 2 doses of 10Pn-PD-DiT vaccine. Unprimed groups included subjects who have not been previously vaccinated with any pneumococcal vaccine, i.e. either plain polysaccharide pneumococcal vaccine, Synflorix (10Pn-PD-DiT), Prevenar or Prevenar13. For each enrolled at-risk subject aged between 24-59 months, a healthy subject of the same age expressed in years from the same country should be enrolled regardless of the priming status. In other words, a healthy subject could be enrolled only once if he/she could be matched with an unmatched at-risk subject of the same age and country.

Serious adverse events	AR-Pr-2-17Y	AR-Un-2-17Y	HE-Un-2-4Y
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Infections and infestations			
Respiratory tract infection			

subjects affected / exposed	0 / 18 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	AR-Pr-2-17Y	AR-Un-2-17Y	HE-Un-2-4Y
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 18 (94.44%)	27 / 28 (96.43%)	6 / 6 (100.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 18 (27.78%)	7 / 28 (25.00%)	0 / 6 (0.00%)
occurrences (all)	5	11	0
Somnolence			
subjects affected / exposed	1 / 18 (5.56%)	3 / 28 (10.71%)	1 / 6 (16.67%)
occurrences (all)	1	3	2
General disorders and administration site conditions			
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 18 (27.78%)	10 / 28 (35.71%)	0 / 6 (0.00%)
occurrences (all)	5	12	0
Injection site pruritus			
subjects affected / exposed	0 / 18 (0.00%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pain			
alternative assessment type: Systematic			
subjects affected / exposed	15 / 18 (83.33%)	24 / 28 (85.71%)	5 / 6 (83.33%)
occurrences (all)	15	41	8
Pyrexia			
subjects affected / exposed	0 / 18 (0.00%)	4 / 28 (14.29%)	1 / 6 (16.67%)
occurrences (all)	0	5	1
Swelling			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 18 (27.78%)	10 / 28 (35.71%)	3 / 6 (50.00%)
occurrences (all)	5	13	4

Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	3 / 18 (16.67%)	5 / 28 (17.86%)	0 / 6 (0.00%)
occurrences (all)	3	6	0
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	0 / 18 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	7 / 18 (38.89%)	12 / 28 (42.86%)	6 / 6 (100.00%)
occurrences (all)	7	19	10
Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 18 (5.56%)	1 / 28 (3.57%)	4 / 6 (66.67%)
occurrences (all)	1	2	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 28 (3.57%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Respiratory tract infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 28 (3.57%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Rhinitis			
subjects affected / exposed	0 / 18 (0.00%)	4 / 28 (14.29%)	1 / 6 (16.67%)
occurrences (all)	0	4	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 18 (5.56%)	2 / 28 (7.14%)	4 / 6 (66.67%)
occurrences (all)	1	3	6
Vitamin D deficiency			
subjects affected / exposed	1 / 18 (5.56%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 November 2012	As requested by the Committee for Medicinal Products for Human Use (CHMP), the definition of priming status has been further clarified to consider for inclusion in the primed groups children who have been previously vaccinated with at least one dose of a pneumococcal conjugate vaccine (i.e. either Synflorix (10Pn-PD-DiT), Prevenar or Prevenar13) and/or with plain polysaccharide pneumococcal vaccine more than 2 years (24 months) and less than 5 years (60 months) before enrolment. Children who have not been previously vaccinated with any pneumococcal vaccine (i.e. either plain polysaccharide pneumococcal vaccine, Synflorix (10Pn-PD-DiT), Prevenar or Prevenar13) will be considered for inclusion in the unprimed groups. In addition clarifications have been made to the definition of at-risk subjects and recording of pneumococcal vaccination history of primed subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported