Clinical trial results:
A phase III, controlled, single-blind study to assess the reactogenicity, safety and immunogenicity of a booster dose of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine or Prevenar™ when co-administered with Hiberix™ at 12-18 months of age in children primed with the same vaccines in study 10PN-PD-DIT-036 (110808).

Summary

EudraCT number	2015-001506-34
Trial protocol	Outside EU/EEA
Global end of trial date	11 January 2010
Results information	
Result version number	v2 (current)
This version publication date	13 December 2020
First version publication date	25 July 2015
Version creation reason	• Correction of full data set Minor corrections in safety section.

Trial information

Trial identification	
Sponsor protocol code	112933
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00911144
WHO universal trial number (UTN)	-

Notes:

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

Notes:

Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 June 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 January 2010
Global end of trial reached?	Yes
Global end of trial date	11 January 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety of a booster dose of 10Pn-PD-DiT vaccine in terms of the occurrence of adverse events (AEs) with intensity grade 3, when co-administered with Hib vaccine at 12-18 months of age in children primed with the same vaccines at 2, 4 and 6 months of age in study 10PN-PD-DIT-036 (110808).

Protection of trial subjects:

All subjects were supervised after vaccination/product administration with appropriate medical treatment readily available. Vaccines were administered by qualified and trained personnel. Vaccines were administered only to eligible subjects that had no contraindications to any components of the vaccines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 June 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	Korea, Republic of: 450
Worldwide total number of subjects	450
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	450
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Two subjects enrolled in the protocol received commercial Prevenar and Hiberix vaccines instead of the clinical vaccines planned to be injected and are as such not included in the number of started subjects below.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

This study was conducted in a single-blind manner meaning that the investigator and/or his staff were aware of the treatment assignment but the subjects' parent(s)/guardian(s) were not.

Arms

Are arms mutually exclusive?	Yes
Arm title	Synflorix Group

Arm description:

Subjects previously primed (NCT00680914) with 3 doses of Synflorix and Hiberix in the first year of life receiving a booster dose of the same vaccines in the second year of life by intramuscular injection into the right and the left thigh or deltoid, respectively.

Arm type	Experimental
Investigational medicinal product name	GSK Biologicals' Synflorix™ (Pneumococcal vaccine GSK1024850A)
Investigational medicinal product code	
Other name	Pneumococcal vaccine GSK1024850A
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection, administered as a single dose.

Investigational medicinal product name	GSK Biologicals' Hiberix™
Investigational medicinal product code	
Other name	Hib
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection, administered as a single dose.

Arm title	Prevenar Group

Arm description:

Subjects previously primed (NCT00680914) with 3 doses of Prevenar and Hiberix in the first year of life receiving a booster dose of Prevenar and Hiberix in the second year of life by intramuscular injection into the right and the left thigh or deltoid, respectively.

Arm type	Active comparator

Investigational medicinal product name	Wyeth-Lederle's Prevenar™
Investigational medicinal product code	
Other name	7Pn
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection, administered as a single dose.

Investigational medicinal product name	GSK Biologicals' Hiberix™
Investigational medicinal product code	
Other name	Hib
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection, administered as a single dose.

Number of subjects in period 1[1]	Synflorix Group	Prevenar Group
Started	335	113
Completed	319	108
Not completed	16	5
Consent withdrawn by subject	16	5

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: Out of the total 450 subjects enrolled in the study, 2 subjects received commercial Prevenar and Hiberix vaccines instead of the clinical vaccines planned to be injected and are as such not included in the number of subjects who started the study.

Baseline characteristics

Reporting groups	
Reporting group title	Synflorix Group
Reporting group description:	
Subjects previously primed (NCT00680914) with 3 doses of Synflorix and Hiberix in the first year of life receiving a booster dose of the same vaccines in the second year of life by intramuscular injection into the right and the left thigh or deltoid, respectively.	
Reporting group title	Prevenar Group
Reporting group description:	
Subjects previously primed (NCT00680914) with 3 doses of Prevenar and Hiberix in the first year of life receiving a booster dose of Prevenar and Hiberix in the second year of life by intramuscular injection into the right and the left thigh or deltoid, respectively.	

Reporting group values	Synflorix Group	Prevenar Group	Total
Number of subjects	335	113	448
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	13.6	13.7	
standard deviation	± 1.07	± 1	-
Gender categorical Units: Subjects			
Female	168	59	227
Male	167	54	221

End points

End points reporting groups

Reporting group title	Synflorix Group

Reporting group description:

Subjects previously primed (NCT00680914) with 3 doses of Synflorix and Hiberix in the first year of life receiving a booster dose of the same vaccines in the second year of life by intramuscular injection into the right and the left thigh or deltoid, respectively.

Reporting group title	Prevenar Group

Reporting group description:

Subjects previously primed (NCT00680914) with 3 doses of Prevenar and Hiberix in the first year of life receiving a booster dose of Prevenar and Hiberix in the second year of life by intramuscular injection into the right and the left thigh or deltoid, respectively.

Primary: Number of subjects reporting grade 3 adverse events

End point title	Number of subjects reporting grade 3 adverse events[1]

End point description:

Grade 3 adverse events are severe symptoms that prevent normal, everyday activities.

End point type	Primary

End point timeframe:

Within 31 days (Day 0 - Day 30) after booster vaccination.

Notes:

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

End point values	Synflorix Group	Prevenar Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332	113		
Units: Subjects	42	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting solicited symptoms

End point title	Number of subjects reporting solicited symptoms

End point description:

Solicited local symptoms assessed include pain, redness and swelling at the injection site. Solicited general symptoms assessed include drowsiness, fever (equal to or above 37.5 degrees Celsius), irritability and loss of appetite.

End point type	Secondary

End point timeframe:

Within 4 days (Days 0 to 3) after booster vaccination

End point values	Synflorix Group	Prevenar Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332	113		
Units: Subjects				
Pain	120	39		
Redness	142	55		
Swelling	97	35		
Drowsiness	75	21		
Fever	46	20		
Irritability	141	42		
Loss of appetite	71	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting unsolicited adverse events

End point title	Number of subjects reporting unsolicited adverse events

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 the use of a medicinal product, whether or not considered related to the medicinal product) reported in addition to those solicited during the clinical study. Also any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

End point type	Secondary

End point timeframe:

Within 31 days (Days 0 to 30) after booster vaccination

End point values	Synflorix Group	Prevenar Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	113		
Units: Subjects	118	41		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting serious adverse events

End point title	Number of subjects reporting serious adverse events

End point description:

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

End point type	Secondary

End point timeframe:

After booster vaccination up to study end (Month 0 to Month 1)

End point values	Synflorix Group	Prevenar Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	113		
Units: Subjects	8	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of antibodies against vaccine pneumococcal serotypes

End point title	Concentration of antibodies against vaccine pneumococcal serotypes

End point description:

Concentrations of antibodies are measured by 22F-inhibition enzyme-linked immunosorbent assay (ELISA) and are presented as geometric mean concentrations expressed as microgram per milliliter. Vaccine pneumococcal serotypes included serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.

End point type	Secondary

End point timeframe:

One month after booster vaccination (Month 1)

End point values	Synflorix Group	Prevenar Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317	102		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-1 (n= 317, 100)	4.03 (3.66 to 4.43)	0.06 (0.05 to 0.07)		
Anti-4 (n= 317, 102)	5.77 (5.25 to 6.34)	12.19 (10.11 to 14.69)		
Anti-5 (n= 317, 102)	5.51 (5.08 to 5.98)	0.19 (0.16 to 0.23)		
Anti-6B (n= 317, 102)	2.78 (2.48 to 3.12)	7.09 (5.82 to 8.63)		
Anti-7F (n= 317, 102)	5.39 (4.97 to 5.85)	0.06 (0.04 to 0.07)		
Anti-9V (n= 317, 102)	4.99 (4.55 to 5.46)	12.72 (10.86 to 14.88)		

Anti-14 (n= 316, 102)	7.73 (7.09 to 8.43)	22.22 (18.96 to 26.03)		
Anti-18C (n= 317, 102)	13.14 (11.9 to 14.52)	14.53 (12.1 to 17.44)		
Anti-19F (n= 317, 101)	16.89 (14.87 to 19.2)	4.82 (3.97 to 5.85)		
Anti-23F (n= 317, 102)	3.75 (3.37 to 4.16)	14.81 (11.61 to 18.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Opsonophagocytic activity against vaccine pneumococcal serotypes

End point title	Opsonophagocytic activity against vaccine pneumococcal serotypes

End point description:

Streptococcus pneumoniae opsonophagocytic activity was measured by a killing-assay using a HL 60 cell line. The results are presented as the dilution of serum (opsonic titer) able to sustain 50% killing of live pneumococci under the assay conditions. Vaccine pneumococcal serotypes included serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.

End point type	Secondary

End point timeframe:

One month after booster vaccination (Month 1)

End point values	Synflorix Group	Prevenar Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	47		
Units: Titer				
geometric mean (confidence interval 95%)				
Opsono-1 (n= 148, 47)	363.7 (275.3 to 480.5)	4.7 (3.9 to 5.6)		
Opsono-4 (n= 149, 45)	1058 (893.9 to 1252.3)	3717 (2759.3 to 5007)		
Opsono-5 (n= 150, 46)	233.9 (189.8 to 288.3)	4 (4 to 4)		
Opsono-6B (n= 150, 46)	546.5 (415.9 to 718)	3826.8 (2518 to 5815.9)		
Opsono-7F (n= 145, 46)	5467.5 (4698.1 to 6363)	1038.2 (609.9 to 1767.2)		
Opsono-9V (n= 151, 44)	1707.5 (1497.6 to 1946.8)	5204 (3842.8 to 7047.4)		
Opsono-14 (n= 150, 46)	1814.6 (1577.4 to 2087.5)	3958.4 (2888.1 to 5425.4)		
Opsono-18C (n= 147, 45)	607.9 (498.2 to 741.6)	1723.3 (1196.4 to 2482.3)		

Opsono-19F (n= 149, 44)	1284.5 (1027.2 to 1606.3)	277.3 (171.6 to 448.2)		
Opsono-23F (n= 149, 44)	2702.9 (2234.9 to 3268.9)	29918.6 (17115.7 to 52298.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of antibodies against cross-reactive pneumococcal serotypes 6A and 19A

End point title	Concentration of antibodies against cross-reactive pneumococcal serotypes 6A and 19A

End point description:

Concentrations of antibodies are measured by 22F-inhibition ELISA and are presented as geometric mean concentrations expressed as microgram per milliliter.

End point type	Secondary

End point timeframe:

One month after booster vaccination (Month 1)

End point values	Synflorix Group	Prevenar Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317	102		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-6A	0.99 (0.84 to 1.17)	2.51 (1.79 to 3.51)		
Anti-19A	1.54 (1.27 to 1.87)	0.32 (0.24 to 0.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Opsonophagocytic activity against cross-reactive pneumococcal serotypes 6A and 19A

End point title	Opsonophagocytic activity against cross-reactive pneumococcal serotypes 6A and 19A

End point description:

Streptococcus pneumoniae opsonophagocytic activity was measured by a killing-assay using a HL 60 cell line. The results are presented as the dilution of serum (opsonic titer) able to sustain 50% killing of live pneumococci under the assay conditions.

End point type	Secondary

End point timeframe:

One month after booster vaccination (Month 1)

End point values	Synflorix Group	Prevenar Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146	44		
Units: Titer				
geometric mean (confidence interval 95%)				
Opsono-6A (n= 137, 44)	196.1 (134.6 to 285.9)	1415.7 (891.2 to 2248.9)		
Opsono-19A (n= 146, 44)	64.9 (44.6 to 94.5)	15.5 (8.1 to 29.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of antibodies against protein D (PD)

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

End point description:

Concentrations of antibodies are presented as geometric mean concentrations expressed as Enzyme-Linked Immuno-Sorbent Assay (ELISA) units per milliliter.

End point type	Secondary

End point timeframe:

One month after booster vaccination (Month 1)

End point values	Synflorix Group	Prevenar Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	101		
Units: EU/mL				
geometric mean (confidence interval 95%)	1288.9 (1175.6 to 1413.2)	92 (78.3 to 108.1)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Concentrations of antibodies are presented as geometric mean concentrations expressed as microgram per milliliter.

End point type	Secondary

End point timeframe:

One month after booster vaccination (Month 1)

End point values	Synflorix Group	Prevenar Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	54		
Units: µg/mL				
geometric mean (confidence interval 95%)	152.97 (130.307 to 179.575)	99.738 (72.964 to 136.335)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious AEs were assessed up to one month following booster vaccination (Month 1). The time frames for Other AEs reporting were 4 days and 31 days following booster vaccination for events collected by systematic and non-systematic methods, respectively.

Adverse event reporting additional description:

Subjects at risk for systematically assessed other (non-serious) adverse events has been set to the number of subjects that had returned their symptom sheet. The occurrence of reported AEs (all/related) was not available and is encoded as equal to the number of subjects affected.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Prevenar Group

Reporting group description:

Subjects previously primed (NCT00680914) with 3 doses of Prevenar and Hiberix in the first year of life receiving a booster dose of Prevenar and Hiberix in the second year of life by intramuscular injection into the right and the left thigh or deltoid, respectively.

Reporting group title	Synflorix Group

Reporting group description:

Subjects previously primed (NCT00680914) with 3 doses of Synflorix and Hiberix in the first year of life receiving a booster dose of the same vaccines in the second year of life by intramuscular injection into the right and the left thigh or deltoid, respectively.

Serious adverse events	Prevenar Group	Synflorix Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 113 (3.54%)	8 / 335 (2.39%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 113 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Pharyngitis			
subjects affected / exposed	2 / 113 (1.77%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	1 / 113 (0.88%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 113 (0.00%)	2 / 335 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 335 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 113 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	0 / 113 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 113 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	0 / 113 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile convulsion			

subjects affected / exposed	0 / 113 (0.00%)	1 / 335 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Prevenar Group	Synflorix Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 113 (72.57%)	243 / 335 (72.54%)	
General disorders and administration site conditions			
Pain at the injection site			
alternative assessment type: Systematic			
subjects affected / exposed	39 / 113 (34.51%)	120 / 335 (35.82%)	
occurrences (all)	39	120	
Redness at the injection site			
alternative assessment type: Systematic			
subjects affected / exposed	55 / 113 (48.67%)	142 / 335 (42.39%)	
occurrences (all)	55	142	
Swelling at the injection site			
alternative assessment type: Systematic			
subjects affected / exposed	35 / 113 (30.97%)	97 / 335 (28.96%)	
occurrences (all)	35	97	
Drowsiness			
alternative assessment type: Systematic			
subjects affected / exposed	21 / 113 (18.58%)	75 / 335 (22.39%)	
occurrences (all)	21	75	
Fever			
alternative assessment type: Systematic			
subjects affected / exposed	20 / 113 (17.70%)	46 / 335 (13.73%)	
occurrences (all)	20	46	
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	42 / 113 (37.17%)	141 / 335 (42.09%)	
occurrences (all)	42	141	

Loss of appetite alternative assessment type: Systematic subjects affected / exposed occurrences (all)	29 / 113 (25.66%) 29	71 / 335 (21.19%) 71	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	12 / 113 (10.62%) 12	30 / 335 (8.96%) 30	
Nasopharyngitis subjects affected / exposed occurrences (all)	10 / 113 (8.85%) 10	19 / 335 (5.67%) 19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2009	Comments received from the Korean FDA.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported