

**Clinical trial results:**

A phase IIIb, open-label, multicentre study to assess the safety and immunogenicity of GlaxoSmithKline (GSK) Biologicals' combined diphtheria-tetanus-acellular pertussis (DTPa)- Haemophilus influenzae type b (Hib) vaccine (DTPa/Hib) compared with GSK Biologicals' DTPa and Hib vaccines co-administered at different injection sites, when administered as booster vaccination to healthy Chinese subjects aged 18 to 24 months previously primed with the same vaccines in study DTPa-131 (104567)

Summary

EudraCT number	2015-001507-31
Trial protocol	Outside EU/EEA
Global end of trial date	26 July 2008

Results information

Result version number	v1 (current)
This version publication date	20 November 2018
First version publication date	05 July 2015

Trial information**Trial identification**

Sponsor protocol code	111535
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00696423
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 Trails Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trails 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	20 February 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 July 2008
Global end of trial reached?	Yes
Global end of trial date	26 July 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the immune response to all vaccine antigens, i.e. diphtheria and tetanus toxoids, pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN), and polyribosyl-ribitol-phosphate (PRP), one month after booster vaccination with the DTPa/Hib vaccine or with the DTPa and Hib vaccines administered separately.

Protection of trial subjects:

All subjects were supervised closely for at least 30 minutes following vaccination with appropriate medical treatment readily available. Vaccines were administered by qualified and trained personnel. Vaccines were administered only to eligible subjects that had no contraindications to any components of the vaccines. Subjects were followed-up from the time the subject consents to participate in the study until she/he is discharged.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 June 2008
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	China: 467
Worldwide total number of subjects	467
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)	467
Children (2-11 years)	0

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

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

During the screening the following steps occurred: check for inclusion/exclusion criteria, contraindications/precautions, medical history of the subjects and signing informed consent forms.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Infanrix/Hib Group

Arm description:

Subjects who had received Infanrix/Hib vaccine administered in one injection in the primary study received a booster dose of the same vaccine in this study.

Arm type	Experimental
Investigational medicinal product name	Infanrix™
Investigational medicinal product code	
Other name	DTPa
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received 1 dose of Infanrix™ extemporaneously mixed with Hiberix™. The vaccine was administered intramuscularly into the left anterolateral thigh.

Investigational medicinal product name	Hiberix™
Investigational medicinal product code	
Other name	Hib
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

The vaccine was administered intramuscularly into the left anterolateral thigh, one dose, mixed extemporaneously with the Infanrix™ (DTPa) vaccine.

Arm title	Infanrix + Hiberix Group
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Arm description:

Subjects who had received Infanrix (DTPa) and Hiberix (Hib) vaccines, co-administered at separate injection sites in the primary study received a booster dose of the same vaccines in this study.

Arm type	Active comparator
Investigational medicinal product name	Infanrix™
Investigational medicinal product code	
Other name	DTPa
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received two separate injections, one of Infanrix™ and one of Hiberix™. The Infanrix™ vaccine was administered intramuscularly into the left anterolateral thigh.

Investigational medicinal product name	Hiberix™
Investigational medicinal product code	
Other name	Hib
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

The vaccine was administered intramuscularly into the right anterolateral thigh.

Number of subjects in period 1	Infanrix/Hib Group	Infanrix + Hiberix Group
Started	244	223
Completed	244	218
Not completed	0	5
Migrated/moved from study area	-	5

Baseline characteristics

Reporting groups

Reporting group title	Infanrix/Hib Group
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Reporting group description:

Subjects who had received Infanrix/Hib vaccine administered in one injection in the primary study received a booster dose of the same vaccine in this study.

Reporting group title	Infanrix + Hiberix Group
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Reporting group description:

Subjects who had received Infanrix (DTPa) and Hiberix (Hib) vaccines, co-administered at separate injection sites in the primary study received a booster dose of the same vaccines in this study.

Reporting group values	Infanrix/Hib Group	Infanrix + Hiberix Group	Total
Number of subjects	244	223	467
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	19.2	19.2	
standard deviation	± 0.79	± 0.75	-
Gender categorical Units: Subjects			
Female	113	111	224
Male	131	112	243

End points

End points reporting groups

Reporting group title	Infanrix/Hib Group
Reporting group description: Subjects who had received Infanrix/Hib vaccine administered in one injection in the primary study received a booster dose of the same vaccine in this study.	
Reporting group title	Infanrix + Hiberix Group
Reporting group description: Subjects who had received Infanrix (DTPa) and Hiberix (Hib) vaccines, co-administered at separate injection sites in the primary study received a booster dose of the same vaccines in this study.	

Primary: Anti-polyribosyl-ribitol-phosphate (PRP) antibody concentrations

End point title	Anti-polyribosyl-ribitol-phosphate (PRP) antibody concentrations ^[1]
End point description: Geometric mean concentrations are given in microgram per milliliter ($\mu\text{g/mL}$).	
End point type	Primary
End point timeframe: One month 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	Infanrix/Hib Group	Infanrix + Hiberix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	216		
Units: $\mu\text{g/mL}$				
geometric mean (confidence interval 95%)				
Anti-polyribosyl-ribitol-phosphate (PRP) antibody	34.428 (29.452 to 40.244)	132.075 (112.563 to 154.97)		

Statistical analyses

No statistical analyses for this end point

Primary: Anti-diphtheria toxoid antibody concentrations

End point title	Anti-diphtheria toxoid antibody concentrations ^[2]
End point description: Geometric mean concentrations are given in international Unit per milliliter (IU/mL).	
End point type	Primary
End point timeframe: One month after booster vaccination	

Notes:

[2] - 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	Infanrix/Hib Group	Infanrix + Hiberix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	214		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-diphtheria toxoid antibody concentrations	0.945 (0.905 to 0.987)	0.926 (0.887 to 0.966)		

Statistical analyses

No statistical analyses for this end point

Primary: Anti-tetanus toxoid antibody concentrations

End point title	Anti-tetanus toxoid antibody concentrations ^[3]
End point description:	Geometric mean concentrations are given in IU/mL.
End point type	Primary
End point timeframe:	One month after booster vaccination

Notes:

[3] - 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	Infanrix/Hib Group	Infanrix + Hiberix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	214		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-tetanus toxoid antibody concentrations	7.455 (6.881 to 8.077)	10.104 (9.08 to 11.242)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Anti-pertussis toxoid (PT), anti-filamentous haemagglutinin (FHA) and anti-pertactin (PRN) antibody concentrations ^[4]
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End point description:

Geometric mean concentrations are given in Enzyme-Linked Immuno Sorbent Assay (ELISA) unit per milliliter (EL.U/mL).

End point type	Primary
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End point timeframe:

One month after booster vaccination

Notes:

[4] - 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	Infanrix/Hib Group	Infanrix + Hiberix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	216		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-PT	52.2 (48.1 to 56.7)	55.8 (51.7 to 60.3)		
Anti-FHA	93.3 (82.6 to 105.4)	92.8 (83.3 to 103.4)		
Anti-PRN	235.9 (208.7 to 266.5)	241.6 (213.6 to 273.2)		

Statistical analyses

No statistical analyses for this end point

Primary: The number of subjects seroprotected for anti-PRP, anti-diphtheria and anti-tetanus antibodies and seropositive for anti-PT, anti-FHA and anti-PRN antibodies

End point title	The number of subjects seroprotected for anti-PRP, anti-diphtheria and anti-tetanus antibodies and seropositive for anti-PT, anti-FHA and anti-PRN antibodies ^[5]
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End point description:

Assay cut-offs indicating seroprotection or seropositivity for the different antigens were the following: anti-PRP antibody concentrations ≥ 0.15 $\mu\text{g/mL}$, anti-diphtheria and anti-tetanus antibody concentrations ≥ 0.1 IU/mL, anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 20 EL.U/mL.

End point type	Primary
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End point timeframe:

One month after booster vaccination

Notes:

[5] - 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	Infanrix/Hib Group	Infanrix + Hiberix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	216		
Units: Subjects				
Seroprotection against PRP (n=238, 216)	238	216		
Seroprotection against diphtheria (n=237, 214)	237	214		
Seroprotection against tetanus (n=237, 214)	237	214		
Seropositivity for anti-PT (n=239, 216)	226	213		
Seropositivity for anti-FHA (n=239, 216)	238	216		
Seropositivity for anti-PRN (n=239, 216)	239	215		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-PRP antibody concentrations

End point title	Anti-PRP antibody concentrations
End point description:	
Geometric mean concentrations are given in µg/mL.	
End point type	Secondary
End point timeframe:	
Before booster vaccination	

End point values	Infanrix/Hib Group	Infanrix + Hiberix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	216		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-PRP antibody concentrations	1.24 (1.085 to 1.418)	2.461 (2.136 to 2.837)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-diphtheria toxoid antibody concentrations

End point title	Anti-diphtheria toxoid antibody concentrations
End point description:	
Geometric mean concentrations are given in IU/mL.	

End point type	Secondary
End point timeframe:	
Before booster vaccination	

End point values	Infanrix/Hib Group	Infanrix + Hiberix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	214		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-diphtheria toxoid antibody concentrations	0.055 (0.053 to 0.058)	0.054 (0.052 to 0.057)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-tetanus toxoid antibody concentrations

End point title	Anti-tetanus toxoid antibody concentrations
End point description:	
Geometric mean concentrations are given in IU/mL.	
End point type	Secondary
End point timeframe:	
Before booster vaccination	

End point values	Infanrix/Hib Group	Infanrix + Hiberix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	214		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-tetanus toxoid antibody concentrations	0.219 (0.195 to 0.247)	0.311 (0.274 to 0.353)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-PT, anti-FHA and anti-PRN antibody concentrations

End point title	Anti-PT, anti-FHA and anti-PRN antibody concentrations
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End point description:

Geometric mean concentrations are given in EL.U/mL.

End point type Secondary

End point timeframe:

Before booster vaccination

End point values	Infanrix/Hib Group	Infanrix + Hiberix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	216		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-PT	10 (10 to 10)	10 (10 to 10.1)		
Anti-FHA	10.1 (10 to 10.2)	10.3 (9.9 to 10.7)		
Anti-PRN	10.2 (10 to 10.4)	10.3 (10 to 10.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: The number of subjects seroprotected for anti-PRP, anti-diphtheria and anti-tetanus antibodies and seropositive for anti-PT, anti-FHA and anti-PRN antibodies

End point title The number of subjects seroprotected for anti-PRP, anti-diphtheria and anti-tetanus antibodies and seropositive for anti-PT, anti-FHA and anti-PRN antibodies

End point description:

Assay cut-offs indicating seroprotection or seropositivity for the different antigens were the following: anti-PRP antibody concentrations ≥ 0.15 $\mu\text{g/mL}$, anti-diphtheria and anti-tetanus antibody concentrations ≥ 0.1 IU/mL, anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 20 EL.U/mL.

End point type Secondary

End point timeframe:

Before booster vaccination

End point values	Infanrix/Hib Group	Infanrix + Hiberix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	216		
Units: Subjects				
Seroprotection against PRP (n= 237, 216)	236	216		
Seroprotection against diphtheria (n= 237, 214)	21	16		
Seroprotection against tetanus (n= 237, 214)	209	198		

Seropositivity for anti-PT (n= 239, 216)	0	1		
Seropositivity for anti-FHA (n= 239, 216)	2	3		
Seropositivity for anti-PRN (n= 239, 216)	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting solicited local and general symptoms

End point title	Number of subjects reporting solicited local and general symptoms
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End point description:

Solicited local symptoms assessed include pain, redness and swelling. Solicited general symptoms assessed include drowsiness, fever, irritability, and loss of appetite.

End point type	Secondary
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End point timeframe:

During the 4-day follow-up period after booster vaccination

End point values	Infanrix/Hib Group	Infanrix + Hiberix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	220		
Units: Subjects				
Pain	26	26		
Redness	16	8		
Swelling	9	1		
Drowsiness	26	20		
Fever	73	93		
Irritability	43	46		
Loss of appetite	40	39		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting unsolicited adverse events (AE)

End point title	Number of subjects reporting unsolicited adverse events (AE)
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End point description:

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

End point type	Secondary
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End point timeframe:

During the 31-day follow-up period after booster vaccination

End point values	Infanrix/Hib Group	Infanrix + Hiberix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	223		
Units: Subjects				
Any AEs	66	56		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Serious Adverse Events (SAE)

End point title	Number of Subjects Reporting Serious Adverse Events (SAE)
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End point description:

An SAE is any untoward medical occurrence that: results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect in the offspring of a study subject, or may evolve into one of the outcomes listed above.

End point type	Secondary
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End point timeframe:

During the 31-day follow-up period after booster vaccination

End point values	Infanrix/Hib Group	Infanrix + Hiberix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	223		
Units: Subjects				
Any SAEs	1	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The occurrence of reported AEs (all/related) was not available and is encoded as equal to the number of subjects affected.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.1
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Reporting groups

Reporting group title	Infanrix/Hib Single Injection Group
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Reporting group description:

Subjects who had received Infanrix/Hib vaccine administered in one injection in the primary study received a booster dose of the same vaccine in this study.

Reporting group title	Infanrix + Hiberix Group
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Reporting group description:

Subjects who had received Infanrix (DTPa) and Hiberix (Hib) vaccines, co-administered at separate injection sites in the primary study received a booster dose of the same vaccines in this study.

Serious adverse events	Infanrix/Hib Single Injection Group	Infanrix + Hiberix Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 244 (0.41%)	3 / 223 (1.35%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 244 (0.41%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 244 (0.00%)	1 / 223 (0.45%)	
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	Infanrix/Hib Single Injection Group	Infanrix + Hiberix Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	244 / 244 (100.00%)	223 / 223 (100.00%)	
General disorders and administration site conditions			
Pain at injection site			
alternative assessment type: Systematic			
subjects affected / exposed	26 / 244 (10.66%)	26 / 223 (11.66%)	
occurrences (all)	26	26	
Redness at injection site			
alternative assessment type: Systematic			
subjects affected / exposed	16 / 244 (6.56%)	8 / 223 (3.59%)	
occurrences (all)	16	8	
Drowsiness			
alternative assessment type: Systematic			
subjects affected / exposed	26 / 244 (10.66%)	20 / 223 (8.97%)	
occurrences (all)	26	20	
Fever			
alternative assessment type: Systematic			
subjects affected / exposed	73 / 244 (29.92%)	93 / 223 (41.70%)	
occurrences (all)	73	93	
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	43 / 244 (17.62%)	46 / 223 (20.63%)	
occurrences (all)	43	46	
Loss of appetite			
alternative assessment type: Systematic			
subjects affected / exposed	40 / 244 (16.39%)	39 / 223 (17.49%)	
occurrences (all)	40	39	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	39 / 244 (15.98%)	24 / 223 (10.76%)	
occurrences (all)	39	24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported