

**Clinical trial results:**

**A phase II, observer-blind, randomized study to evaluate the immunogenicity, safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals' combined DSSITGDPa-HBV-IPV/Hib vaccine containing diphtheria toxoid from the Statens Serum Institute (SSI) of Denmark and tetanus toxoid from GSK Biologicals' Kft [GD], compared to the currently licensed GSK Biologicals' DTPa-HBV-IPV/Hib vaccine (Infanrix hexa) when administered to healthy infants at 2, 3 and 4 months of age.**

**Summary**

EudraCT number	2006-000554-46
Trial protocol	FI
Global end of trial date	31 May 2007

**Results information**

Result version number	v2 (current)
This version publication date	31 July 2016
First version publication date	03 June 2015
Version creation reason	• Correction of full data set Data (typos) were corrected.

**Trial information****Trial identification**

Sponsor protocol code	106786
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00376779
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, 004 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 004 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	07 August 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2007
Global end of trial reached?	Yes
Global end of trial date	31 May 2007
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate that the immunogenicity of the DSSITGDPa-HBV-IPV/Hib vaccine (preservative-free formulation) in terms of antibody response to all vaccine antigens is non-inferior to that of the DTPa-HBV-IPV/Hib vaccine, one month after a three-dose primary vaccination course.

Protection of trial subjects:

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	12 October 2006
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	Finland: 455
Worldwide total number of subjects	455
EEA total number of subjects	455

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)	455
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 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Preservative-Free Formulation Group

Arm description:

Subjects received the preservative-free (PF) formulation of DSSITGDPa-HBV-IPV/Hib.

Arm type	Experimental
Investigational medicinal product name	DSSITGDPa-HBV-IPV/Hib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

The vaccine was administered intramuscularly into the anterolateral quadrant of the right thigh according to a 3-dose vaccination schedule at 2, 3 and 4 months of age.

<b>Arm title</b>	Preservative-Containing Formulation Group
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Arm description:

Subjects received the preservative-containing (PC) formulation of DSSITGDPa-HBV-IPV/Hib.

Arm type	Experimental
Investigational medicinal product name	DSSITGDPa-HBV-IPV/Hib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

The vaccine was administered intramuscularly into the anterolateral quadrant of the right thigh according to a 3-dose vaccination schedule at 2, 3 and 4 months of age.

<b>Arm title</b>	Infanrix-hexa Group
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Arm description:

Subjects received the licensed formulation of DTPa-HBV-IPV/Hib.

Arm type	Experimental
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Investigational medicinal product name	Infanrix hexa
Investigational medicinal product code	
Other name	DTPa-HBV-IPV/Hib
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

The vaccine was administered intramuscularly into the anterolateral quadrant of the right thigh according to a 3-dose vaccination schedule at 2, 3 and 4 months of age.

Number of subjects in period 1	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group
Started	153	150	152
Completed	151	148	152
Not completed	2	2	0
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	1	1	-
Migrated/moved from study area	1	-	-

## Baseline characteristics

### Reporting groups

Reporting group title	Preservative-Free Formulation Group
Reporting group description:	
Subjects received the preservative-free (PF) formulation of DSSITGDPa-HBV-IPV/Hib.	
Reporting group title	Preservative-Containing Formulation Group
Reporting group description:	
Subjects received the preservative-containing (PC) formulation of DSSITGDPa-HBV-IPV/Hib.	
Reporting group title	Infanrix-hexa Group
Reporting group description:	
Subjects received the licensed formulation of DTPa-HBV-IPV/Hib.	

Reporting group values	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group
Number of subjects	153	150	152
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: weeks			
arithmetic mean	9.9	10	10.1
standard deviation	± 1.51	± 1.45	± 1.35
Gender categorical Units: Subjects			
Female	68	75	64
Male	85	75	88

Reporting group values	Total		
Number of subjects	455		
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)	0 0 0 0 0 0		

Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: weeks			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	207		
Male	248		

## End points

### End points reporting groups

Reporting group title	Preservative-Free Formulation Group
Reporting group description: Subjects received the preservative-free (PF) formulation of DSSITGDPa-HBV-IPV/Hib.	
Reporting group title	Preservative-Containing Formulation Group
Reporting group description: Subjects received the preservative-containing (PC) formulation of DSSITGDPa-HBV-IPV/Hib.	
Reporting group title	Infanrix-hexa Group
Reporting group description: Subjects received the licensed formulation of DTPa-HBV-IPV/Hib.	

### Primary: Number of subjects with anti-diphtheria (Anti-D) [by Vero-cell neutralization assay] antibody concentrations equal to or above ( $\geq$ ) 0.016 international units per milliliter (IU/mL)

End point title	Number of subjects with anti-diphtheria (Anti-D) [by Vero-cell neutralization assay] antibody concentrations equal to or above ( $\geq$ ) 0.016 international units per milliliter (IU/mL)
End point description:	
End point type	Primary
End point timeframe: One month after the third dose of vaccine (POST)	

End point values	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	138	134	145	
Units: Subjects				
Anti-diphtheria, POST	135	133	145	

### Statistical analyses

Statistical analysis title	Immune response to anti-D antibodies (Vero-assay)
Statistical analysis description: To demonstrate that the immunogenicity of the GSK Biologicals' DSSITGDPa-HBV-IPV/Hib vaccine (preservative-free formulation) in terms of antibody response to anti-diphtheria antigens is non-inferior to that of the <i>Infanrix hexa</i> <sup>TM</sup> vaccine, one month after a three-dose primary vaccination course.	
Comparison groups	Preservative-Free Formulation Group v <i>Infanrix-hexa</i> Group



Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[1]</sup>
Parameter estimate	Difference in seroprotection rate
Point estimate	2.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	6.2

Notes:

[1] - For diphtheria (Vero-cell neutralization assay): the upper limit of the standardized asymptotic 95% confidence interval (CI) on the group difference [Infanrix-hexa Group minus Preservative-Free Formulation Group] in the percentage of seroprotected subjects is  $\leq 10\%$ .

### **Primary: Number of subjects with anti-tetanus toxoids (Anti-TT) antibody concentrations $\geq 0.1$ IU/mL**

End point title	Number of subjects with anti-tetanus toxoids (Anti-TT) antibody concentrations $\geq 0.1$ IU/mL
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End point description:

End point type	Primary
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End point timeframe:

One month after the third dose of vaccine (POST)

<b>End point values</b>	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	138	134	146	
Units: Subjects				
Anti-tetanus, POST	138	134	146	

### **Statistical analyses**

<b>Statistical analysis title</b>	Immune response to anti-T antibodies
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Statistical analysis description:

To demonstrate that the immunogenicity of the GSK Biologicals' DSSITGDPa-HBV-IPV/Hib vaccine (preservative-free formulation) in terms of antibody response to anti-tetanus antigens is non-inferior to that of the *Infanrix hexa*<sup>TM</sup> vaccine, one month after a three-dose primary vaccination course.

Comparison groups	Infanrix-hexa Group v Preservative-Free Formulation Group
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[2]</sup>
Parameter estimate	Difference in seroprotection rate
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.56
upper limit	2.71

Notes:

[2] - For tetanus: the upper limit of the standardized asymptotic 95% confidence interval (CI) on the group difference [Infanrix-hexa Group minus Preservative-Free Formulation Group] in the percentage of seroprotected subjects is  $\leq 10\%$ .

**Primary: Number of subjects with anti-hepatitis B surface antigen (anti-HBs) antibody concentrations  $\geq 10.0$  mili-international units per millilitre (mIU/mL)**

End point title	Number of subjects with anti-hepatitis B surface antigen (anti-HBs) antibody concentrations $\geq 10.0$ mili-international units per millilitre (mIU/mL)
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End point description:

End point type	Primary
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End point timeframe:

One month after the third dose of vaccine (POST)

End point values	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	135	131	143	
Units: Subjects				
Anti-HBs, POST	125	125	141	

**Statistical analyses**

<b>Statistical analysis title</b>	Immune response to anti-HBs antibodies
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Statistical analysis description:

To demonstrate that the immunogenicity of the GSK Biologicals' DSSITGDPa-HBV-IPV/Hib vaccine (preservative-free formulation) in terms of antibody response to anti-Hepatitis B is non-inferior to that of the *Infanrix hexa*<sup>TM</sup> vaccine, one month after a three-dose primary vaccination course.

Comparison groups	Preservative-Free Formulation Group v <i>Infanrix-hexa</i> Group
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[3]</sup>
Parameter estimate	Difference in seroprotection rate
Point estimate	6.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.42
upper limit	11.87

Notes:

[3] - For Hepatitis B: the upper limit of the standardized asymptotic 95% confidence interval (CI) on the group difference [Infanrix-hexa Group minus Preservative-Free Formulation Group] in the percentage of seroprotected subjects is  $\leq 10\%$ .

### Primary: Number of subjects with anti-polio type 1, 2 and 3 antibody titers $\geq 8$

End point title	Number of subjects with anti-polio type 1, 2 and 3 antibody titers $\geq 8$
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End point description:

End point type	Primary
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End point timeframe:

One month after the third dose of vaccine (POST)

End point values	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131	123	130	
Units: Subjects				
Anti-Polio 1, POST [N=128;123;121]	119	114	117	
Anti-Polio 2, POST [N=121;119;130]	90	95	99	
Anti-Polio 3, POST [N=131;122;128]	126	116	125	

### Statistical analyses

Statistical analysis title	Immune response to anti-Polio 1 antibodies
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Statistical analysis description:

To demonstrate that the immunogenicity of the GSK Biologicals' DSSITGDPa-HBV-IPV/Hib vaccine (preservative-free formulation) in terms of antibody response to anti-Polio type 1 antigens is non-inferior to that of the *Infanrix hexa*<sup>TM</sup> vaccine, one month after a three-dose primary vaccination course.

Comparison groups	Infanrix-hexa Group v Preservative-Free Formulation Group
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[4]</sup>
Parameter estimate	Difference in seroprotection rate
Point estimate	3.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.06
upper limit	9.97

Notes:

[4] - For poliovirus type 1: the upper limit of the standardized asymptotic 95% confidence interval (CI) on the group difference [Infanrix-hexa Group minus Preservative-Free Formulation Group] in the percentage of seroprotected subjects is  $\leq 10\%$ .

Statistical analysis title	Immune response to anti-Polio 2 antibodies
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**Statistical analysis description:**

To demonstrate that the immunogenicity of the GSK Biologicals' DSSITGDPa-HBV-IPV/Hib vaccine (preservative-free formulation) in terms of antibody response to anti-Polio type 2 antigens is non-inferior to that of the Infanrix hexa™ vaccine, one month after a three-dose primary vaccination course.

Comparison groups	Preservative-Free Formulation Group v Infanrix-hexa Group
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[5]</sup>
Parameter estimate	Difference in seroprotection rate
Point estimate	1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.89
upper limit	12.52

**Notes:**

[5] - For poliovirus type 2: the upper limit of the standardized asymptotic 95% confidence interval (CI) on the group difference [Infanrix-hexa Group minus Preservative-Free Formulation Group] in the percentage of seroprotected subjects is  $\leq 10\%$ .

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<b>Statistical analysis title</b>	Immune response to anti-Polio 3 antibodies
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**Statistical analysis description:**

To demonstrate that the immunogenicity of the GSK Biologicals' DSSITGDPa-HBV-IPV/Hib vaccine (preservative-free formulation) in terms of antibody response to anti-Polio type 3 antigens is non-inferior to that of the Infanrix hexa™ vaccine, one month after a three-dose primary vaccination course.

Comparison groups	Infanrix-hexa Group v Preservative-Free Formulation Group
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[6]</sup>
Parameter estimate	Difference in seroprotection rate
Point estimate	1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.32
upper limit	6.59

**Notes:**

[6] - For poliovirus type 3: the upper limit of the standardized asymptotic 95% confidence interval (CI) on the group difference [Infanrix-hexa Group minus Preservative-Free Formulation Group] in the percentage of seroprotected subjects is  $\leq 10\%$ .

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**Primary: Number of subjects with anti-polyribosylribitol phosphate (Anti-PRP) concentrations equal to or above cut-off value of 0.15 µg/mL**

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End point title	Number of subjects with anti-polyribosylribitol phosphate (Anti-PRP) concentrations equal to or above cut-off value of 0.15 µg/mL
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**End point description:**

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End point type	Primary
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End point timeframe:

One month after the third dose of vaccine (POST)

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End point values	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	138	134	145	
Units: Subjects				
Anti-PRP, POST	132	129	138	

## Statistical analyses

Statistical analysis title	Immune response to anti-PRP antibodies
Statistical analysis description:	
To demonstrate that the immunogenicity of the GSK Biologicals' DSSITGDPa-HBV-IPV/Hib vaccine (preservative-free formulation) in terms of antibody response to anti-PRP antigens is non-inferior to that of the <i>Infanrix hexa</i> <sup>TM</sup> vaccine, one month after a three-dose primary vaccination course.	
Comparison groups	Preservative-Free Formulation Group v <i>Infanrix-hexa</i> Group
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[7]</sup>
Parameter estimate	Difference in seroprotection rate
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.86
upper limit	4.94

Notes:

[7] - For polyribosyl-ribitol phosphate: the upper limit of the standardized asymptotic 95% confidence interval (CI) on the group difference [*Infanrix-hexa* Group minus Preservative-Free Formulation Group] in the percentage of seroprotected subjects is  $\leq 10\%$ .

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

End point title	Anti-pertussis toxoid (anti-PT), anti-filamentous haemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) antibody concentrations
End point description:	
End point type	Primary
End point timeframe:	
One month after the third dose of vaccine (POST)	

End point values	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	138	134	146	
Units: EL.U/ml				

geometric mean (confidence interval 95%)				
Anti-PT, POST [N=138;134;146]	59.2 (54.2 to 64.5)	49.6 (44.9 to 54.8)	67.4 (61.9 to 73.3)	
Anti-FHA, POST [N=138;134;146]	135 (120.7 to 151.1)	137.5 (122.8 to 154)	200.3 (181.1 to 221.5)	
Anti-PRN, POST [N=138;134;146]	68.6 (59.8 to 78.6)	75.3 (64.6 to 87.7)	119.9 (105.5 to 136.2)	

## Statistical analyses

<b>Statistical analysis title</b>	Immune response to anti-PT antigens
Statistical analysis description:	
To demonstrate that the immunogenicity of the GSK Biologicals' DSSITGDPa-HBV-IPV/Hib vaccine (preservative-free formulation) in terms of antibody response to anti-pertussis toxoid antigens is noninferior to that of the Infanrix hexa™ vaccine, one month after a three-dose primary vaccination course.	
Comparison groups	Preservative-Free Formulation Group v Infanrix-hexa Group
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[8]</sup>
Method	ANCOVA
Parameter estimate	GMC ratio
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.29

Notes:

[8] - For pertussis toxoids: the upper limit of the 95% CI on the ratio of geometric mean concentrations (GMCs) of antibodies [Infanrix-hexa Group divided by Preservative-Free Formulation Group] is  $\leq 1.5$ .

<b>Statistical analysis title</b>	Immune response to anti-FHA antigens
Statistical analysis description:	
To demonstrate that the immunogenicity of the GSK Biologicals' DSSITGDPa-HBV-IPV/Hib vaccine (preservative-free formulation) in terms of antibody response to anti-filamentous hemagglutinin antigens is non-inferior to that of the Infanrix hexa™ vaccine, one month after a three-dose primary vaccination course.	
Comparison groups	Preservative-Free Formulation Group v Infanrix-hexa Group
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[9]</sup>
Method	ANCOVA
Parameter estimate	GMC ratio
Point estimate	1.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.26
upper limit	1.67

Notes:

[9] - For filamentous hemagglutinin: the upper limit of the 95% CI on the ratio of geometric mean concentrations (GMCs) of antibodies [Infanrix-hexa Group divided by Preservative-Free Formulation Group] is  $\leq 1.5$ .

<b>Statistical analysis title</b>	Immune response to anti-PRN antigens
Statistical analysis description:	
To demonstrate that the immunogenicity of the GSK Biologicals' DSSITGDPa-HBV-IPV/Hib vaccine (preservative-free formulation) in terms of antibody response to anti-pertactin antigens is non-inferior to that of the <i>Infanrix hexa</i> <sup>TM</sup> vaccine, one month after a three-dose primary vaccination course.	
Comparison groups	Preservative-Free Formulation Group v <i>Infanrix-hexa</i> Group
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[10]</sup>
Method	ANCOVA
Parameter estimate	GMC ratio
Point estimate	1.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	1.95

Notes:

[10] - For pertactin: the upper limit of the 95% CI on the ratio of geometric mean concentrations (GMCs) of antibodies [Infanrix-hexa Group divided by Preservative-Free Formulation Group] is  $\leq 1.5$ .

### **Primary: Number of subjects with anti-diphtheria (Anti-DT) antibody concentrations $\geq 0.1$ IU/mL**

End point title	Number of subjects with anti-diphtheria (Anti-DT) antibody concentrations $\geq 0.1$ IU/mL
End point description:	
End point type	Primary
End point timeframe:	
One month after the third dose of vaccine (POST)	

<b>End point values</b>	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	<i>Infanrix-hexa</i> Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	138	134	146	
Units: Subjects				
Anti-diphtheria, POST	136	134	146	

## **Statistical analyses**

<b>Statistical analysis title</b>	Immune response to anti-D antibodies (ELISA)
Statistical analysis description:	
To demonstrate that the immunogenicity of the GSK Biologicals' DSSITGDPa-HBV-IPV/Hib vaccine (preservative-free formulation) in terms of antibody response to anti-diphtheria antigens is non-inferior to that of the Infanrix hexa™ vaccine, one month after a three-dose primary vaccination course.	
Comparison groups	Preservative-Free Formulation Group v Infanrix-hexa Group
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[11]</sup>
Parameter estimate	Difference in seroprotection rate
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.13
upper limit	5.13

Notes:

[11] - For diphtheria (ELISA assay): the upper limit of the standardized asymptotic 95% confidence interval (CI) on the group difference [Infanrix-hexa Group minus Preservative-Free Formulation Group] in the percentage of seroprotected subjects is  $\leq 10\%$ .

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

End point title	Anti-pertussis toxoid (anti-PT), anti-filamentous haemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) antibody concentrations <sup>[12]</sup>
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End point description:

End point type	Primary
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End point timeframe:

Before the first dose of the vaccine (PRE)

Notes:

[12] - 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.

<b>End point values</b>	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	140	139	145	
Units: EL.U/ml				
geometric mean (confidence interval 95%)				
Anti-PT, PRE [N=140;139;145]	3.4 (3 to 3.8)	3.7 (3.3 to 4.2)	3.4 (3.1 to 3.8)	
Anti-FHA, PRE [N=138;139;143]	11.2 (9.3 to 13.4)	8.8 (7.3 to 10.6)	10 (8.5 to 11.8)	
Anti-PRN, PRE [N=140;139;145]	5.8 (4.9 to 7)	5.8 (4.9 to 7)	4.9 (4.2 to 5.7)	

## **Statistical analyses**



No statistical analyses for this end point

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**Secondary: Number of subjects with vaccine response to anti-pertussis toxoid (anti-PT), anti-filamentous haemagglutinin (anti-FHA) and anti-pertactin (anti-PRN)**

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End point title	Number of subjects with vaccine response to anti-pertussis toxoid (anti-PT), anti-filamentous haemagglutinin (anti-FHA) and anti-pertactin (anti-PRN)
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End point description:

Vaccine response defined as appearance of antibodies in subjects who were initially seronegative (i.e. with concentrations < cut-off value) or at least maintenance of pre-vaccination antibody concentrations in subjects who were initially seropositive (i.e. with concentrations ≥ cut-off value), taking into consideration the decreasing maternal antibodies.

End point type	Secondary
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End point timeframe:

One month after the third dose of vaccine (POST)

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End point values	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	134	131	142	
Units: Subjects				
Anti-PT, POST [N=134;131;142]	132	127	141	
Anti-FHA, POST [N=133;131;140]	126	124	139	
Anti-PRN, POST [N=134;131;142]	120	121	137	

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Anti-diphtheria (Anti-DT) and anti-tetanus toxoids (Anti-TT) antibody concentrations**

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End point title	Anti-diphtheria (Anti-DT) and anti-tetanus toxoids (Anti-TT) antibody concentrations
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End point description:

End point type	Secondary
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End point timeframe:

Before the first dose (PRE) and one month after the third dose of the vaccine (POST)

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End point values	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	140	139	146	
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-diphtheria, PRE [N=140;139;145]	0.174 (0.144 to 0.21)	0.227 (0.184 to 0.282)	0.183 (0.148 to 0.226)	
Anti-diphtheria, POST [N=138;134;146]	0.51 (0.441 to 0.59)	0.513 (0.445 to 0.592)	0.75 (0.658 to 0.854)	
Anti-tetanus, PRE [N=140;139;145]	0.654 (0.562 to 0.76)	0.71 (0.606 to 0.833)	0.708 (0.627 to 0.8)	
Anti-tetanus, POST [N=138;134;146]	1.423 (1.28 to 1.582)	1.438 (1.296 to 1.596)	1.758 (1.591 to 1.941)	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Anti-HBs antibody concentrations

End point title	Anti-HBs antibody concentrations
End point description:	
End point type	Secondary
End point timeframe:	
One month after the third dose of vaccine (POST)	

End point values	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	135	131	143	
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-HBs, POST	166.1 (131.6 to 209.5)	173.4 (140.3 to 214.3)	299 (254.1 to 351.8)	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Anti-polio type 1, 2 and 3 antibody titers

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

End point type	Secondary
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End point timeframe:

One month after the third dose of vaccine (POST)

End point values	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131	123	130	
Units: Titers				
geometric mean (confidence interval 95%)				
Anti-Polio 1, POST [N=128;123;121]	36.8 (29.8 to 45.4)	41.8 (33.5 to 52.1)	74.6 (57.5 to 96.7)	
Anti-Polio 2, POST [N=121;119;130]	21.5 (16.4 to 28.1)	16.9 (13.5 to 21.1)	22.4 (17.6 to 28.5)	
Anti-Polio 3, POST [N=131;122;128]	51.4 (41.4 to 63.9)	67 (52.1 to 86.1)	113.9 (85.6 to 151.5)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Anti-PRP concentrations

End point title	Anti-PRP concentrations
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End point description:

End point type	Secondary
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End point timeframe:

One month after the third dose of vaccine (POST)

End point values	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	138	134	145	
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-PRP, POST [N=138;134;145]	1.174 (0.961 to 1.435)	1.098 (0.894 to 1.349)	1.661 (1.326 to 2.081)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with solicited local symptoms

End point title	Number of subjects with solicited local symptoms
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End point description:

End point type	Secondary
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End point timeframe:

Within 8 days (Day 0-Day 7) after each vaccine dose

End point values	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	150	152	
Units: Subjects				
Any Pain Dose 1 [N=153;150;152]	55	38	48	
Any Redness Dose 1 [N=153;150;152]	41	33	37	
Any Swelling Dose 1 [N=153;150;152]	36	28	32	
Any Pain Dose 2 [N=152;149;152]	34	27	35	
Any Redness Dose 2 [N=152;149;152]	46	66	73	
Any Swelling Dose 2 [N=152;149;152]	33	36	46	
Any Pain Dose 3 [N=151;148;152]	17	16	24	
Any Redness Dose 3 [N=151;148;152]	49	53	67	
Any Swelling Dose 3 [N=151;148;152]	32	31	44	
Any Pain Across doses [N=153;150;152]	73	52	65	
Any Redness Across doses [N=153;150;152]	81	89	97	
Any Swelling Across doses [N=153;150;152]	62	65	75	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with solicited general symptoms

End point title	Number of subjects with solicited general symptoms
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End point description:

End point type	Secondary
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End point timeframe:

Within 8 days (Day 0-Day 7) after each vaccine dose

End point values	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	150	152	
Units: Subjects				
Any Drowsiness Dose 1 [N=153;150;152]	88	82	85	
Any Fever Dose 1 [N=153;150;152]	29	30	24	
Any Irritability Dose 1 [N=153;150;152]	114	102	112	
Any Loss of appetite Dose 1 [N=153;150;152]	45	32	32	
Any Drowsiness Dose 2 [N=152;149;152]	55	55	63	
Any Fever Dose 2 [N=152;149;152]	29	17	34	
Any Irritability Dose 2 [N=152;149;152]	87	85	99	
Any Loss of appetite Dose 2 [N=152;149;152]	28	32	19	
Any Drowsiness Dose 3 [N=151;148;152]	47	44	47	
Any Fever Dose 3 [N=151;148;152]	24	17	36	
Any Irritability Dose 3 [N=151;148;152]	74	68	82	
Any Loss of appetite Dose 3 [N=151;148;152]	28	25	20	
Any Drowsiness Across doses [N=153;150;152]	111	105	103	
Any Fever Across doses [N=153;150;152]	58	51	67	
Any Irritability Across doses [N=153;150;152]	140	128	135	
Any Loss of appetite Across doses [N=153;150;152]	66	58	51	

## Statistical analyses

No statistical analyses for this end point

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

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

End point type	Secondary
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End point timeframe:

Within 31 days (Day 0-Day 30)

End point values	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	150	152	
Units: Subjects				
AEs	111	110	117	

### 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)
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End point description:

End point type	Secondary
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End point timeframe:

During the entire study period

End point values	Preservative-Free Formulation Group	Preservative-Containing Formulation Group	Infanrix-hexa Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	150	152	
Units: Subjects				
SAEs	2	5	5	

### 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	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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### Reporting groups

Reporting group title	Preservative-Free Formulation Group
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Reporting group description: -

Reporting group title	Infanrix-hexa Group
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Reporting group description: -

Reporting group title	Preservative-Containing Formulation Group
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Reporting group description: -

<b>Serious adverse events</b>	Preservative-Free Formulation Group	Infanrix-hexa Group	Preservative-Containing Formulation Group
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 153 (1.31%)	5 / 152 (3.29%)	5 / 150 (3.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 153 (0.00%)	0 / 152 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 153 (0.00%)	0 / 152 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 153 (0.00%)	0 / 152 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	0 / 153 (0.00%)	1 / 152 (0.66%)	0 / 150 (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
Psychiatric disorders			
Listless			
subjects affected / exposed	0 / 153 (0.00%)	0 / 152 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Laryngitis			
subjects affected / exposed	1 / 153 (0.65%)	1 / 152 (0.66%)	0 / 150 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 153 (0.00%)	1 / 152 (0.66%)	0 / 150 (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
Gastroenteritis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 152 (0.00%)	0 / 150 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 153 (0.00%)	1 / 152 (0.66%)	0 / 150 (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
Pyelonephritis			
subjects affected / exposed	0 / 153 (0.00%)	1 / 152 (0.66%)	0 / 150 (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
Pyelonephritis acute			



subjects affected / exposed	0 / 153 (0.00%)	0 / 152 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 153 (0.00%)	0 / 152 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 153 (0.00%)	0 / 152 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

<b>Non-serious adverse events</b>	Preservative-Free Formulation Group	Infanrix-hexa Group	Preservative-Containing Formulation Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	111 / 153 (72.55%)	117 / 152 (76.97%)	110 / 150 (73.33%)
General disorders and administration site conditions			
Injection site induration			
subjects affected / exposed	10 / 153 (6.54%)	19 / 152 (12.50%)	18 / 150 (12.00%)
occurrences (all)	10	19	18
Pyrexia			
subjects affected / exposed	15 / 153 (9.80%)	11 / 152 (7.24%)	18 / 150 (12.00%)
occurrences (all)	15	11	18
Eye disorders			
Conjunctivitis			
subjects affected / exposed	15 / 153 (9.80%)	9 / 152 (5.92%)	16 / 150 (10.67%)
occurrences (all)	15	9	16
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 153 (7.84%)	21 / 152 (13.82%)	6 / 150 (4.00%)
occurrences (all)	12	21	6
Constipation			

subjects affected / exposed occurrences (all)	5 / 153 (3.27%) 5	4 / 152 (2.63%) 4	11 / 150 (7.33%) 11
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	8 / 153 (5.23%) 8	9 / 152 (5.92%) 9	13 / 150 (8.67%) 13
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	5 / 153 (3.27%) 5	10 / 152 (6.58%) 10	9 / 150 (6.00%) 9
Infections and infestations Rhinitis subjects affected / exposed occurrences (all)	28 / 153 (18.30%) 28	22 / 152 (14.47%) 22	23 / 150 (15.33%) 23
Upper respiratory tract infection subjects affected / exposed occurrences (all)	35 / 153 (22.88%) 35	22 / 152 (14.47%) 22	16 / 150 (10.67%) 16
Otitis media subjects affected / exposed occurrences (all)	6 / 153 (3.92%) 6	13 / 152 (8.55%) 13	12 / 150 (8.00%) 12

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2006	<p>Amendment 2</p> <p>GSK Biologicals is currently validating new providers of the diphtheria toxoid (Statens Serum Institute [SSI], Denmark) and of the tetanus toxoid (GSK Biologicals Korlatolt Felelossegu Tarsasag [Kft] in Gödöllő [GD], Hungary) for inclusion in DTPa based vaccines. The purpose of this study is to demonstrate that the immunogenicity of the hexavalent DSSITGDPa-HBV-IPV/Hib vaccine containing diphtheria toxoid provided by the Statens Serum Institute of Denmark (DSSI) and tetanus toxoid provided by GSK Biologicals Kft in Gödöllő (TGD) is non-inferior to the immunogenicity of the currently licensed formulation of the vaccine. The vaccine will be administered as a primary vaccination course to healthy infants at 2, 3 and 4 months of age and its safety and reactogenicity will also be assessed. Two formulations of the DSSITGDPa-HBV-IPV/Hib vaccine will be evaluated: one in which the vaccine will be manufactured according to the new preservative-free process and the other in which the vaccine will be manufactured with preservative as the currently licensed formulation.</p>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported