

**Clinical trial results:**

An open, phase IV, multicentre study to assess the long-term persistence of antibodies against hepatitis B and the immune response to a hepatitis B vaccine challenge in healthy children 7 to 9 years old, previously vaccinated with 4 doses of GlaxoSmithKline (GSK) Biologicals' DTPa-HBV-IPV/Hib vaccine or 4 doses of GSK Biologicals' HBV vaccine, in clinical trials conducted by GSK Biologicals.

Summary

EudraCT number	2006-000549-20
Trial protocol	DE
Global end of trial date	05 March 2007

Results information

Result version number	v1
This version publication date	02 May 2016
First version publication date	04 December 2014

Trial information**Trial identification**

Sponsor protocol code	106744
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00356564
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium, B-1330
Public contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	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	30 April 2007
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 March 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the anti-HBs antibody response to a challenge dose of HBV vaccine in subjects aged 7 to 9 years, previously primed and boosted with 4 doses of Infanrix hexa in the first two years of life.

Protection of trial subjects:

As with all injectable vaccines, appropriate medical treatment was always readily available in case of anaphylactic reactions following the administration of the vaccine.

For this reason, the vaccinee remained under medical supervision for 30 minutes after vaccination.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 July 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 224
Worldwide total number of subjects	224
EEA total number of subjects	224

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	224
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	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Infanrix hexa Group

Arm description:

Subjects previously vaccinated with 4 doses of Infanrix hexa™ vaccine in the first 2 years of life.

Arm type	Experimental
Investigational medicinal product name	Engerix™-B Kinder
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 dose, intramuscular use

Arm title	Engerix-B Kinder Group
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Arm description:

Subjects previously vaccinated with 4 doses of Engerix™-B Kinder vaccine co-administered with Infanrix hexa™ vaccine in the first 2 years of life.

Arm type	Active comparator
Investigational medicinal product name	Engerix™-B Kinder
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 dose, intramuscular use

Arm title	No vaccination Group
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Arm description:

Subjects in this group were enrolled even though they had no previous vaccination history.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Arm title	All subjects Group
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Arm description:

Pooled group including subjects from the other three groups.

Arm type	Merged group
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Investigational medicinal product name	Engerix™-B Kinder
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 dose, intramuscular use

Number of subjects in period 1	Infanrix hexa Group	Engerix-B Kinder Group	No vaccination Group
Started	200	11	13
Completed	200	11	13

Number of subjects in period 1	All subjects Group
Started	224
Completed	224

Baseline characteristics

Reporting groups

Reporting group title	Infanrix hexa Group
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Reporting group description:

Subjects previously vaccinated with 4 doses of Infanrix hexa™ vaccine in the first 2 years of life.

Reporting group title	Engerix-B Kinder Group
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Reporting group description:

Subjects previously vaccinated with 4 doses of Engerix™-B Kinder vaccine co-administered with Infanrix hexa™ vaccine in the first 2 years of life.

Reporting group title	No vaccination Group
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Reporting group description:

Subjects in this group were enrolled even though they had no previous vaccination history.

Reporting group title	All subjects Group
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Reporting group description:

Pooled group including subjects from the other three groups.

Reporting group values	Infanrix hexa Group	Engerix-B Kinder Group	No vaccination Group
Number of subjects	200	11	13
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
geometric mean	8	8	7.9
standard deviation	± 0.17	± 0	± 0.28
Gender categorical Units: Subjects			
Female	85	6	6
Male	115	5	7

Reporting group values	All subjects Group	Total	
Number of subjects	224	224	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years geometric mean standard deviation	 8 ± 0.32	 -	
Gender categorical Units: Subjects			
Female Male	97 127	97 127	

End points

End points reporting groups

Reporting group title	Infanrix hexa Group
Reporting group description:	Subjects previously vaccinated with 4 doses of Infanrix hexa™ vaccine in the first 2 years of life.
Reporting group title	Engerix-B Kinder Group
Reporting group description:	Subjects previously vaccinated with 4 doses of Engerix™-B Kinder vaccine co-administered with Infanrix hexa™ vaccine in the first 2 years of life.
Reporting group title	No vaccination Group
Reporting group description:	Subjects in this group were enrolled even though they had no previous vaccination history.
Reporting group title	All subjects Group
Reporting group description:	Pooled group including subjects from the other three groups.

Primary: Number of subjects with anti-HBs antibody concentrations \geq 100 mIU/mL.

End point title	Number of subjects with anti-HBs antibody concentrations \geq 100 mIU/mL. ^{[1][2]}
End point description:	The data for the Infanrix hexa Group are the primary efficacy results.
End point type	Primary
End point timeframe:	1 month after challenge dose of Engerix™-B Kinder vaccine

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 results were tabulated only for the Infanrix hexa and Engerix-B Kinder groups.

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

Justification: The results were tabulated only for the Infanrix hexa and Engerix-B Kinder groups.

End point values	Infanrix hexa Group	Engerix-B Kinder Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	9		
Units: Subjects				
Anti-Hbs 100mIU/mL	175	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-HBs antibody concentrations \geq 10 mIU/mL.

End point title	Number of subjects with anti-HBs antibody concentrations \geq 10
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End point description:

1 month after challenge dose of Engerix-B Kinder vaccine

End point type

Secondary

End point timeframe:

1 month after challenge dose of HBV vaccine

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The results were tabulated only for the Infanrix hexa and Engerix-B Kinder groups.

End point values	Infanrix hexa Group	Engerix-B Kinder Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	9		
Units: Subjects				
Anti-HBs 10 mIU/mL	184	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HBs antibody concentrations.

End point title

Anti-HBs antibody concentrations.^[4]

End point description:

Concentrations were expressed as geometric mean concentrations (GMCs) for the cut-off value of ≥ 100 mIU/mL (milli-international units per milliliter).

End point type

Secondary

End point timeframe:

1 month after challenge dose of Engerix™-B Kinder vaccine

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The results were tabulated only for the Infanrix hexa and Engerix-B Kinder groups.

End point values	Infanrix hexa Group	Engerix-B Kinder Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	9		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-HBs	4093.9 (2930.9 to 5718.3)	7698.5 (1314.4 to 45089.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-HBs antibody concentrations between set cut-off values.

End point title	Number of subjects with anti-HBs antibody concentrations between set cut-off values. ^[5]
End point description:	The cut-off values assessed for this outcome were ≥ 10 mIU/mL, ≥ 100 mIU/mL and 10 mIU/mL - 100 mIU/mL.
End point type	Secondary
End point timeframe:	Before challenge dose of Engerix™-B Kinder vaccine

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The results were tabulated only for the Infanrix hexa and Engerix-B Kinder groups.

End point values	Infanrix hexa Group	Engerix-B Kinder Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	11		
Units: Subjects				
Anti-HBs 10 mIU/mL	149	10		
Anti-HBs 10 mIU/mL - 100 mIU/mL	83	8		
Anti-HBs 100 mIU/mL	66	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HBs antibody concentrations.

End point title	Anti-HBs antibody concentrations. ^[6]
End point description:	Concentrations were expressed as GMCs for the 10 mIU/mL - 100 mIU/mL cut-off.
End point type	Secondary
End point timeframe:	Before challenge dose of Engerix™-B Kinder vaccine.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The results were tabulated only for the Infanrix hexa and Engerix-B Kinder groups.

End point values	Infanrix hexa Group	Engerix-B Kinder Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	11		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-HBs antibody concentrations	42.1 (33.4 to 53)	34.4 (13.8 to 86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroprotected subjects for anti-diphtheria (anti-D) and anti-tetanus (anti-T).

End point title	Number of seroprotected subjects for anti-diphtheria (anti-D) and anti-tetanus (anti-T). ^[7]
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End point description:

A seroprotected subject was defined as a subject with anti-D and anti-T antibody concentrations ≥ 0.1 IU/mL.

End point type	Secondary
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End point timeframe:

Before challenge dose of HBV vaccine

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The results were tabulated only for the Infanrix hexa and Engerix-B Kinder groups.

End point values	Infanrix hexa Group	Engerix-B Kinder Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	11		
Units: Subjects				
Anti-D	161	10		
Anti-T	175	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroprotected subjects for anti-polyribosyl ribitol phosphate (anti-PRP)

End point title	Number of seroprotected subjects for anti-polyribosyl ribitol phosphate (anti-PRP) ^[8]
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End point description:

A seroprotected subject was defined as a subject with anti-PRP antibody concentrations ≥ 0.15 micrograms per milliliter (g/mL) and ≥ 1 g/mL.

End point type	Secondary
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End point timeframe:

Before challenge dose of Engerix™-B Kinder vaccine

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The results were tabulated only for the Infanrix hexa and Engerix-B Kinder groups.

End point values	Infanrix hexa Group	Engerix-B Kinder Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	11		
Units: Subjects				
Anti-PRP \geq 0.15 g/mL	192	11		
Anti-PRP \geq 1 g/mL	121	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroprotected subjects for anti-poliovirus types 1, 2 and 3.

End point title	Number of seroprotected subjects for anti-poliovirus types 1, 2 and 3. ^[9]
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End point description:

A seroprotected subject was defined as a subject with anti-polio types 1, 2 and 3 antibody concentrations \geq 8.

End point type	Secondary
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End point timeframe:

Before challenge dose of Engerix™-B Kinder vaccine

Notes:

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

Justification: The results were tabulated only for the Infanrix hexa and Engerix-B Kinder groups.

End point values	Infanrix hexa Group	Engerix-B Kinder Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	11		
Units: Subjects				
Anti-polio 1 (N=176, 10)	165	8		
Anti-polio 2 (N=181,11)	169	10		
Anti-polio 3 (N=177,11)	173	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seropositive subjects for anti-pertussis toxoid (anti-PT), anti-filamentous haemagglutinin (anti-FHA) and anti-pertactin (anti-PRN).

End point title	Number of seropositive subjects for anti-pertussis toxoid (anti-PT), anti-filamentous haemagglutinin (anti-FHA) and anti-pertactin (anti-PRN). ^[10]
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End point description:

A seropositive subject was defined as a subject with anti-PT, anti-FHA and anti-PRN antibody concentrations \geq 5 EL.U/mL

End point type	Secondary
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End point timeframe:

Before challenge dose of Engerix™-B Kinder vaccine

Notes:

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

Justification: The results were tabulated only for the Infanrix hexa and Engerix-B Kinder groups.

End point values	Infanrix hexa Group	Engerix-B Kinder Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	11		
Units: Subjects				
Anti-PT (N=191,11)	73	5		
Anti-FHA (N=192, 11)	189	11		
Anti-PRN (N=193,11)	173	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-D, anti-T, anti-PT, anti-FHA, anti-PRN, anti-PRP antibody concentrations and anti-poliovirus types 1, 2 & 3 antibody titres.

End point title	Anti-D, anti-T, anti-PT, anti-FHA, anti-PRN, anti-PRP antibody concentrations and anti-poliovirus types 1, 2 & 3 antibody titres. ^[11]
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End point description:

End point type	Secondary
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End point timeframe:

Before challenge dose of HBV vaccine

Notes:

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

Justification: The results were tabulated only for the Infanrix hexa and Engerix-B Kinder groups.

End point values	Infanrix hexa Group	Engerix-B Kinder Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	11		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-D (N=193, 11)	0.452 (0.369 to 0.554)	0.447 (0.214 to 0.934)		
Anti-T (N=193,11)	1.465 (1.16 to 1.851)	1.777 (0.615 to 5.137)		
Anti-PT (N=191,11)	5.4 (4.6 to 6.4)	5.6 (2.8 to 11)		
Anti-FHA (N=192,11)	63.7 (53.8 to 75.4)	39 (18.1 to 84.3)		
Anti-PRN (N=193,11)	25.5 (20.7 to 31.3)	25.3 (10.1 to 63.3)		

Anti-polio 1 (N=176,10)	73.8 (59.1 to 92.1)	59.7 (15.4 to 232.1)		
Anti-polio 2 (N=181,11)	68.6 (55.1 to 85.4)	30 (13.5 to 66.2)		
Anti-polio 3 (N=177,11)	136.9 (108.5 to 172.7)	124.1 (40 to 385.1)		
Anti-PRP 3 (N=193,11)	1.584 (1.33 to 1.886)	2.225 (1.229 to 4.03)		

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 ^[12]
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End point description:

End point type	Secondary
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End point timeframe:

During the 4-day (Day 0-3) follow-up period after the challenge dose of HBV vaccine

Notes:

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

Justification: The numbers of subjects with SAEs were tabulated for the pooled group.

End point values	All subjects Group			
Subject group type	Reporting group			
Number of subjects analysed	224			
Units: Subjects				
Pain	52			
Redness	71			
Swelling	28			

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 ^[13]
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End point description:

End point type	Secondary
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End point timeframe:

During the 4-day (Day 0-3) follow-up period after the challenge dose of HBV vaccine

Notes:

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

Justification: The numbers of subjects with SAEs were tabulated for the pooled group.

End point values	All subjects Group			
Subject group type	Reporting group			
Number of subjects analysed	224			
Units: Subjects				
Fatigue	23			
Fever	7			
Gastrointestinal	14			
Headache	25			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with unsolicited symptoms

End point title | Number of subjects with unsolicited symptoms^[14]

End point description:

End point type | Secondary

End point timeframe:

During the 31-day (Day 0-30) follow-up period after the challenge dose of HBV vaccine

Notes:

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

Justification: The numbers of subjects with SAEs were tabulated for the pooled group.

End point values	All subjects Group			
Subject group type	Reporting group			
Number of subjects analysed	224			
Units: Subjects				
Subjects with any AEs	34			

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)^[15]

End point description:

End point type Secondary

End point timeframe:
during the entire study period

Notes:

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

Justification: The numbers of subjects with SAEs were tabulated for the pooled group.

End point values	All subjects Group			
Subject group type	Reporting group			
Number of subjects analysed	224			
Units: Subjects				
Subjects with any SAEs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroprotected subjects for anti-diphtheria

End point title Number of seroprotected subjects for anti-diphtheria^[16]

End point description:

End point type Secondary

End point timeframe:
Before challenge dose

Notes:

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

Justification: The results were tabulated only for the Infanrix hexa and Engerix-B Kinder groups.

End point values	Infanrix hexa Group	Engerix-B Kinder Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	11		
Units: Subjects				
Seroprotected subjects	185	11		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited symptoms: 4 - day follow-up period after vaccination (Day 0 - Day 3); Unsolicited AEs: 31 - day follow-up period after vaccination (Day 0 - Day 30); SAEs: during the entire study period.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	9.0
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Reporting groups

Reporting group title	All Subjects Group
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Reporting group description: -

Serious adverse events	All Subjects Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 224 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	All Subjects Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 224 (31.70%)		
General disorders and administration site conditions			
Pain			
alternative assessment type: Systematic			
subjects affected / exposed	52 / 224 (23.21%)		
occurrences (all)	52		
Redness			
alternative assessment type: Systematic			
subjects affected / exposed	71 / 224 (31.70%)		
occurrences (all)	71		
Swelling			
alternative assessment type: Systematic			

subjects affected / exposed	28 / 224 (12.50%)		
occurrences (all)	28		
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	23 / 224 (10.27%)		
occurrences (all)	23		
Gastrointestinal			
alternative assessment type: Systematic			
subjects affected / exposed	14 / 224 (6.25%)		
occurrences (all)	14		
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	25 / 224 (11.16%)		
occurrences (all)	25		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2006	This amendment was prepared to take advantage of higher enrolment capacity than envisaged earlier and increase the sample size of the DTPa-HBV-IPV/Hib group. The number of subjects to be enrolled in that group is increased from 100 to at least 200, which results in increased power of the study to define the percentage of children showing boostability of the HBV response.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported