Clinical trial results:
A Phase III Observer blind Single-Coordinating Center Pediatric Study in China Comparing a Booster Dose of Vaxem™ Hib to HIBERIX® When Given as Part of a Local Dosing Regimen in Infants

Summary

EudraCT number	2014-005135-13
Trial protocol	Outside EU/EEA
Global end of trial date	21 December 2010

Results information

Result version number	v1 (current)
This version publication date	30 May 2016
First version publication date	09 May 2015

Trial information

Trial identification

Sponsor protocol code	V37_07E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01226953
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics
Sponsor organisation address	Via Fiorentina, 1, Siena, Italy, 53100
Public contact	Posting Director, Novartis Vaccines and Diagnostics, RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccines and Diagnostics, RegistryContactVaccinesUS@novartis.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	27 May 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 December 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the immune response of Vaxem™ Hib booster is non-inferior to the immune response of comparator vaccine HIBERIX® booster as assessed by the percentage of subjects with anti-PRP (polyribosyl-ribitol-phosphate) antibody levels ≥1.0µg/mL 30 days after booster vaccination.

Protection of trial subjects:

This clinical study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations, including the European Directive 2001/20/EC, the US CFR Title 21, Novartis codes on the protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 October 2010
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: 660
Worldwide total number of subjects	660
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)	660
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:

Subjects were recruited from 1 site in China.

Pre-assignment

Screening details:

All enrolled subjects were included in the trial.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	VaxemHib

Arm description:

Subjects who received the VaxemHib vaccine in the parent study and received one booster dose of the same vaccine in this study.

Arm type	Experimental
Investigational medicinal product name	Haemophilus influenzae type b conjugate vaccine (CRM197 Conjugate)
Investigational medicinal product code	
Other name	VaxemHib
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

A single dose of 0.5 mL VaxemHib was to be administered intramuscularly into the deltoid muscle.

Arm title	HIBERIX

Arm description:

Subjects who received the HIBERIX vaccine in the parent study and received one booster dose of the same vaccine in this study.

Arm type	Active comparator
Investigational medicinal product name	Haemophilus influenzae type b Conjugate Vaccine (Tetanus Toxoid Conjugate)
Investigational medicinal product code	
Other name	HIBERIX
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

A single dose of 0.5 mL HIBERIX was to be administered intramuscularly into the deltoid muscle.

Number of subjects in period 1	VaxemHib	HIBERIX
Started	327	333
Completed	327	333

Baseline characteristics

Reporting groups	
Reporting group title	VaxemHib
Reporting group description:	
Subjects who received the VaxemHib vaccine in the parent study and received one booster dose of the same vaccine in this study.	
Reporting group title	HIBERIX
Reporting group description:	
Subjects who received the HIBERIX vaccine in the parent study and received one booster dose of the same vaccine in this study.	

Reporting group values	VaxemHib	HIBERIX	Total
Number of subjects	327	333	660
Age categorical Units: Subjects			
Age continuous Units: days arithmetic mean standard deviation	 448 ± 49.7	 446.8 ± 49	 -
Gender categorical Units: Subjects			
Female	150	161	311
Male	177	172	349

End points

End points reporting groups

Reporting group title	VaxemHib

Reporting group description:

Subjects who received the VaxemHib vaccine in the parent study and received one booster dose of the same vaccine in this study.

Reporting group title	HIBERIX

Reporting group description:

Subjects who received the HIBERIX vaccine in the parent study and received one booster dose of the same vaccine in this study.

Subject analysis set title	All Enrolled Population, Demography
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who have signed an informed consent.

Subject analysis set title	Per protocol (PP) population, Immunogenicity
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects in the Full Analysis Set (FAS)/Modified Intention-to-treat (MITT) Immunogenicity population who:
- correctly receive the vaccine, and
- provide evaluable serum samples at the relevant time points, and
- have no major protocol violation as defined prior to analysis.

A major deviation is defined as a protocol deviation that is considered to have a significant impact on the immunogenicity result of the subject.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects in the exposed population who provide post vaccination safety data.

Primary: 1. Percentage of subjects achieving an anti-PRP concentration ≥1.0 µg/mL 30 days after booster vaccination.

End point title	1. Percentage of subjects achieving an anti-PRP concentration ≥1.0 µg/mL 30 days after booster vaccination.

End point description:

The immune response of VaxemHib booster was assessed by the percentage of subjects with anti-PRP (polyribosyl-ribitol-phosphate) antibody levels ≥1.0µg/mL 30 days after booster vaccination.
Analysis was performed on the per protocol population.

End point type	Primary

End point timeframe:

30 days after booster vaccination

End point values	VaxemHib	HIBERIX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	302		
Units: Percentages Of Subjects				
number (confidence interval 95%)				
Baseline	98 (96 to 99)	98 (96 to 99)		
One month post vaccination	100 (98 to 100)	100 (99 to 100)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Non-inferiority of VaxemHib immune response following booster vaccination as compared to the immune response of comparator vaccine HIBERIX booster 30 days after vaccination.

Comparison groups	VaxemHib v HIBERIX
Number of subjects included in analysis	603
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Vaccine Group Differences
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	1

Notes:

[1] - Non-inferiority was assessed using a non-inferiority margin of -5% for the vaccine group difference in proportions of subjects achieving an anti-PRP concentration ≥1.0 µg/mL.

Secondary: 2. Percentage of subjects achieving an anti-PRP concentration ≥0.15 µg/mL 30 days after booster vaccination

End point title	2. Percentage of subjects achieving an anti-PRP concentration ≥0.15 µg/mL 30 days after booster vaccination

End point description:

The immune response of VaxemHib booster was assessed by the percentage of subjects with anti-PRP antibody levels ≥0.15 µg/mL, 30 days after booster vaccination.
Analysis was performed on the per protocol population.

End point type	Secondary

End point timeframe:

30 days after booster vaccination

End point values	VaxemHib	HIBERIX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	302		
Units: Percentages of subjects				
number (confidence interval 95%)				
Baseline	98 (96 to 99)	99 (97 to 100)		
One month post vaccination	100 (98 to 100)	100 (99 to 100)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Non-inferiority of VaxemHib immune response following booster vaccination as compared to the immune response of comparator vaccine HIBERIX booster 30 days after vaccination.

Comparison groups	HIBERIX v VaxemHib
Number of subjects included in analysis	603
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Vaccine Group Differences
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	1

Notes:

[2] - Non-inferiority was assessed using a non-inferiority margin of -5% for the vaccine group difference in proportions of subjects achieving an anti-PRP concentration ≥0.15 µg/mL.

Secondary: 3. Geometric mean of anti-PRP antibody concentration 30 days after booster vaccination

End point title	3. Geometric mean of anti-PRP antibody concentration 30 days after booster vaccination

End point description:

The immune response of VaxemHib booster was assessed by anti-PRP antibody geometric mean concentrations (GMCs), 30 days after booster vaccination.
Analysis was performed on the per protocol population.

End point type	Secondary

End point timeframe:

30 days after booster vaccination

End point values	VaxemHib	HIBERIX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	302		
Units: Ab concentrations (µg/mL)				
geometric mean (confidence interval 95%)				
Visit 1/Baseline	8.16 (7.23 to 9.2)	10 (9.05 to 12)		
Visit 2/One month post vaccination	57 (50 to 64)	68 (60 to 77)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Non-inferiority of VaxemHib immune response following booster vaccination as compared to the immune response of comparator vaccine HIBERIX booster

Comparison groups	VaxemHib v HIBERIX
Number of subjects included in analysis	603
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Vaccine Group Ratios
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1

Notes:

[3] - Non-inferiority was assessed using a non-inferiority margin of non-inferiority of 0.67 for the ratio of vaccine group anti-PRP GMCs

Secondary: 4. Numbers of subjects with reported solicited local and systemic adverse events (AEs) recorded for 7 days (day 1-7) after the vaccination.

End point title	4. Numbers of subjects with reported solicited local and systemic adverse events (AEs) recorded for 7 days (day 1-7) after the vaccination.

End point description:

The numbers of subjects with reported solicited local and systemic adverse events (AEs) were recorded for 7 days after the vaccination.
Analysis was performed on the safety population.

End point type	Secondary

End point timeframe:

day 1-7 after the vaccination

End point values	VaxemHib	HIBERIX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	327	333		
Units: Number of subjects				
Any solicited local AE	127	83		
Tenderness	51	32		
Erythema (N=325, 333)	87	56		
Induration (N=326, 333)	68	39		
Any solicited systemic AE	52	54		
Change Eat. Habits	15	15		
Sleepiness	11	14		
Unusual Crying	20	24		
Irritability	17	17		
Rash	4	1		
Fever (>= 37.5C)	32	30		
Analg. Antipyr. Med. Used	20	20		

Statistical analyses

No statistical analyses for this end point

Secondary: 5. Numbers of subjects with reported unsolicited adverse events (AEs) recorded for 7 days (day 1-7) after the vaccination.

End point title	5. Numbers of subjects with reported unsolicited adverse events (AEs) recorded for 7 days (day 1-7) after the vaccination.

End point description:

The numbers of subjects with reported unsolicited adverse events (AEs) were recorded for 7 days after the vaccination.
Analysis was performed on the safety population.

End point type	Secondary

End point timeframe:

day 1-7 after the vaccination

End point values	VaxemHib	HIBERIX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	327	333		
Units: Number of subjects				
Any unsolicited AE	69	67		
Abdominal distension	2	0		
Diarrhoea	33	26		
Dyspepsia	1	0		
Enteritis	0	1		
Mouth ulceration	0	1		
Vomiting	1	0		
Induration	1	1		
Irritability	0	2		
Pyrexia	3	2		
Bronchitis	2	2		
Nasopharyngitis	24	20		
Upper respiratory tract infection	21	23		
Thermal burn	1	0		
Crying	0	2		
Somnolence	0	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events were collected from day 1 to 30. Solicited local and systemic reactions were collected from day 1 to 7.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	VaxemHib

Reporting group description:

Subjects who received the VaxemHib vaccine in the parent study and received one booster dose of the same vaccine.

Reporting group title	HIBERIX

Reporting group description:

Subjects who received the HIBERIX vaccine in the parent study and received one booster dose of the same vaccine.

Serious adverse events	VaxemHib	HIBERIX	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 327 (0.00%)	0 / 333 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	VaxemHib	HIBERIX	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	167 / 327 (51.07%)	135 / 333 (40.54%)	
General disorders and administration site conditions			
Crying			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	20 / 327 (6.12%)	24 / 333 (7.21%)	
occurrences (all)	21	27	
Injection site erythema			
alternative dictionary used: MedDRA 17.1			
alternative assessment type: Systematic			

subjects affected / exposed	89 / 327 (27.22%)	56 / 333 (16.82%)	
occurrences (all)	89	56	
Injection site induration			
alternative dictionary used: MedDRA 17.1			
alternative assessment type: Systematic			
subjects affected / exposed	69 / 327 (21.10%)	39 / 333 (11.71%)	
occurrences (all)	69	39	
Injection site pain			
alternative dictionary used: MedDRA 17.1			
alternative assessment type: Systematic			
subjects affected / exposed	51 / 327 (15.60%)	32 / 333 (9.61%)	
occurrences (all)	52	32	
Pyrexia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	33 / 327 (10.09%)	31 / 333 (9.31%)	
occurrences (all)	37	35	
Gastrointestinal disorders			
Diarrhoea			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	33 / 327 (10.09%)	26 / 333 (7.81%)	
occurrences (all)	33	27	
Psychiatric disorders			
Irritability			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	17 / 327 (5.20%)	17 / 333 (5.11%)	
occurrences (all)	18	19	
Infections and infestations			
Nasopharyngitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	24 / 327 (7.34%)	20 / 333 (6.01%)	
occurrences (all)	24	21	
Upper respiratory tract infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	21 / 327 (6.42%)	23 / 333 (6.91%)	
occurrences (all)	21	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