Clinical trial results:
A Phase III Observer-Blind, Randomized, Controlled, Single-Coordinating Center Pediatric Study in China Comparing Vaxem Hib to HIBERIX® Using a Local Dosing Regimen in Infants

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2014-005136-33
Trial protocol	Outside EU/EEA
Global end of trial date	17 July 2010

Results information

Result version number	v2 (current)
This version publication date	16 June 2016
First version publication date	06 June 2015
Version creation reason	• Correction of full data set e-QC of the study needed because of EudraCT system glitch and updates are required.

Trial information

Trial identification

Sponsor protocol code	V37_07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01044316
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	31 May 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 July 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that 2 doses of Vaxem Hib given to children between the ages of 180 to 364 days are non-inferior to 2 doses of a comparator vaccine HIBERIX®.

Protection of trial subjects:

This clinical trial was carried out in accordance with relevant requirements of Regulation on Drug Registration and Good Clinical Practice (GCP) as well as Technical Guideline on Clinical Trial of Vaccine that were issued by the State Food and Drug Administration (SFDA), and was conducted in compliance with principles of Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 April 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: 670
Worldwide total number of subjects	670
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)	670
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	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 one dose of the VaxemHib vaccine at day 1 and day 31.

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 one dose of the HIBERIX vaccine at day 1 and day 31.

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	335	335
Completed	314	308
Not completed	21	27
Consent withdrawn by subject	21	27

Baseline characteristics

Reporting groups	
Reporting group title	VaxemHib
Reporting group description:	
Subjects who received one dose of the VaxemHib vaccine at day 1 and day 31.	
Reporting group title	HIBERIX
Reporting group description:	
Subjects who received one dose of the HIBERIX vaccine at day 1 and day 31.	

Reporting group values	VaxemHib	HIBERIX	Total
Number of subjects	335	335	670
Age categorical Units: Subjects			
Age continuous Units: days			
arithmetic mean	264.5	262.2	
standard deviation	± 49.4	± 49	-
Gender categorical Units: Subjects			
Female	153	161	314
Male	182	174	356

End points

End points reporting groups

Reporting group title	VaxemHib
Reporting group description:	
Subjects who received one dose of the VaxemHib vaccine at day 1 and day 31.	
Reporting group title	HIBERIX
Reporting group description:	
Subjects who received one dose of the HIBERIX vaccine at day 1 and day 31.	
Subject analysis set title	All Enrolled Population, Demography
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects whose parents or legal guardians had signed an informed consent.	
Subject analysis set title	Exposed Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects in the enrolled population who received vaccination.	
Subject analysis set title	Per Protocol Set (PP)
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects in the FAS population who: - correctly received the vaccine, and - provided evaluable serum samples at the relevant time points, and - had no major protocol violation as defined prior to analysis.	

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects in the exposed population who provided post-vaccination safety data.	

Primary: 1. Proportion of Subjects with Serum Anti-PRP Antibody Concentrations ≥ 0.15 µg/mL

End point title	1. Proportion of Subjects with Serum Anti-PRP Antibody Concentrations ≥ 0.15 µg/mL
End point description:	
The immunogenicity was assessed based on the percentage of subjects with anti-PRP (Polyribosyl-ribitol-phosphate capsular polysaccharide) antibody concentrations ≥ 0.15 µg/mL one month after the second vaccination. Analysis was performed on the per protocol set.	
End point type	Primary
End point timeframe:	
one month after the second vaccination	

End point values	VaxemHib	HIBERIX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	308		
Units: Percentage of subjects				
number (confidence interval 95%)				
≥ 0.15µg/mL	96.5 (93.82 to 98.24)	97.73 (95.37 to 99.08)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
The non-inferiority of VaxemHib vaccine relative to HIBERIX was considered as the difference in proportion between the two groups.	
Comparison groups	VaxemHib v HIBERIX
Number of subjects included in analysis	622
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	difference in proportions
Point estimate	-1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.86
upper limit	1.4

Notes:

[1] - Margin of non-inferiority (-5.00%)

Secondary: 2. Proportion of Subjects with Anti-PRP Antibody Concentration ≥ 1.0 µg/mL

End point title	2. Proportion of Subjects with Anti-PRP Antibody Concentration ≥ 1.0 µg/mL
End point description:	
The proportion was assessed based on the percentage of subjects with anti-PRP antibody concentrations ≥ 1.0 µg/mL one month after the second vaccination. Analysis was performed on the per protocol set.	
End point type	Secondary
End point timeframe:	
one month after the second vaccination	

End point values	VaxemHib	HIBERIX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	308		
Units: Percentage of subjects				
number (confidence interval 95%)				
≥ 1.0 µg/mL	96.5 (93.82 to 98.24)	97.73 (95.37 to 99.08)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The non-inferiority of VaxemHib vaccine relative to HIBERIX was considered as the difference in proportion between the two groups.

Comparison groups	VaxemHib v HIBERIX
Number of subjects included in analysis	622
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	difference in proportions
Point estimate	-1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.86
upper limit	1.4

Notes:

[2] - Margin of non-inferiority (-5.00%)

Secondary: 3. Geometric mean of anti-PRP antibody concentrations

End point title	3. Geometric mean of anti-PRP antibody concentrations

End point description:

The geometric mean of anti-PRP antibody concentrations one month after the second vaccination was assessed for both groups.
Analysis was performed on the per protocol set.

End point type	Secondary

End point timeframe:

one month after the second vaccination

End point values	VaxemHib	HIBERIX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	314	308		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Antibodies concentration	20.39 (17.16 to 24.24)	27.02 (23.15 to 31.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: 4. Numbers of subjects with local or systemic adverse reactions within 7 days of either vaccination.

End point title	4. Numbers of subjects with local or systemic adverse reactions within 7 days of either vaccination.

End point description:

The numbers of subjects with solicited local or systemic adverse reactions were recorded within 7 days of either vaccination.
Analysis was performed on the safety population.

End point type	Secondary

End point timeframe:

day 1-7 after either vaccination

End point values	VaxemHib	HIBERIX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	335		
Units: Number of Subjects				
Any local reaction	197	160		
Any systemic reaction	259	244		

Statistical analyses

No statistical analyses for this end point

Secondary: 5. Numbers of subjects with local or systemic adverse reactions within 7 days of first vaccination.

End point title	5. Numbers of subjects with local or systemic adverse reactions within 7 days of first vaccination.

End point description:

The numbers of subjects with local or systemic adverse reactions were recorded within 7 days of first vaccination.
Analysis was performed on the safety population.

End point type	Secondary

End point timeframe:

day 1-7 after the first vaccination

End point values	VaxemHib	HIBERIX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	335		
Units: Number of Subjects				
Any local reaction	134	107		
Erythema (1-15mm)	29	30		
Erythema (15-30mm)	61	42		
Erythema >30 mm	11	5		
Tenderness (mild)	45	36		
Tenderness (moderate)	9	5		
Induration (1-15mm)	29	24		
Induration (15-30mm)	26	25		
Induration >30 mm	7	4		

Any systemic reaction	202	191		
Fever (mild)	125	116		
Fever (moderate)	40	47		
Fever (severe)	6	2		
Rash	25	15		
Sleepiness	30	27		
Irritability	49	27		
Unusual crying	57	36		
Change in eating habits	23	16		
Other (Analgesic/antipyretic medication use)	47	42		

Statistical analyses

No statistical analyses for this end point

Secondary: 6. Numbers of subjects with local or systemic adverse reactions within 7 days of second vaccination.

End point title	6. Numbers of subjects with local or systemic adverse reactions within 7 days of second vaccination.

End point description:

The numbers of subjects with local or systemic adverse reactions were recorded within 7 days of second vaccination.
Analysis was performed on the safety population.

End point type	Secondary

End point timeframe:

day 1-7 after the second vaccination

End point values	VaxemHib	HIBERIX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	335		
Units: Number of Subjects				
Any local reaction	133	112		
Erythema (1-15mm)	16	25		
Erythema (15-30mm)	67	59		
Erythema >30 mm	35	14		
Tenderness (mild)	36	27		
Tenderness (moderate)	4	7		
Tenderness (severe)	1	0		
Induration (1-15mm)	20	23		
Induration (15-30mm)	33	21		
Induration >30 mm	7	6		
Any systemic reaction	165	154		
Fever (mild)	99	105		
Fever (moderate)	42	37		
Fever (severe)	4	0		
Rash	15	16		

Sleepiness	11	8		
Irritability	18	10		
Unusual crying	24	24		
Change in eating habits	7	8		
Other (Analgesic/antipyretic medication use)	34	40		

Statistical analyses

No statistical analyses for this end point

Secondary: 7. Numbers of subjects with unsolicited adverse reactions during the study

End point title	7. Numbers of subjects with unsolicited adverse reactions during the study

End point description:

The numbers of subjects with unsolicited adverse reactions were recorded for day 1 to day 61. Analysis was performed on the safety population.

End point type	Secondary

End point timeframe:

Day 1 – Day 61

End point values	VaxemHib	HIBERIX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	197		
Units: Number of Subjects				
Not Related Adverse Events (AEs)	199	180		
Possibly Related AEs	17	11		
Probably Related AEs	10	6		
AEs leading to withdrawal	0	0		
Seariuos Adverse Events (SAEs)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Solicited adverse events were collected within 7 days after each vaccination. Unsolicited adverse events were collected through the entire period of the study (day 1 - day 61)	
Adverse event reporting additional description:	
For reporting the Adverse Events, MedDRA version 17.1 was used.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	HIBERIX
Reporting group description:	
Subjects who received one dose of the HIBERIX vaccine at day 1 and day 31.	
Reporting group title	VaxemHib
Reporting group description:	
Subjects who received one dose of the VaxemHib vaccine at day 1 and day 31.	

Serious adverse events	HIBERIX	VaxemHib	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 323 (0.00%)	0 / 327 (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	HIBERIX	VaxemHib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	291 / 323 (90.09%)	304 / 327 (92.97%)	
Nervous system disorders			
Somnolence			
alternative dictionary used: MedDRA 17.1			
alternative assessment type: Systematic			
subjects affected / exposed	33 / 323 (10.22%)	38 / 327 (11.62%)	
occurrences (all)	39	43	
General disorders and administration site conditions			

Crying alternative dictionary used: MedDRA 17.1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	53 / 323 (16.41%) 64	71 / 327 (21.71%) 87	
Injection site erythema alternative dictionary used: MedDRA 17.1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	136 / 323 (42.11%) 176	173 / 327 (52.91%) 219	
Injection site induration alternative dictionary used: MedDRA 17.1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	82 / 323 (25.39%) 103	103 / 327 (31.50%) 122	
Injection site pain alternative dictionary used: MedDRA 17.1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	60 / 323 (18.58%) 75	78 / 327 (23.85%) 95	
Pyrexia alternative dictionary used: MedDRA 17.1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	230 / 323 (71.21%) 624	237 / 327 (72.48%) 677	
Gastrointestinal disorders Diarrhoea alternative dictionary used: MedDRA 17.1 subjects affected / exposed occurrences (all)	31 / 323 (9.60%) 34	34 / 327 (10.40%) 38	
Skin and subcutaneous tissue disorders Rash alternative dictionary used: MedDRA 17.1 alternative assessment type: Systematic			

subjects affected / exposed	32 / 323 (9.91%)	43 / 327 (13.15%)	
occurrences (all)	39	53	
Psychiatric disorders			
Eating disorder			
alternative dictionary used: MedDRA 17.1			
alternative assessment type: Systematic			
subjects affected / exposed	23 / 323 (7.12%)	27 / 327 (8.26%)	
occurrences (all)	27	36	
Irritability			
alternative dictionary used: MedDRA 17.1			
alternative assessment type: Systematic			
subjects affected / exposed	33 / 323 (10.22%)	61 / 327 (18.65%)	
occurrences (all)	43	74	
Infections and infestations			
Upper respiratory tract infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	87 / 323 (26.93%)	82 / 327 (25.08%)	
occurrences (all)	104	98	

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23964690