Clinical trial results:
A Phase III Open Label, Multi-Center Pediatric Study in China Comparing a Booster Dose of Vaxem™ Hib to HIBERIX®

Summary

EudraCT number	2014-005013-23
Trial protocol	Outside EU/EEA
Global end of trial date	14 December 2009

Results information

Result version number	v1 (current)
This version publication date	11 May 2016
First version publication date	27 May 2015

Trial information

Trial identification

Sponsor protocol code	M37P2E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01025544
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 , RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccines , 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	10 April 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 December 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that a Vaxem™ Hib booster given to children aged 12–18 months is non-inferior to the comparator vaccine HIBERIX®. Non-inferiority was assessed as the percentage of subjects with anti-Polyribosyl-Ribitol-Phosphate (PRP) antibody levels ≥ 1.0 µg/mL one month after booster vaccination (i.e. long-term seroprotection rate).

To compare safety and tolerability of the booster dose of Vaxem™ Hib with the control booster dose of HIBERIX® when given to toddlers aged 12-18 months.

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. The trial was organised by Hebei Center for Disease Control (CDC). The study protocol and relevant documents were approved upon review by the Ethics Committee (EC) of Hebei CDC on August 18, 2008, and the study was conducted by qualified scientists and medical experts; the legal guardian of each subject signed a written Informed Consent Form (ICF) before initiation of the clinical trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 September 2009
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: 846
Worldwide total number of subjects	846
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	846

months)	
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 enrolled from 2 sites 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	Not blinded

Blinding implementation details:

This was an open label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Vaxem Hib

Arm description:

Subjects who received primary vaccination with Vaxem Hib in the parent study (M37P2), received a booster dose of Vaxem Hib in this study.

Arm type	Experimental
Investigational medicinal product name	Capsular oligosaccharide of Haemophilus influenzae type b conjugated to CRM 197
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received one injection of 0.5 mL in the deltoid region.

Arm title	HIBERIX

Arm description:

Subjects who received primary vaccination with HIBERIX in the parent study (M37P2), received a booster dose of HIBERIX in this study.

Arm type	Active comparator
Investigational medicinal product name	Capsular oligosaccharide of Haemophilus influenzae type b conjugated to tetanus toxoid.
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received one injection of 0.5 mL in the deltoid region.

Number of subjects in period 1	Vaxem Hib	HIBERIX
Started	566	280
Completed	566	278
Not completed	0	2
Consent withdrawn by subject	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Vaxem Hib
Reporting group description:	
Subjects who received primary vaccination with Vaxem Hib in the parent study (M37P2), received a booster dose of Vaxem Hib in this study.	
Reporting group title	HIBERIX
Reporting group description:	
Subjects who received primary vaccination with HIBERIX in the parent study (M37P2), received a booster dose of HIBERIX in this study.	

Reporting group values	Vaxem Hib	HIBERIX	Total
Number of subjects	566	280	846
Age categorical			
Units: Subjects			
Infants and toddlers (28 days-23 months)	566	280	846
Age continuous			
Units: days			
arithmetic mean	460	456.9	
standard deviation	± 35.5	± 32.8	-
Gender categorical			
Units: Subjects			
Female	275	135	410
Male	291	145	436

End points

End points reporting groups

Reporting group title	Vaxem Hib
Reporting group description:	
Subjects who received primary vaccination with Vaxem Hib in the parent study (M37P2), received a booster dose of Vaxem Hib in this study.	
Reporting group title	HIBERIX
Reporting group description:	
Subjects who received primary vaccination with HIBERIX in the parent study (M37P2), received a booster dose of HIBERIX in this study.	
Subject analysis set title	Exposed Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects in the enrolled population who received vaccination	
Subject analysis set title	All Enrolled Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who have signed an informed consent and have been enrolled (eg, data collection).	
Subject analysis set title	Full Analysis Set (FAS-Immunogenicity)
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects in the enrolled population who actually received a study vaccination and provided at least one evaluable serum sample before or after baseline. Baseline is defined as the time immediately before vaccination.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects in the exposed population who provided safety data after baseline. Baseline is defined as the time immediately before vaccination.	
Subject analysis set title	Per Protocol Set (PPS-Immunogenicity)
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects in the FAS population who correctly received the vaccine, provided evaluable serum samples at the relevant time points (for subjects in the immunogenicity subset) and have no major protocol violation as defined prior to analysis.	

Primary: 1. Percentages of subjects achieving an anti-Polyribosil-Ribitol-Phosphate (PRP) concentration ≥ 1.0 µg/mL

End point title	1. Percentages of subjects achieving an anti-Polyribosil-Ribitol-Phosphate (PRP) concentration ≥ 1.0 µg/mL
End point description:	
Non-inferiority of immune response of Vaxem Hib when compared to HIBERIX was assessed in terms of percentages of subjects achieving an anti-PRP concentration ≥ 1.0 µg/mL approximately one month post booster vaccination. Analysis was done on the Per Protocol (PP) dataset.	
End point type	Primary
End point timeframe:	
Day 31	

End point values	Vaxem Hib	HIBERIX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	272		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-PRP ≥ 1µg/mL	100 (98.65 to 100)	100 (98.65 to 100)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Non-inferiority of immune response of Vaxem Hib when compared to HIBERIX was assessed as the between group difference in percentages of subjects achieving an anti-PRP concentration ≥ 1.0 µg/mL.

Comparison groups	HIBERIX v Vaxem Hib
Number of subjects included in analysis	543
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	t-test, 1-sided
Parameter estimate	Difference in percentages of subjects
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9999
upper limit	9999
Variability estimate	Standard error of the mean

Notes:

[1] - Success criterion: immune response of Vaxem Hib when compared to HIBERIX was to be considered non inferior if the lower two-sided 95% confidence limit of difference in the long-term protection rates of antibodies between the VaxemTM Hib group and the HIBERIX®
group is not beyond -5%
The approximation method used by the CRO in charge of the statistical analysis of the study, was not able to compute the 95% CI for the difference in proportions when values in both groups were equal to 100%.

Secondary: 2. Percentages of subjects achieving an anti- Polyribosil-Ribitol-Phosphate (PRP) concentration ≥ 0.15 µg/mL

End point title	2. Percentages of subjects achieving an anti- Polyribosil-Ribitol-Phosphate (PRP) concentration ≥ 0.15 µg/mL

End point description:

Immune response of Vaxem Hib when compared to HIBERIX was assessed in terms of percentages of subjects achieving an anti-PRP concentration ≥ 0.15 µg/mL approximately one month post booster vaccination.
Analysis was done on PP dataset.

End point type	Secondary

End point timeframe:

Day 31

End point values	Vaxem Hib	HIBERIX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	272		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-PRP ≥ 0.15 µg/mL	100 (98.65 to 100)	100 (98.65 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: 3. Anti-PRP geometric mean concentration (GMC)

End point title	3. Anti-PRP geometric mean concentration (GMC)

End point description:

Immune response of Vaxem Hib when compared to HIBERIX was assessed in terms of Anti-PRP GMC approximately one month post booster vaccination.
Analysis was done on PP dataset.

End point type	Secondary

End point timeframe:

Day 31

End point values	Vaxem Hib	HIBERIX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	272		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-PRP GMC	245.9 (219.6 to 275.5)	184.2 (162.7 to 208.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: 4. Number of subjects reporting selected indicators of reactogenicity local and/or systemic reactions.

End point title	4. Number of subjects reporting selected indicators of reactogenicity local and/or systemic reactions.

End point description:

Safety and tolerability of the booster dose of Vaxem Hib when compared with the control booster dose of HIBERIX are assessed in terms of number of subjects reporting selected indicators of reactogenicity, ie, local and systemic reactions.
Analysis was done on Safety dataset.

End point type	Secondary

End point timeframe:

From day 1 through 7 after vaccination.

End point values	Vaxem Hib	HIBERIX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	566	280		
Units: Number of subjetcs				
Any local	46	16		
Eryhtema (< 15mm)	5	4		
Erythema (15-30mm)	7	0		
Erythema (> 30mm)	1	0		
Tenderness	36	14		
Induration (< 15mm)	10	3		
Induration (15-30mm)	6	1		
Any systemic	153	60		
Rash	0	0		
Sleepiness	4	2		
Irritability	8	1		
Unusual crying	15	2		
Change in eating habits	22	7		
Fever (37.1°C-37.5°C)	109	44		
Fever (37.6°C-39.0°C)	30	10		
Fever (> 39.0°C)	0	1		
Analgesic/antipyretic medication use	34	13		

Statistical analyses

No statistical analyses for this end point

Secondary: 5. Number of subjects reporting unsolicited adverse events (AEs) and/or serious adverse events (SAEs)

End point title	5. Number of subjects reporting unsolicited adverse events (AEs) and/or serious adverse events (SAEs)

End point description:

Safety and tolerability of the booster dose of Vaxem Hib when compared with the control booster dose of HIBERIX are assessed in terms of number of subjects reporting unsolicited adverse events (AEs), vaccine-related AEs and/or serious AEs (SAEs).
Analysis was done on the Safety dataset.

End point type	Secondary

End point timeframe:

Throughout the entire study period.

End point values	Vaxem Hib	HIBERIX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	566	280		
Units: Number of subjects				
Any unsolicited AEs	122	58		
Vaccine-related AEs	6	3		
Any SAEs	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Selected indicators of reactogenicity were recorded from day 1 to 7 after vaccination; unsolicited AEs and SAEs were recorded throughout the entire study period.

Adverse event reporting additional description:

Selected indicators of reactogenicity were collected by systematic assessment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	HIBERIX

Reporting group description:

Subjects who received primary vaccination with HIBERIX in the parent study (M37P2), received a booster dose of HIBERIX in this study.

Reporting group title	Vaxem Hib

Reporting group description:

Subjects who received primary vaccination with Vaxem Hib in the parent study (M37P2), received a booster dose of Vaxem Hib in this study.

Serious adverse events	HIBERIX	Vaxem Hib	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 280 (0.00%)	0 / 566 (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	Vaxem Hib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	95 / 280 (33.93%)	225 / 566 (39.75%)	
General disorders and administration site conditions			
Injection site pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	14 / 280 (5.00%)	36 / 566 (6.36%)	
occurrences (all)	14	36	
Pyrexia			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed occurrences (all)	55 / 280 (19.64%) 64	143 / 566 (25.27%) 177	
Infections and infestations Upper respiratory tract infection alternative dictionary used: MedDRA 17.1 subjects affected / exposed occurrences (all)	40 / 280 (14.29%) 41	84 / 566 (14.84%) 87	

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