Clinical trial results:
A Phase III, Observer-Blind, Randomized, Controlled, Single Center Study To Investigate Immunogenicity And Safety Of Vaxem Hib In 13 - 59 Months Old Healthy Children In China, According To The Recommended Regimen Of 1 Dose.

Summary

EudraCT number	2014-005246-22
Trial protocol	Outside EU/EEA
Global end of trial date	30 October 2009

Results information

Result version number	v1 (current)
This version publication date	30 May 2016
First version publication date	06 June 2015

Trial information

Trial identification

Sponsor protocol code	V37_06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01125527
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics S.r.l.
Sponsor organisation address	Via Fiorentina 1, Siena, Italy, 53100
Public contact	Posting Director, Novartis Vaccines and Diagnostics S.r.l., RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccines and Diagnostics S.r.l., 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	08 April 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 October 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that Vaxem Hib given to children aged 13-59 months at study entry is non-inferior to comparator vaccine HIBERIX with regard to percentage of subjects with antibody levels of ≥ 0.15μg/mL one month after vaccination as measured by anti- PRP ELISA.

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:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	23 August 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: 729
Worldwide total number of subjects	729
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)	287
Children (2-11 years)	442
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 at 1 center in China.

Pre-assignment

Screening details:

All subjects enrolled 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

Blinding implementation details:

The study was designed as an observer-blind trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Vaxem Hib Group

Arm description:

Subjects received a single 0.5mL dose of Vaxem Hib.

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

Dosage and administration details:

One dose of 0.5 mL.

Arm title	HIBERIX Group

Arm description:

Subjects received a single 0.5 mL dose of HIBERIX.

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

Dosage and administration details:

One dose of 0.5 mL.

Number of subjects in period 1	Vaxem Hib Group	HIBERIX Group
Started	365	364
Completed	348	352
Not completed	17	12
Consent withdrawn by subject	5	5
Adverse event	1	-
Lost to follow-up	11	7

Baseline characteristics

Reporting groups	
Reporting group title	Vaxem Hib Group
Reporting group description:	
Subjects received a single 0.5mL dose of Vaxem Hib.	
Reporting group title	HIBERIX Group
Reporting group description:	
Subjects received a single 0.5 mL dose of HIBERIX.	

Reporting group values	Vaxem Hib Group	HIBERIX Group	Total
Number of subjects	365	364	729
Age categorical Units: Subjects			
Age continuous Units: months			
arithmetic mean	29.4	29.5	
standard deviation	± 10.5	± 10.7	-
Gender categorical Units: Subjects			
Female	186	169	355
Male	179	195	374

Subject analysis sets	
Subject analysis set title	All Enrolled Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who signed an informed consent and were enrolled.	
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 (PPS, Immunogenicity)
Subject analysis set type	Per protocol
Subject analysis set description:	
All enrolled subjects who correctly received the vaccine, provided evaluable serum samples at the relevant time points (for subjects in the immunogenicity subset), 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 safety data after baseline.	

Reporting group values	All Enrolled Population	Exposed Population	Per Protocol Set (PPS, Immunogenicity)
Number of subjects	729	728	695

Age categorical Units: Subjects			

Age continuous Units: months arithmetic mean standard deviation	 29.5 ± 10.6	 ±	 ±
Gender categorical Units: Subjects			
Female Male	355 374		

Reporting group values	Safety Population		
Number of subjects	728		
Age categorical Units: Subjects			

Age continuous Units: months arithmetic mean standard deviation	 ±	 	
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Vaxem Hib Group
Reporting group description:	
Subjects received a single 0.5mL dose of Vaxem Hib.	
Reporting group title	HIBERIX Group
Reporting group description:	
Subjects received a single 0.5 mL dose of HIBERIX.	
Subject analysis set title	All Enrolled Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who signed an informed consent and were enrolled.	
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.	
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All enrolled subjects who correctly received the vaccine, provided evaluable serum samples at the relevant time points (for subjects in the immunogenicity subset), 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 safety data after baseline.	

Primary: Percentages of subjects with an antibody level ≥ 0.15µg/mL one month after the vaccination

End point title	Percentages of subjects with an antibody level ≥ 0.15µg/mL one month after the vaccination
End point description:	
Immunogenicity was assessed as the percentages of subjects with an antibody level ≥ 0.15µg/mL one month after the vaccination. The analysis was performed on the Per Protocol Set.	
End point type	Primary
End point timeframe:	
One month after the vaccination.	

End point values	Vaxem Hib Group	HIBERIX Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	349		
Units: Percentages of subjects				
number (confidence interval 95%)				
≥ 0.15µg/mL	98.84 (97.07 to 99.68)	100 (98.95 to 100)		

Statistical analyses

Statistical analysis title	Non-inferiority of immune response to Vaxem Hib

Statistical analysis description:

Null hypothesis (H0) for the target value of the primary immunogenicity is that the protection rate of anti-PRP antibodies in subjects vaccinated with Vaxem Hib was not lower than that in subjects vaccinated with HIBERIX, non-inferiority threshold 5% and using one-sided 0.025. Therefore, study vaccine Vaxem Hib is not inferior to vaccine HIBERIX if the lower two-sided 95% confidence limit of difference in the long-term protection rates of antibodies is not beyond -5%.

Comparison groups	Vaxem Hib Group v HIBERIX Group
Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	95% Confidence Intervals
Parameter estimate	Percentage group difference
Point estimate	-1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.28
upper limit	-0.03

Secondary: Percentages of subjects with an antibody level ≥ 1.0 µg/mL one month after the vaccination

End point title	Percentages of subjects with an antibody level ≥ 1.0 µg/mL one month after the vaccination

End point description:

Immunogenicity was assessed as the percentages of subjects with an antibody level ≥ 1.0µg/mL one month after the vaccination. Analysis performed on the Per Protocol Set.

End point type	Secondary

End point timeframe:

One month after the vaccination.

End point values	Vaxem Hib Group	HIBERIX Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	349		
Units: Percentages of subjects				
number (confidence interval 95%)				
≥ 1.0µg/mL	98.84 (97.07 to 99.68)	100 (98.95 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric mean of serum antibody concentrations one month after the vaccination

End point title	Geometric mean of serum antibody concentrations one month after the vaccination

End point description:

Immunogenicity was assessed as the geometric mean of serum antibody concentrations (GMC) one month after the vaccination. Analysis performed on the Per Protocol Set.

End point type	Secondary

End point timeframe:

One month after the vaccination.

End point values	Vaxem Hib Group	HIBERIX Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	349		
Units: µg/mL				
geometric mean (confidence interval 95%)				
GMC	93.13 (79.01 to 109.76)	115.31 (102.71 to 129.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting solicited local and systemic reactions during the 7 days following the vaccination

End point title	Number of subjects reporting solicited local and systemic reactions during the 7 days following the vaccination

End point description:

Safety was assessed as the number of subjects who reported solicited local and systemic reactions from day 1 through day 7 after the vaccination. Analysis performed on the safety set.

End point type	Secondary

End point timeframe:

From day 1 to day 7 after vaccination.

End point values	Vaxem Hib Group	HIBERIX Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	363		
Units: Number of subjects				
Any local	40	36		
Any systemic	136	143		
Erythema 1-15mm	21	17		
Erythema 15-30mm	5	2		
Erythema >30mm	1	0		
Tenderness mild	20	20		
Tenderness moderate	1	1		
Induration 1-15mm	23	18		
Induration 15-30mm	3	2		
Induration >30mm	1	1		
Fever mild	84	88		
Fever moderate	43	47		
Fever severe	5	4		
Rash	8	2		
Sleepiness	8	4		
Irritability	3	6		
Unusual crying	7	10		
Change in eating habits	10	11		
Analgesic/antipyretic medication use	48	56		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of subjects reporting any unsolicited adverse event (AE) and serious adverse event (SAE) after the vaccination.

End point title	Incidence of subjects reporting any unsolicited adverse event (AE) and serious adverse event (SAE) after the vaccination.

End point description:

Safety was assessed as the incidence of subjects who reported unsolicited AEs and SAEs up to one month after the vaccination. Analysis performed on the safety set.

End point type	Secondary

End point timeframe:

One month after vaccination.

End point values	Vaxem Hib Group	HIBERIX Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	363		
Units: Number of subjects				
Total incidence rate of AEs	128	128		
Incidence rate of vaccine-related AEs	11	11		
SAE Incidence rate	1	0		
Withdrawal due to AE	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All solicited AEs and unsolicited AEs were collected from Day 1 to Day 7; all other serious and non-serious AEs were collected for approximately one month after the vaccination.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Vaxem Hib Group

Reporting group description:

Subjects received a single 0.5mL dose of Vaxem™Hib.

Reporting group title	HIBERIX Group

Reporting group description:

Subjects received a single 0.5mL dose of HIBERIX

Serious adverse events	Vaxem Hib Group	HIBERIX Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 365 (0.55%)	0 / 363 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Encephalitis viral			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Vaxem Hib Group	HIBERIX Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	203 / 365 (55.62%)	207 / 363 (57.02%)	

General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	27 / 365 (7.40%)	19 / 363 (5.23%)	
occurrences (all)	27	19	
Injection site induration			
subjects affected / exposed	27 / 365 (7.40%)	21 / 363 (5.79%)	
occurrences (all)	27	21	
Injection site pain			
subjects affected / exposed	21 / 365 (5.75%)	21 / 363 (5.79%)	
occurrences (all)	21	21	
Pyrexia			
subjects affected / exposed	145 / 365 (39.73%)	153 / 363 (42.15%)	
occurrences (all)	171	174	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 365 (3.01%)	21 / 363 (5.79%)	
occurrences (all)	11	21	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	65 / 365 (17.81%)	70 / 363 (19.28%)	
occurrences (all)	66	71	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

N/A

Notes: