



## Clinical trial results:

**A Phase III, Observer-blind, randomized, controlled, multi-center study to investigate the immunogenicity and safety of the Vaxem Hib™ in 2-4 months old healthy infants in China, according to the recommended regimen of 3 intramuscular doses given one month apart.**

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

## Summary

EudraCT number	2014-005159-24
Trial protocol	Outside EU/EEA
Global end of trial date	15 February 2009

## Results information

Result version number	v2 (current)
This version publication date	26 May 2016
First version publication date	10 June 2015
Version creation reason	• Correction of full data set re-QC study because of EudraCT system glitch and updates to results are required.

## Trial information

### Trial identification

Sponsor protocol code	M37P2
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### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00808392
WHO universal trial number (UTN)	-

Notes:

## Sponsors

Sponsor organisation name	Novartis Vaccines & 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	21 May 2009
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 February 2009
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Primary study objective:

To demonstrate that Vaxem Hib given to healthy infants aged 2 - 4 months at study entry is non-inferior to comparator vaccine HIBERIX (GlaxoSmithKline) with regard to percentage of subjects with antibody levels of  $\geq 0.15$  micrograms/mL one month after last vaccination dose as measured by anti-PRP ELISA.

Protection of trial subjects:

This clinical trial was carried out in accordance with relative requirements of Provisions for Drug Registration and World Health Organization (WHO) Guidelines for Good Clinical Practice (GCP) and Guidelines on Clinical Evaluation of Vaccines issued by State Food and Drug Administration and under the principle of Helsinki Declaration.

Study vaccines were not administered to individuals with known hypersensitivity to any component of the vaccines. An oral temperature  $\geq 38.0^{\circ}\text{C}$  ( $\geq 100.4^{\circ}\text{F}$ ) or serious active infection was a reason for delaying vaccination. Standard vaccination practices were observed and care was taken to administer the injection intramuscularly. As with all injectable vaccines, appropriate medical treatment and supervision was readily available in case of rare anaphylactic reactions following administration of the study vaccine. Epinephrine 1:1000 and diphenhydramine was available in case of any anaphylactic reactions. Care was taken to ensure that the vaccine was not injected into a blood vessel.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 October 2008
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: 916
Worldwide total number of subjects	916
EEA total number of subjects	0

Notes:

### Subjects enrolled per age group

In utero	0
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Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	916
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 at two sites 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 trial was designed as an observer-blind study.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Vaxem Hib

Arm description:

2-4 month old infants administered with 3 doses of Novartis Vaxem Hib™, each dose given one month apart.

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

Dosage and administration details:

Vaccination consisted of three 0.5 mL doses of Vaxem Hib™, vaccine administered IM into the deltoid muscle.

<b>Arm title</b>	Hiberix
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Arm description:

2-4 month old infants administered with 3 doses of GSK HIBERIX® each dose given one month apart.

Arm type	Active comparator
Investigational medicinal product name	Tetanus Toxoid conjugate Haemophilus influenzae type b (Hib) vaccine
Investigational medicinal product code	
Other name	Hiberix
Pharmaceutical forms	Powder for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of three 0.5 mL doses of GSK HIBERIX® vaccine administered IM into the deltoid muscle.

<b>Number of subjects in period 1</b>	Vaxem Hib	Hiberix
Started	611	305
Completed	576	289
Not completed	35	16
Adverse event, non-fatal	5	1
Lost to follow-up	2	-
Required by their parents	28	14
Protocol deviation	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Vaxem Hib
Reporting group description: 2-4 month old infants administered with 3 doses of Novartis Vaxem Hib™, each dose given one month apart.	
Reporting group title	Hiberix
Reporting group description: 2-4 month old infants administered with 3 doses of GSK HIBERIX® each dose given one month apart.	

Reporting group values	Vaxem Hib	Hiberix	Total
Number of subjects	611	305	916
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	611	305	916
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Subjects	0	0	0
Age continuous Units: months			
arithmetic mean	3.1	3.1	
standard deviation	± 0.8	± 0.8	-
Gender categorical Units: Subjects			
Female	298	147	445
Male	313	158	471

### Subject analysis sets

Subject analysis set title	All enrolled population
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects who had data in the DEMOG panel.	
Subject analysis set title	All exposed population
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects who received study vaccination.	
Subject analysis set title	Full analysis set (FAS, Immunogenicity)
Subject analysis set type	Full analysis
Subject analysis set description: All subjects who have received a study vaccination, and provide at least one evaluable serum sample	

Subject analysis set title	Per Protocol Set (PPS, Immunogenicity)
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects have received all the relevant doses of vaccine correctly, and provide evaluable serum samples at the relevant time points, and have no major protocol violation as defined prior to unblinding	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who provide post-baseline safety data	

Reporting group values	All enrolled population	All exposed population	Full analysis set (FAS, Immunogenicity)
Number of subjects	916	916	231
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	916	916	231
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Subjects	0	0	0
Age continuous			
Units: months			
arithmetic mean			
standard deviation	±	±	±
Gender categorical			
Units: Subjects			
Female			
Male			

Reporting group values	Per Protocol Set (PPS, Immunogenicity)	Safety set	
Number of subjects	212	916	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	212	916	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Subjects	0	0	

Age continuous Units: months arithmetic mean standard deviation	$\pm$	$\pm$	
Gender categorical Units: Subjects			
Female Male			

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## End points

### End points reporting groups

Reporting group title	Vaxem Hib
Reporting group description: 2-4 month old infants administered with 3 doses of Novartis Vaxem Hib™, each dose given one month apart.	
Reporting group title	Hiberix
Reporting group description: 2-4 month old infants administered with 3 doses of GSK HIBERIX® each dose given one month apart.	
Subject analysis set title	All enrolled population
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects who had data in the DEMOG panel.	
Subject analysis set title	All exposed population
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subjects who received study vaccination.	
Subject analysis set title	Full analysis set (FAS, Immunogenicity)
Subject analysis set type	Full analysis
Subject analysis set description: All subjects who have received a study vaccination, and provide at least one evaluable serum sample	
Subject analysis set title	Per Protocol Set (PPS, Immunogenicity)
Subject analysis set type	Per protocol
Subject analysis set description: All subjects have received all the relevant doses of vaccine correctly, and provide evaluable serum samples at the relevant time points, and have no major protocol violation as defined prior to unblinding	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who provide post-baseline safety data	

### Primary: Percentage of subjects with the serum anti-PRP antibody titers $\geq 0.15$ $\mu\text{g/mL}$ at day 90

End point title	Percentage of subjects with the serum anti-PRP antibody titers $\geq 0.15$ $\mu\text{g/mL}$ at day 90
End point description: Immunogenicity was measured as the percentage of subjects with seroconversion rate of anti-PRP antibody levels $\geq 0.15$ $\mu\text{g/mL}$ one month after the third vaccination.	
End point type	Primary
End point timeframe: One month after third vaccination (Day 90)	

End point values	Vaxem Hib	Hiberix		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	73		
Units: Percentage of subjects				
number (not applicable)				
≥ 0.15 µg/mL	100	100		
<0.15 g/mL	0	0		

## Statistical analyses

Statistical analysis title	Non-inferiority of Vaxem Hib vs Hiberix
Statistical analysis description:	
The non-inferiority was statistically confirmed by inspection of the proportions of subjects with anti-PRP ELISA results ≥ 0.15 µg/mL one month after last vaccination.	
Comparison groups	Vaxem Hib v Hiberix
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	Chi-squared
Parameter estimate	Rate difference
Point estimate	0
Confidence interval	
level	95 %
sides	1-sided
upper limit	0

## Secondary: Percentage of subjects with the serum anti-PRP antibody titers ≥ 1.0 µg/mL at day 90

End point title	Percentage of subjects with the serum anti-PRP antibody titers ≥ 1.0 µg/mL at day 90
End point description:	
Immunogenicity was measured as the percentage of subjects with long-term serum protection rate of anti-PRP antibody levels ≥ 1.0 µg/mL one month after the third vaccination in PPS.	
End point type	Secondary
End point timeframe:	
One month after third vaccination (Day 90)	

End point values	Vaxem Hib	Hiberix		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	73		
Units: Percentage of subjects				
number (not applicable)				
≥ 1.0 µg/mL	99.3	97.3		
<1.0 g/mL	0.7	2.7		

## Statistical analyses

<b>Statistical analysis title</b>	Non-inferiority of Vaxem Hib vs Hiberix
Statistical analysis description:	
The non-inferiority was statistically confirmed by inspection of the proportions of subjects with anti-PRP ELISA results $\geq 0.15$ $\mu\text{g/mL}$ one month after last vaccination.	
Comparison groups	Vaxem Hib v Hiberix
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	Chi-squared
Parameter estimate	Rate difference
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.98
upper limit	6.02

## Secondary: Geometric mean of anti-PRP antibody concentrations of Vaxem Hib and Hiberix groups at day 90

End point title	Geometric mean of anti-PRP antibody concentrations of Vaxem Hib and Hiberix groups at day 90
End point description:	
Immunogenicity was measured in terms of Geometric mean concentration with seroconversion rate of anti-PRP antibody levels ( $\mu\text{g/mL}$ ) one month after the third vaccination in PPS.	
End point type	Secondary
End point timeframe:	
One month after third vaccination (Day 90)	

End point values	Vaxem Hib	Hiberix		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	73		
Units: Percentage of subjects				
geometric mean (confidence interval 95%)				
$\mu\text{g/mL}$	60.56 (48.57 to 75.5)	35.62 (25.08 to 50.6)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects Who Reported Local and Systemic Reactions After Each Vaccination of Vaxem Hib Vaccine or Hiberix vaccine.

End point title	Number of Subjects Who Reported Local and Systemic Reactions After Each Vaccination of Vaxem Hib Vaccine or Hiberix vaccine.
End point description:	Safety was assessed as the number of subjects who reported local and systemic reactions in the first 7 days after each of the 3 vaccinations with Vaxem Hib Vaccine or Hiberix vaccine administered at day 0, day 30 and day 60 in safety population.
End point type	Secondary
End point timeframe:	Day 0 through day 6 after each vaccination

End point values	Vaxem Hib	Hiberix		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	611	305		
Units: Number of subjects				
Tenderness - Vaccination 1	4	0		
Tenderness - Vaccination 2	5	2		
Tenderness - Vaccination 3	8	0		
Erythema - Vaccination 1	3	2		
Erythema - Vaccination 2	3	3		
Erythema - Vaccination 3	8	1		
Induration - Vaccination 1	8	1		
Induration - Vaccination 2	5	0		
Induration - Vaccination 3	5	1		
Change in eating habits - Vaccination 1	2	5		
Change in eating habits - Vaccination 2	4	0		
Change in eating habits - Vaccination 3	2	0		
Sleepiness - Vaccination 1	9	6		
Sleepiness - Vaccination 2	4	3		
Sleepiness - Vaccination 3	3	2		
Unusual crying - Vaccination 1	13	11		
Unusual crying - Vaccination 2	9	5		
Unusual crying - Vaccination 3	4	0		
Irritability - Vaccination 1	4	2		
Irritability - Vaccination 2	0	0		
Irritability - Vaccination 3	1	0		
Rash - Vaccination 1	5	3		
Rash - Vaccination 2	0	1		
Rash - Vaccination 3	1	0		
Fever (≥38 °C) - Vaccination 1	6	6		
Fever (≥38 °C) - Vaccination 2	15	6		
Fever (≥38 °C) - Vaccination 3	14	1		
Analg/Antipyr medications used - Vaccination 1	8	6		

Analg/Antipyr medications used - Vaccination 2	12	5		
Analg/Antipyr medications used - Vaccination 3	15	2		

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Throughout the study period (Day 0 to one month after third vaccination)

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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### Reporting groups

Reporting group title	Vaxem Hib
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Reporting group description:

2-4 month old infants administered with 3 doses of Novartis Vaxem Hib™, each dose given one month apart.

Reporting group title	Hiberix
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Reporting group description:

2-4 month old infants administered with 3 doses of GSK HIBERIX® each dose given one month apart.

Serious adverse events	Vaxem Hib	Hiberix	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 611 (0.98%)	2 / 305 (0.66%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	1 / 611 (0.16%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intussusception			
subjects affected / exposed	0 / 611 (0.00%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 611 (0.33%)	1 / 305 (0.33%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			

subjects affected / exposed	1 / 611 (0.16%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 611 (0.16%)	0 / 305 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 611 (0.16%)	0 / 305 (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 %

<b>Non-serious adverse events</b>	Vaxem Hib	Hiberix	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	247 / 611 (40.43%)	132 / 305 (43.28%)	
General disorders and administration site conditions			
Crying			
subjects affected / exposed	22 / 611 (3.60%)	16 / 305 (5.25%)	
occurrences (all)	27	17	
Pyrexia			
subjects affected / exposed	73 / 611 (11.95%)	34 / 305 (11.15%)	
occurrences (all)	90	38	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	69 / 611 (11.29%)	36 / 305 (11.80%)	
occurrences (all)	73	41	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	87 / 611 (14.24%)	45 / 305 (14.75%)	
occurrences (all)	98	50	
Upper respiratory tract infection			

subjects affected / exposed	68 / 611 (11.13%)	36 / 305 (11.80%)	
occurrences (all)	84	42	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.

None
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Notes: