Clinical trial results:
A Phase III, Single Arm, Multi-Center, Open-Label Study to Assess the Immunogenicity, Safety and Tolerability of a Fully Liquid Pentavalent Vaccine Quinvaxem® (DTwP-Hib-HepB Vaccine) when Administered to Indian Infants at 6, 10, and 14 Weeks of Age

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

Summary

EudraCT number	2014-005309-18
Trial protocol	Outside EU/EEA
Global end of trial date	23 April 2012

Results information

Result version number	v2 (current)
This version publication date	03 June 2016
First version publication date	02 April 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	V66_05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01470287
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	25 October 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 April 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess one month after third study injection, the percentage of subjects who develop:
•Seroprotective antibody concentrations to diphtheria, tetanus and Hepatitis B (HepB)
•Antibody concentrations ≥20 EIU/mL or a 4 fold increase from baseline for Bordetella pertussis,
•Anti polyribosyl phosphate (PRP) Enzyme-Linked Immunosorbent Assay (ELISA) antibody concentrations > 0.15 ug/mL for Haemophilus influenzae type b (Hib) (short term protection).

Protection of trial subjects:

This clinical study was designed, implemented and reported in accordance with the International Conference of Harmonization (ICH) Harmonised Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations guidelines issued by the Central Drugs Standard Control Organization (CDSCO) and Ethical Guidelines for Biomedical Research on Human Subjects issued by the Indian Council of Medical Research (ICMR), (and also European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki. Informed consent was obtained from parents or legal guardians of infants.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 November 2011
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	India: 175
Worldwide total number of subjects	175
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)	175
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 3 study centres in India.

Pre-assignment

Screening details:

All enrolled subjects were included in the study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The trial was designed as single arm and open label.

Arms

Arm title	Quinvaxem

Arm description:

Infants, ≥42 to ≤64 days of age, receiving three doses of vaccine at approximately 6, 10, and 14 weeks of age (study days 1, 29 and 57).

Arm type	Experimental
Investigational medicinal product name	DTwP-Hib-HepB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of one 0.5 mL dose administered three times, IM into the antero-lateral area of the thigh, at day 1, 29 and 57.

Number of subjects in period 1	Quinvaxem
Started	175
Completed	165
Not completed	10
Adverse event	1
Lost to follow-up	9

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	175	175	
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)	175	175	
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	
Age continuous Units: days			
arithmetic mean	48.3		
standard deviation	± 5.2	-	
Gender categorical Units: Subjects			
Female	87	87	
Male	88	88	

End points

End points reporting groups

Reporting group title	Quinvaxem

Reporting group description:

Infants, ≥42 to ≤64 days of age, receiving three doses of vaccine at approximately 6, 10, and 14 weeks of age (study days 1, 29 and 57).

Subject analysis set title	All population enrolled
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who signed an informed consent.
All subjects that underwent screening procedures.

Subject analysis set title	Immunogenicity – Per Protocol Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects in the Full Analysis Set (FAS) who received all three vaccinations, provided evaluable serum samples at defined end points and have no major protocol violation.

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects in the enrolled population who received at least one dose of vaccine and provide post vaccination safety data.

Primary: 1.Percentage of subjects with seroprotective antibody concentration to diphtheria.

End point title	1.Percentage of subjects with seroprotective antibody concentration to diphtheria.[1]

End point description:

Seroprotective activity of Quinvaxem against diphtheria was defined as anti-diphtheria antibody concentration ≥0.1 IU/mL.
The percentage of subjects with seroprotective antibody concentration was evaluated one month after the third vaccination with Quinvaxem.
Analysis was done on Immunogenicity – PPS population, ie. all subjects in the FAS who received all three vaccinations, provided evaluable serum samples at defined end points and have no major protocol violation.

End point type	Primary

End point timeframe:

One month after the third vaccination (day 85).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: statistical analyses not applicable for this endpoint.

End point values	Quinvaxem			
Subject group type	Reporting group			
Number of subjects analysed	161			
Units: Percentage of subjects				
number (confidence interval 95%)				
Seroprotection (Day 1)	18 (12 to 25)			
Seroprotection (Day 85)	99 (97 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: 2.Percentage of subjects with seroprotective antibody concentration to tetanus.

End point title	2.Percentage of subjects with seroprotective antibody concentration to tetanus.[2]

End point description:

Seroprotective activity of Quinvaxem against tetanus was defined as anti-tetanus antibody concentration ≥0.1 IU/mL.
The percentage of subjects with seroprotective antibody concentration was evaluated one month after the third vaccination with Quinvaxem.
Analysis was done on Immunogenicity-PPS population, ie. all subjects in the FAS who received all three vaccinations, provided evaluable serum samples at defined end points and have no major protocol violation.

End point type	Primary

End point timeframe:

One month after the third vaccination (day 85).

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: statistical analyses not applicable for this endpoint.

End point values	Quinvaxem			
Subject group type	Reporting group			
Number of subjects analysed	161			
Units: Percentage of subjects				
number (confidence interval 95%)				
Seroprotection (Day 1)	100 (98 to 100)			
Seroprotection (Day 85)	100 (98 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: 3.Percentage of subjects with seroprotective antibody concentration to Hepatitis B.

End point title	3.Percentage of subjects with seroprotective antibody concentration to Hepatitis B.[3]

End point description:

Seroprotective activity of Quinvaxem against Hepatitis B was defined as anti-Hepatitis B antibody concentration ≥10 IU/mL.
The percentage of subjects with seroprotective antibody concentration was evaluated one month after the third vaccination with Quinvaxem.

Analysis was done on Immunogenicity-PPS population, ie. all subjects in the FAS who received all three vaccinations, provided evaluable serum samples at defined end points and have no major protocol violation.

End point type	Primary

End point timeframe:

One month after the third vaccination (day 85).

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: statistical analyses not applicable for this endpoint.

End point values	Quinvaxem			
Subject group type	Reporting group			
Number of subjects analysed	161			
Units: Percentage of subjects				
number (confidence interval 95%)				
Seroprotection (Day 1) (N=160)	11 (6 to 16)			
Seroprotection (Day 85)	98 (94 to 99)			

Statistical analyses

No statistical analyses for this end point

Primary: 4.Percentage of subjects who developed antibody concentration to pertussis above pre-specified threshold.

End point title	4.Percentage of subjects who developed antibody concentration to pertussis above pre-specified threshold.[4]

End point description:

Seroprotective activity of Quinvaxem against pertussis was defined as anti-pertussis antibody concentration ≥20 EIU/mL or a 4-fold increase from baseline
The percentage of subjects with antibody concentration above the pre-specified threshold was evaluated one month after the third vaccination with Quinvaxem.
Analysis was done on Immunogenicity-PPS population, ie. all subjects in the FAS who received all three vaccinations, provided evaluable serum samples at defined end points and have no major protocol violation.

End point type	Primary

End point timeframe:

One month after the third vaccination (day 85).

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: statistical analyses not applicable for this endpoint.

End point values	Quinvaxem			
Subject group type	Reporting group			
Number of subjects analysed	161			
Units: Percentage of subjects				
number (confidence interval 95%)				
Pre-specified threshold (Day 1)	2 (1 to 6)			
Pre-specified threshold (Day 85)	99 (97 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: 5.Percentage of subjects who developed antibody to Haemophilus influenzae type b above pre-specified threshold.

End point title	5.Percentage of subjects who developed antibody to Haemophilus influenzae type b above pre-specified threshold.[5]

End point description:

Seroprotective activity of Quinvaxem against Haemophilus influenzae type b was defined as anti-Polyribosyl phosphate antibody concentration ≥0.15 mcg/ml.
The percentage of subjects with seroprotective antibody concentration was evaluated one month after the third vaccination with Quinvaxem.
Analysis was done on Immunogenicity-PPS population, ie. all subjects in the Full Analysis Set who received all three vaccinations, provided evaluable serum samples at defined end points and have no major protocol violation.

End point type	Primary

End point timeframe:

One month after the third vaccination (day 85).

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: statistical analyses not applicable for this endpoint.

End point values	Quinvaxem			
Subject group type	Reporting group			
Number of subjects analysed	161			
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-PRP >=0.15 mcg/mL (Day 1) Anti-PRP >=0.15 mcg/mL (Day 85)	68 (61 to 75) 100 (93 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: 6.Geometric Mean Concentration of antibody against diphtheria, tetanus, pertussis, Hepatitis B, Haemophilus influenza type b, one month after third vaccination with Quinvaxem.

End point title	6.Geometric Mean Concentration of antibody against diphtheria, tetanus, pertussis, Hepatitis B, Haemophilus influenza type b, one month after third vaccination with Quinvaxem.

End point description:

The human Serum Bactericidal Activity (hSBA) antibody concentration, one month after receiving the third vaccination of Quinvaxem vaccination, is reported as geometric mean concentration (GMC).

Analysis was done on Immunogenicity-PPS population.

End point type	Secondary

End point timeframe:

One month after the third vaccination (day 85).

End point values	Quinvaxem			
Subject group type	Reporting group			
Number of subjects analysed	161			
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-diphtheria GMCs (Day 1)	0.061 (0.057 to 0.066)			
Anti-diphtheria GMCs (Day 85)	1.28 (1.08 to 1.52)			
Anti-tetanus GMCs (Day 1)	2.68 (2.35 to 3.06)			
Anti-tetanus GMCs (Day 85)	2.51 (2.18 to 2.89)			
Anti-pertussis GMCs (Day 1)	4.07 (3.53 to 4.68)			
Anti-pertussis GMCs (Day 85)	54 (51 to 57)			
Anti-Hepatitis B GMCs (Day 1) (N=160)	6.47 (5.56 to 7.53)			
Anti-Hepatitis B GMCs (Day 85)	373 (296 to 470)			
Anti-PRP GMCs (Day 1)	0.27 (0.23 to 0.33)			
Anti-PRP GMCs (Day 85)	15 (12 to 18)			

Statistical analyses

No statistical analyses for this end point

Secondary: 7.Percentage of subjects with antibody concentration anti-Polyribosylphosphate (PRP) ≥1.0 mcg/mL

End point title	7.Percentage of subjects with antibody concentration anti-Polyribosylphosphate (PRP) ≥1.0 mcg/mL

End point description:

Long term seroprotective activity of Quinvaxem against Haemophilus influenzae type b was defined as anti-PRP antibody concentration ≥1.0 mcg/mL.
The percentage of subjects with antibody concentration >=1.0 mcg/mL was evaluated one month after the third vaccination with Quinvaxem.
Analysis was done on Immunogenicity-PPS population, ie. all subjects in the FAS who received all three vaccinations, provided evaluable serum samples at defined end points and have no major protocol violation.

End point type	Secondary

End point timeframe:

One month after the third vaccination (day 85).

End point values	Quinvaxem			
Subject group type	Reporting group			
Number of subjects analysed	161			
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-PRP ≥1.0 mcg/mL (day 1)	14 (9 to 21)			
Anti-PRP ≥1.0 mcg/mL (day 85)	95 (90 to 98)			

Statistical analyses

No statistical analyses for this end point

Secondary: 8.Number of subjects reporting solicited local and systemic adverse events after each vaccination.

End point title	8.Number of subjects reporting solicited local and systemic adverse events after each vaccination.

End point description:

Safety was determined by solicited local and systemic adverse events (AEs) reported 7 days after each vaccination and defined by percentage of subjects with reactogenicity.
Analysis was done on Safety population. ie all subjects in the enrolled population who received at least one dose of vaccine and provided post vaccination safety data.

End point type	Secondary

End point timeframe:

7 days after each vaccination day (day 7, day 35 and day 63).

End point values	Quinvaxem			
Subject group type	Reporting group			
Number of subjects analysed	172			
Units: Number of subjects				
Injection site Erythema (1st vaccination, N=172)	34			
Injection site Induration (1st vaccination, N=172)	22			
Injection site Tenderness (1st vaccination, N=172)	50			
Fever ≥ 38 °C (1st vaccination, N=172)	36			
Injection site Erythema (2nd vaccination, N=169)	23			
Injection site Induration (2nd vaccination, N=169)	17			
Injection site Tenderness (2nd vaccination, N=169)	30			
Fever ≥ 38 °C (2nd vaccination, N=169)	30			
Injection site Erythema (3rd vaccination, N=165)	18			

Injection site Induration (3rd vaccination, N=165)	7			
Injection site Tenderness (3rd vaccination, N=165)	17			
Fever ≥ 38 °C (3rd vaccination, N=165)	62			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout duration of the study.

Adverse event reporting additional description:

All AEs (including Serious Adverse Events (SAEs) and AEs leading to withdrawal of subject) and concomitant medications were collected throughout the duration of the study (day 1 through day 85 or time of early termination).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Quinvaxem

Reporting group description:

Infants, ≥42 to ≤64 days of age, receiving three doses of vaccine at approximately 6, 10, and 14 weeks of age (study days 1, 29 and 57).

Serious adverse events	Quinvaxem		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 172 (0.58%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 172 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 172 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 172 (0.58%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Quinvaxem		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	113 / 172 (65.70%)		
General disorders and administration site conditions			
Injection site induration			
subjects affected / exposed	31 / 172 (18.02%)		
occurrences (all)	47		
Injection site erythema			
subjects affected / exposed	48 / 172 (27.91%)		
occurrences (all)	79		
Pyrexia			
subjects affected / exposed	66 / 172 (38.37%)		
occurrences (all)	100		
Injection site pain			
subjects affected / exposed	64 / 172 (37.21%)		
occurrences (all)	97		
Infections and infestations			
Rhinitis			
subjects affected / exposed	9 / 172 (5.23%)		
occurrences (all)	10		

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/23783081