



## Clinical trial results:

### A Study in Healthy Infants of the Safety, Tolerability, and Immunogenicity of Haemophilus influenzae, Type b/Hepatitis B Vaccine Manufactured With a Modified Process

#### Summary

EudraCT number	2006-003648-46
Trial protocol	FI
Global end of trial date	03 June 2008

#### Results information

Result version number	v1 (current)
This version publication date	10 February 2016
First version publication date	03 June 2015

#### Trial information

##### Trial identification

Sponsor protocol code	V121-019
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00441012
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Merck Sharp & Dohme Corp., Clinical Trials Disclosure, ClinicalTrialsDisclosure@merck.com
Scientific contact	Merck Sharp & Dohme Corp., Clinical Trials Disclosure, ClinicalTrialsDisclosure@merck.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	03 June 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 June 2008
Global end of trial reached?	Yes
Global end of trial date	03 June 2008
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To determine if there is an improvement in the immune response to HBsAg (hepatitis B virus surface antigen) in healthy infants using a modified process in a combination Haemophilus Influenzae, type b/Hepatitis B vaccine and a currently licensed Haemophilus Influenzae, type b/Hepatitis B vaccine.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 December 2006
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	Finland: 426
Country: Number of subjects enrolled	Canada: 120
Worldwide total number of subjects	546
EEA total number of subjects	426

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)	546
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0



## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participants were excluded for history of or prior vaccination for hepatitis B (Hep B) or Haemophilus influenzae Type B (Hib) disease and for administration of blood products. Participants also excluded if mother received Hep B, Hib vaccine, or blood products 6 months prior to participant birth. Other inclusion and exclusion criteria applied.

### 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, Carer

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Modified Process Vaccine

Arm description:

Modified process vaccine HBsAg and Polyribosylribitol Phosphate (PRP) in a 3-dose regimen at 2, 4, and 12 months of age. All participants also received Prevnar® vaccine in a 4-dose regimen at 2, 4, 6, and 12 months of age. Duration of treatment is 11 months.

Arm type	Experimental
Investigational medicinal product name	Modified Process Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Modified process vaccine HBsAg 5 ug/0.5 mL and PRP 7.5 ug/0.5 mL in a 3-dose regimen at 2, 4, and 12 months of age

Investigational medicinal product name	Prevnar® Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Prevnar® Vaccine 0.5 mL intramuscular injection (in the limb opposing that used for Modified Process Vaccine injection) in a 4-dose regimen at 2, 4, 6, and 12 months of age

<b>Arm title</b>	COMVAX™ Vaccine
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Arm description:

COMVAX™ vaccine HBsAg and PRP in a 3-dose regimen at 2, 4, and 12 months of age. All participants also received Prevnar® vaccine in a 4-dose regimen at 2, 4, 6, and 12 months of age. Duration of treatment is 11 months.

Arm type	Active comparator
Investigational medicinal product name	COMVAX™ Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

COMVAX™ vaccine HBsAg 5 ug/0.5 mL and PRP 7.5 ug/0.5 mL in a 3-dose regimen at 2, 4, and 12 months of age

Investigational medicinal product name	Pevnar® vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Pevnar® Vaccine 0.5 mL intramuscular injection (in the limb opposing that used for Modified Process Vaccine injection) in a 4-dose regimen at 2, 4, 6, and 12 months of age

<b>Number of subjects in period 1</b>	Modified Process Vaccine	COMVAX™ Vaccine
Started	270	276
Received first dose of study vaccine	269	276
Received second dose of study vaccine	267	272
Received third dose of study vaccine	265	269
Completed	252	263
Not completed	18	13
Consent withdrawn by subject	4	-
Adverse event, non-fatal	-	1
Randomized but not vaccinated	1	-
Lost to follow-up	3	3
Protocol deviation	10	9

## Baseline characteristics

### Reporting groups

Reporting group title	Modified Process Vaccine
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Reporting group description:

Modified process vaccine HBsAg and Polyribosylribitol Phosphate (PRP) in a 3-dose regimen at 2, 4, and 12 months of age. All participants also received Prevnar® vaccine in a 4-dose regimen at 2, 4, 6, and 12 months of age. Duration of treatment is 11 months.

Reporting group title	COMVAX™ Vaccine
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Reporting group description:

COMVAX™ vaccine HBsAg and PRP in a 3-dose regimen at 2, 4, and 12 months of age. All participants also received Prevnar® vaccine in a 4-dose regimen at 2, 4, 6, and 12 months of age. Duration of treatment is 11 months.

Reporting group values	Modified Process Vaccine	COMVAX™ Vaccine	Total
Number of subjects	270	276	546
Age categorical Units: Subjects			
Age continuous Units: days			
arithmetic mean	67.7	68.3	
standard deviation	± 8.9	± 8.5	-
Gender categorical Units: Subjects			
Female	129	142	271
Male	141	134	275

## End points

### End points reporting groups

Reporting group title	Modified Process Vaccine
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Reporting group description:

Modified process vaccine HBsAg and Polyribosylribitol Phosphate (PRP) in a 3-dose regimen at 2, 4, and 12 months of age. All participants also received Prevnar® vaccine in a 4-dose regimen at 2, 4, 6, and 12 months of age. Duration of treatment is 11 months.

Reporting group title	COMVAX™ Vaccine
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Reporting group description:

COMVAX™ vaccine HBsAg and PRP in a 3-dose regimen at 2, 4, and 12 months of age. All participants also received Prevnar® vaccine in a 4-dose regimen at 2, 4, 6, and 12 months of age. Duration of treatment is 11 months.

Subject analysis set title	Modified Process Vaccine - Per Protocol
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Subject analysis set type	Per protocol
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Subject analysis set description:

The Per-Protocol Population is defined as the participants that were able to complete the study as defined by the protocol.

Subject analysis set title	COMVAX™ Vaccine - Per Protocol
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Subject analysis set type	Per protocol
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Subject analysis set description:

The Per-Protocol Population is defined as the participants that were able to complete the study as defined by the protocol.

Subject analysis set title	Modified Process Vaccine - Safety
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The Safety Analysis Set is defined as all participants who receive at least one injection of vaccine.

Subject analysis set title	COMVAX™ - Safety
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The Safety Analysis Set is defined as all participants who receive at least one injection of vaccine.

### Primary: Percentage of Anti-Hepatitis B Seroprotected Participants One Month after the Third Dose

End point title	Percentage of Anti-Hepatitis B Seroprotected Participants One Month after the Third Dose <sup>[1]</sup>
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End point description:

The percentage of participants as measured by the seroprotection rate (anti-hepatitis B surface antibodies greater than or equal to 10 milli International Units [mIU] /mL). Anti-HBs (Antibodies against hepatitis B surface antigen) titers were measured from blood samples taken at Month 11 (1 month after the third dose). An adequate response requires the lower bound of the two-sided 95% confidence interval for the seroprotection rate to exceed 90%.

End point type	Primary
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End point timeframe:

One month after dose 3 (11 months)

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: No between-group statistical analyses were conducted for this endpoint

<b>End point values</b>	Modified Process Vaccine - Per Protocol	COMVAX™ Vaccine - Per Protocol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	230	228		
Units: Percentage of participants				
number (confidence interval 95%)	100 (98.7 to 100)	99.1 (96.9 to 99.9)		

### Statistical analyses

No statistical analyses for this end point

### Primary: Geometric Mean Titer of Anti-Hepatitis B Antibodies One Month after the Third Dose

End point title	Geometric Mean Titer of Anti-Hepatitis B Antibodies One Month after the Third Dose
End point description:	
Geometric Mean Titer (GMT in milli International units [mIU]/mL) – This is an Antibody titer that is measured using a laboratory test to detect the presence and amount of antibodies in a person's blood. Anti-HBs (Antibodies against hepatitis B surface antigen) and Geometric Mean Titers were measured from blood samples taken at Month 11 (1 month after the third dose).	
End point type	Primary
End point timeframe:	
One month after dose 3 (11 months)	

<b>End point values</b>	Modified Process Vaccine - Per Protocol	COMVAX™ Vaccine - Per Protocol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	230	228		
Units: mIU/mL				
geometric mean (confidence interval 95%)	4204.4 (3411.2 to 5182)	1683.4 (1350.4 to 2098.6)		

### Statistical analyses

Statistical analysis title	Non-inferiority
Comparison groups	Modified Process Vaccine - Per Protocol v COMVAX™ Vaccine - Per Protocol

Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[2]</sup>
Parameter estimate	GMT Ratio (Modified / COMVAX)
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.9
upper limit	3.3

Notes:

[2] - The Modified Process Vaccine is non-inferior to COMVAX with respect to anti-HBs GMT. The non-inferiority criterion requires that the lower bound of the two-sided 95% confidence interval on the ratio of the Month 11 GMTs [GMT modified process vaccine/GMT COMVAX™] is >0.67.

### Secondary: Number of Participants with Serious Vaccine-related Clinical Adverse Experiences

End point title	Number of Participants with Serious Vaccine-related Clinical Adverse Experiences
End point description:	
End point type	Secondary
End point timeframe:	
Up to 11 months (recorded from the first dose until completion or discontinuation)	

End point values	Modified Process Vaccine - Safety	COMVAX™ - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	269	273		
Units: Participants	0	0		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Anti-PRP Seroprotected Participants One Month after the Third Dose

End point title	Percentage of Anti-PRP Seroprotected Participants One Month after the Third Dose
End point description:	
The number of participants as measured by the seroprotection rate (anti-polyribosylribitol phosphate antibodies greater than 1 µg/mL). Anti-PRP (Antibodies against polyribosylribitol phosphate) titers were measured from blood samples taken at Month 11 (1 month after the third dose).	
End point type	Secondary
End point timeframe:	
One month after dose 3 (11 months)	

<b>End point values</b>	Modified Process Vaccine - Per Protocol	COMVAX™ Vaccine - Per Protocol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	230	228		
Units: Percentage of participants				
number (confidence interval 95%)	93.9 (90 to 96.6)	92.1 (87.8 to 95.3)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Geometric Mean Titer of Anti-PRP Antibodies One Month after the Third Dose

End point title	Geometric Mean Titer of Anti-PRP Antibodies One Month after the Third Dose
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End point description:

Geometric Mean Titer (GMT) – This is an Antibody titer that is measured using a laboratory test to detect the presence and amount of antibodies in a person's blood. Anti-PRP (Antibodies against polyribosylribitol phosphate) titers were measured from blood samples taken at Month 11 (1 month after the third dose).

End point type	Secondary
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End point timeframe:

One month after dose 3 (11 months)

<b>End point values</b>	Modified Process Vaccine - Per Protocol	COMVAX™ Vaccine - Per Protocol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	230	228		
Units: µg/mL				
geometric mean (confidence interval 95%)	7.1 (6 to 8.4)	8 (6.7 to 9.6)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Systemic adverse events: Day 1 - 15 after any vaccination; injection-site adverse events: Day 1 - 5 after any vaccination

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

### Reporting groups

Reporting group title	Modified Process Vaccine - Safety
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Reporting group description:

The Safety Analysis Set is defined as all participants who receive at least one injection of vaccine and had safety follow-up.

Reporting group title	COMVAX™ - Safety
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Reporting group description:

The Safety Analysis Set is defined as all participants who receive at least one injection of vaccine and had safety follow-up.

<b>Serious adverse events</b>	Modified Process Vaccine - Safety	COMVAX™ - Safety	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 269 (0.00%)	3 / 273 (1.10%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Medication error			
subjects affected / exposed	0 / 269 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 269 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 269 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

<b>Non-serious adverse events</b>	Modified Process Vaccine - Safety	COMVAX™ - Safety	
Total subjects affected by non-serious adverse events subjects affected / exposed	259 / 269 (96.28%)	264 / 273 (96.70%)	
Investigations Body temperature increased subjects affected / exposed occurrences (all)	6 / 269 (2.23%) 6	8 / 273 (2.93%) 8	
Nervous system disorders Somnolence subjects affected / exposed occurrences (all)  Poor quality sleep subjects affected / exposed occurrences (all)	27 / 269 (10.04%) 37  4 / 269 (1.49%) 4	31 / 273 (11.36%) 37  3 / 273 (1.10%) 3	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)  Injection site bruising subjects affected / exposed occurrences (all)  Injection site erythema subjects affected / exposed occurrences (all)  Injection site induration subjects affected / exposed occurrences (all)  Injection site pain subjects affected / exposed occurrences (all)	19 / 269 (7.06%) 19  9 / 269 (3.35%) 9  174 / 269 (64.68%) 309  33 / 269 (12.27%) 53  195 / 269 (72.49%) 379	15 / 273 (5.49%) 17  9 / 273 (3.30%) 10  179 / 273 (65.57%) 308  31 / 273 (11.36%) 42  213 / 273 (78.02%) 408	

Injection site swelling subjects affected / exposed occurrences (all)	164 / 269 (60.97%) 268	146 / 273 (53.48%) 247	
Irritability subjects affected / exposed occurrences (all)	117 / 269 (43.49%) 195	131 / 273 (47.99%) 228	
Pyrexia subjects affected / exposed occurrences (all)	162 / 269 (60.22%) 255	167 / 273 (61.17%) 287	
Injection site nodule subjects affected / exposed occurrences (all)	6 / 269 (2.23%) 7	6 / 273 (2.20%) 7	
Injection site haematoma subjects affected / exposed occurrences (all)	3 / 269 (1.12%) 3	1 / 273 (0.37%) 1	
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	6 / 269 (2.23%) 6	8 / 273 (2.93%) 8	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	24 / 269 (8.92%) 31	26 / 273 (9.52%) 32	
Flatulence subjects affected / exposed occurrences (all)	8 / 269 (2.97%) 11	14 / 273 (5.13%) 16	
Teething subjects affected / exposed occurrences (all)	10 / 269 (3.72%) 10	17 / 273 (6.23%) 19	
Vomiting subjects affected / exposed occurrences (all)	10 / 269 (3.72%) 14	15 / 273 (5.49%) 15	
Abdominal pain upper subjects affected / exposed occurrences (all)	6 / 269 (2.23%) 6	6 / 273 (2.20%) 7	
Constipation			

subjects affected / exposed occurrences (all)	4 / 269 (1.49%) 4	6 / 273 (2.20%) 6	
Regurgitation subjects affected / exposed occurrences (all)	6 / 269 (2.23%) 7	11 / 273 (4.03%) 11	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	9 / 269 (3.35%) 11	21 / 273 (7.69%) 21	
Nasal congestion subjects affected / exposed occurrences (all)	6 / 269 (2.23%) 6	8 / 273 (2.93%) 9	
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	14 / 269 (5.20%) 16	10 / 273 (3.66%) 12	
Dermatitis diaper subjects affected / exposed occurrences (all)	5 / 269 (1.86%) 7	4 / 273 (1.47%) 4	
Eczema subjects affected / exposed occurrences (all)	3 / 269 (1.12%) 3	2 / 273 (0.73%) 2	
Erythema subjects affected / exposed occurrences (all)	1 / 269 (0.37%) 1	4 / 273 (1.47%) 4	
Urticaria subjects affected / exposed occurrences (all)	3 / 269 (1.12%) 3	1 / 273 (0.37%) 1	
Psychiatric disorders			
Crying subjects affected / exposed occurrences (all)	58 / 269 (21.56%) 95	63 / 273 (23.08%) 92	
Restlessness subjects affected / exposed occurrences (all)	4 / 269 (1.49%) 4	15 / 273 (5.49%) 19	
Insomnia			

subjects affected / exposed occurrences (all)	6 / 269 (2.23%) 6	4 / 273 (1.47%) 5	
<b>Infections and infestations</b>			
<b>Rhinitis</b>			
subjects affected / exposed occurrences (all)	25 / 269 (9.29%) 26	31 / 273 (11.36%) 38	
<b>Upper respiratory tract infection</b>			
subjects affected / exposed occurrences (all)	16 / 269 (5.95%) 17	13 / 273 (4.76%) 13	
<b>Ear infection</b>			
subjects affected / exposed occurrences (all)	5 / 269 (1.86%) 5	3 / 273 (1.10%) 3	
<b>Exanthema subitum</b>			
subjects affected / exposed occurrences (all)	3 / 269 (1.12%) 3	0 / 273 (0.00%) 0	
<b>Gastroenteritis</b>			
subjects affected / exposed occurrences (all)	3 / 269 (1.12%) 4	3 / 273 (1.10%) 3	
<b>Influenza</b>			
subjects affected / exposed occurrences (all)	8 / 269 (2.97%) 8	9 / 273 (3.30%) 9	
<b>Laryngitis</b>			
subjects affected / exposed occurrences (all)	0 / 269 (0.00%) 0	4 / 273 (1.47%) 4	
<b>Nasopharyngitis</b>			
subjects affected / exposed occurrences (all)	8 / 269 (2.97%) 9	11 / 273 (4.03%) 11	
<b>Otitis media</b>			
subjects affected / exposed occurrences (all)	12 / 269 (4.46%) 12	12 / 273 (4.40%) 13	
<b>Respiratory tract infection</b>			
subjects affected / exposed occurrences (all)	3 / 269 (1.12%) 3	2 / 273 (0.73%) 2	
<b>Metabolism and nutrition disorders</b>			
<b>Anorexia</b>			

subjects affected / exposed	14 / 269 (5.20%)	10 / 273 (3.66%)	
occurrences (all)	17	10	

## **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**

None reported