



## Clinical trial results:

### A Study in Healthy Neonates of Safety, Tolerability, and Immunogenicity of Recombinant Hepatitis B Vaccine Manufactured Using a Modified Process

#### Summary

EudraCT number	2016-003981-15
Trial protocol	Outside EU/EEA
Global end of trial date	20 July 2007

#### Results information

Result version number	v1 (current)
This version publication date	03 February 2017
First version publication date	03 February 2017

#### Trial information

##### Trial identification

Sponsor protocol code	V232-056
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00322361
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Registration Number: 2006_007

Notes:

##### Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., 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	20 July 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 July 2007
Global end of trial reached?	Yes
Global end of trial date	20 July 2007
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Hepatitis B Vaccine [Recombinant] is a well established vaccine which has been used extensively, worldwide since its initial licensure in 1986. Hepatitis B vaccines: [1] induce protection against the morbidity and mortality of acute hepatitis B virus infection, [2] reduce the incidence of chronic infection in vaccinated populations, and [3] thereby, reduce the incidence of hepatocellular carcinoma. The purpose of the trial was to assess if the new manufacturing process of the Hepatitis B Vaccine [Recombinant] vaccine showed the same or better level of hepatitis B antibody response than does the currently licensed Hepatitis B Vaccine [Recombinant] vaccine. This study was also to confirm that the new process vaccine is as well tolerated as the current vaccine in neonates.

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.

The following additional measure defined for this individual study was in place for the protection of trial participants: participants who did not develop seroprotective levels of anti-HBs, 1 month after the third dose, may have been offered additional vaccination, outside of the protocol, at the discretion of the investigator.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 May 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 35
Country: Number of subjects enrolled	United States: 531
Worldwide total number of subjects	566
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)	566
Infants and toddlers (28 days-23 months)	0
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:

Healthy male and female full-term (37-42 weeks gestation) neonates (birth to 10 days of age) born to mothers with documented negative test for hepatitis B surface antigen (HBsAg) within 9 months prior to delivery.

### Pre-assignment

Screening details:

No pre-screening for antibody to hepatitis B surface antigen (anti-HBs) or hepatitis B core antigen (anti-HBc) was conducted.

### 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 Hepatitis B Vaccine

Arm description:

Modified Process Hepatitis B three 5 mcg dose regimen administered via intramuscular injection at birth (up to 10 days of age), 1 month after Dose 1, and 6 months after Dose 1.

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

Dosage and administration details:

5 mcg (0.5 mL) per dose

<b>Arm title</b>	RECOMBIVAX HB™ Vaccine
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Arm description:

RECOMBIVAX HB™ three 5 mcg dose regimen administered via intramuscular injection at birth (up to 10 days of age), 1 month after Dose 1, and 6 months after Dose 1.

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

Dosage and administration details:

5 mcg (0.5 mL) per dose

<b>Number of subjects in period 1</b>	Modified Process Hepatitis B Vaccine	RECOMBIVAX HB™ Vaccine
Started	283	283
Vaccine 1	282	283
Vaccine 2	267	263
Vaccine 3	214	215
Completed	194	193
Not completed	89	90
Participant moved	6	9
Consent withdrawn by subject	22	20
Other reason not specified	22	22
Adverse event, non-fatal	1	-
Lost to follow-up	18	13
Protocol deviation	20	26

## Baseline characteristics

### Reporting groups

Reporting group title	Modified Process Hepatitis B Vaccine
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Reporting group description:

Modified Process Hepatitis B three 5 mcg dose regimen administered via intramuscular injection at birth (up to 10 days of age), 1 month after Dose 1, and 6 months after Dose 1.

Reporting group title	RECOMBIVAX HB™ Vaccine
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Reporting group description:

RECOMBIVAX HB™ three 5 mcg dose regimen administered via intramuscular injection at birth (up to 10 days of age), 1 month after Dose 1, and 6 months after Dose 1.

Reporting group values	Modified Process Hepatitis B Vaccine	RECOMBIVAX HB™ Vaccine	Total
Number of subjects	283	283	566
Age Categorical Units: Subjects			

Age Continuous Units: days arithmetic mean standard deviation	6.5 ± 2.29	6.6 ± 2.4	-
Gender Categorical Units: Subjects			
Female	156	138	294
Male	127	145	272

## End points

### End points reporting groups

Reporting group title	Modified Process Hepatitis B Vaccine
Reporting group description: Modified Process Hepatitis B three 5 mcg dose regimen administered via intramuscular injection at birth (up to 10 days of age), 1 month after Dose 1, and 6 months after Dose 1.	
Reporting group title	RECOMBIVAX HB™ Vaccine
Reporting group description: RECOMBIVAX HB™ three 5 mcg dose regimen administered via intramuscular injection at birth (up to 10 days of age), 1 month after Dose 1, and 6 months after Dose 1.	

### Primary: Geometric mean titer (GMT) to anti-HBs at Month 7

End point title	Geometric mean titer (GMT) to anti-HBs at Month 7
End point description: Geometric mean antibody titers to hepatitis B surface antigen (milli international units/milliliter [mIU/mL]) were measured 4 weeks after the third vaccination. Analysis population: per-protocol population included all participants who met the inclusion criteria, were not protocol violators and had serology and vaccinations within the specified day ranges.	
End point type	Primary
End point timeframe: Month 7 (1 month post vaccination 3)	

End point values	Modified Process Hepatitis B Vaccine	RECOMBIVAX HB™ Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	187		
Units: mIU/mL				
geometric mean (confidence interval 95%)	843.7 (680.8 to 1045.5)	670.1 (549.2 to 817.5)		

### Statistical analyses

Statistical analysis title	GMT ratio
Statistical analysis description: The lower bound of the 95% confidence interval (CI) on the GMT ratio greater than the pre-specified clinically relevant values of 0.67 (i.e., a 1.5-fold decrease) and 1.00 (identity) allows for a conclusion of non-inferiority or superiority, respectively.	
Comparison groups	Modified Process Hepatitis B Vaccine v RECOMBIVAX HB™ Vaccine

Number of subjects included in analysis	378
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT ratio
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.69

### Secondary: Percentage of participants who experienced an adverse event

End point title	Percentage of participants who experienced an adverse event
End point description:	
Adverse experience means any unfavorable and unintended change in the structure (signs), function (symptoms), or chemistry (laboratory data) of the body temporally associated with any use of a Merck product whether or not considered related to the use of the product. Participant's parents/legal guardians recorded in the Vaccination Report Card (VRC) systemic and injection-site adverse experiences, temperatures, and any other vaccines or medications administered during Day 1 through Day 14. Analysis population: all participants who received at least 1 injection of vaccine in this study and had safety follow-up data for at least 1 day following an injection.	
End point type	Secondary
End point timeframe:	
Up to 42 days (including follow-up 14 days post vaccination 1, 2, & 3)	

End point values	Modified Process Hepatitis B Vaccine	RECOMBIVAX HB™ Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	272		
Units: Percentage of participants				
number (not applicable)	72.2	72.4		

### Statistical analyses

Statistical analysis title	Difference in risk
Statistical analysis description:	
Risk differences in percentage points (Modified Process Hepatitis B Vaccine - RECOMBIVAX HB™ Vaccine) and confidence intervals are based on pooled incidence rates across all study centers.	
Comparison groups	Modified Process Hepatitis B Vaccine v RECOMBIVAX HB™ Vaccine

Number of subjects included in analysis	545
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	7.3

### Secondary: Percentage of participants who discontinued from study therapy due to an adverse event

End point title	Percentage of participants who discontinued from study therapy due to an adverse event
End point description:	
Adverse experience means any unfavorable and unintended change in the structure (signs), function (symptoms), or chemistry (laboratory data) of the body temporally associated with any use of a Merck product whether or not considered related to the use of the product. Participant's parents/legal guardians recorded in the Vaccination Report Card (VRC) systemic and injection-site adverse experiences, temperatures, and any other vaccines or medications administered during Day 1 through Day 14. Analysis population: all participants who received at least 1 injection of vaccine in this study and had safety follow-up data for at least 1 day following an injection.	
End point type	Secondary
End point timeframe:	
Up to 28 days (including follow-up 14 days post vaccination 1 & 2)	

End point values	Modified Process Hepatitis B Vaccine	RECOMBIVAX HB™ Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	272		
Units: Percentage of participants				
number (not applicable)	0.4	0		

### Statistical analyses

Statistical analysis title	Difference in risk
Statistical analysis description:	
Risk differences in percentage points (Modified Process Hepatitis B Vaccine - RECOMBIVAX HB™ Vaccine) and confidence intervals are based on pooled incidence rates across all study centers.	
Comparison groups	Modified Process Hepatitis B Vaccine v RECOMBIVAX HB™ Vaccine

Number of subjects included in analysis	545
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	2.1

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### Secondary: Percentage of Participants with Seroprotection (anti-HBsAg $\geq$ 10 mIU/mL) at Month 7

End point title	Percentage of Participants with Seroprotection (anti-HBsAg $\geq$ 10 mIU/mL) at Month 7
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End point description:

Seroprotection rate was measured as the percentage of participants with anti-HBsAg  $\geq$  10 mIU/mL at Month 7. Anti-hepatitis B surface antigen titers were measured 4 weeks after the third vaccination. Analysis population: per-protocol population included all participants who met the inclusion criteria, were not protocol violators and had serology and vaccinations within the specified day ranges.

End point type	Secondary
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End point timeframe:

Month 7 (1 month post vaccination 3)

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End point values	Modified Process Hepatitis B Vaccine	RECOMBIVAX HB™ Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	187		
Units: Percentage of participants				
number (confidence interval 95%)	97.9 (95.6 to 100)	98.9 (97.2 to 100)		

### Statistical analyses

No statistical analyses for this end point

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## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Serious adverse events: Up to 7 months (entire study);

Non-serious systemic adverse events: Days 1-14 following any vaccination visit;

Non-serious injection-site adverse events: Days 1-5 following any vaccination visit

Adverse event reporting additional description:

Population included all randomized participants who received at least 1 injection of vaccine in this study and had safety follow-up data for at least 1 day following an injection.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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### Reporting groups

Reporting group title	RECOMBIVAX HB™ Vaccine
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Reporting group description:

RECOMBIVAX HB™ three 5 mcg dose regimen administered via intramuscular injection at birth (up to 10 days of age), 1 month after Dose 1, and 6 months after Dose 1 schedule.

Reporting group title	Modified Process Hepatitis B Vaccine
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Reporting group description:

Modified Process Hepatitis B three 5 mcg dose regimen administered via intramuscular injection at birth (up to 10 days of age), 1 month after Dose 1, and 6 months after Dose 1 schedule.

Serious adverse events	RECOMBIVAX HB™ Vaccine	Modified Process Hepatitis B Vaccine	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 272 (1.47%)	3 / 273 (1.10%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Blindness congenital			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyloric stenosis			
subjects affected / exposed	0 / 272 (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	
Retinal anomaly congenital			

subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Nervous system disorders</b>			
Myoclonus			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>General disorders and administration site conditions</b>			
Pyrexia			
subjects affected / exposed	2 / 272 (0.74%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
Sepsis			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Metabolism and nutrition disorders</b>			
Dehydration			
subjects affected / exposed	0 / 272 (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	
Failure to thrive			
subjects affected / exposed	0 / 272 (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: 5 %

<b>Non-serious adverse events</b>	RECOMBIVAX HB™ Vaccine	Modified Process Hepatitis B Vaccine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	167 / 272 (61.40%)	168 / 273 (61.54%)	
General disorders and administration site conditions			

Irritability			
subjects affected / exposed	27 / 272 (9.93%)	22 / 273 (8.06%)	
occurrences (all)	35	24	
Pyrexia			
subjects affected / exposed	21 / 272 (7.72%)	30 / 273 (10.99%)	
occurrences (all)	25	35	
Injection site erythema			
subjects affected / exposed	97 / 272 (35.66%)	103 / 273 (37.73%)	
occurrences (all)	148	155	
Injection site pain			
subjects affected / exposed	87 / 272 (31.99%)	103 / 273 (37.73%)	
occurrences (all)	133	165	
Injection site swelling			
subjects affected / exposed	66 / 272 (24.26%)	59 / 273 (21.61%)	
occurrences (all)	96	85	
Gastrointestinal disorders			
Flatulence			
subjects affected / exposed	24 / 272 (8.82%)	26 / 273 (9.52%)	
occurrences (all)	35	33	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	16 / 272 (5.88%)	8 / 273 (2.93%)	
occurrences (all)	16	9	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2006	Amendment 1: protocol was amended to change the age of the participant at study entry, clarify the time of scheduled study visits, change the time the informed consent will be obtained from the parent/guardian, clarify information in the Study Flow Chart, incorporate some infant immunogenicity data into the Background and Rationale, and clarify the phosphate/aluminum content in the adjuvant.
14 April 2006	Amendment 2: protocol was amended to add safety evaluation committee, capture additional information on the vaccination report card, and revise study window visits, inclusion/exclusion criteria, special handling requirements, prior and concomitant medication(s)/treatment(s).
23 August 2006	Amendment 3: protocol was amended to change from U.S. IND. US Study to Worldwide, and revise primary Packaging and Labeling Information

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported