



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 |
|-----------------------|----------|

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 |
| Arm title | 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

| | |
|------------------|------------------------|
| Arm title | RECOMBIVAX HB™ Vaccine |
|------------------|------------------------|

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

| Number of subjects in period 1 | 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 |
|-----------------------|--------------------------------------|

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.

| 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 |

Secondary: Percentage of Participants with Seroprotection (anti-HBsAg ≥ 10 mIU/mL) at Month 7

| | |
|--|---|
| End point title | Percentage of Participants with Seroprotection (anti-HBsAg ≥ 10 mIU/mL) at Month 7 |
| End point description: | |
| Seroprotection rate was measured as the percentage of participants with anti-HBsAg ≥ 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 |
| 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: 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

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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 10.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------|
| 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 schedule.

| | |
|-----------------------|--------------------------------------|
| 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 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 | |
| Nervous system disorders | | | |
| 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 | |
| General disorders and administration site conditions | | | |
| 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 | |
| Infections and infestations | | | |
| 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 | |
| Metabolism and nutrition disorders | | | |
| 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 %

| Non-serious adverse events | 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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported