SYNOPSIS

Name of Sponsor/Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product Modified Process RECOMBIVAX HB™ (HBVaxPRO®) 10 µg / 1 mL	Volume	
Name of Active Ingredient(s) Hepatitis B virus surface antigen, recombinant, 10 µg	Page	

TITLE OF STUDY

A study to estimate the immune response following a challenge dose in adults (≥50 years old) vaccinated with a primary series of an hepatitis B vaccine.

Study Identification Number: rHB01C (V232-059-10)

EudraCT Number: 2009-016721-33

COORDINATING INVESTIGATORS

Canada: None

Denmark: Lars OSTERGAARD, MD. Dept of Infectious Diseases, Skejby Hospital, Brendstrupsgaardsvej.

Sweden: Clas AHLM, MD. Dept of Infectious Diseases, Umeå University Hospital, Umeå.

United Kingdom (UK): Rajiv SHARMA, MD, Sea Road Surgery, East Sussex.

STUDY CENTERS

There were 20 centers in Canada, Denmark, Sweden and the UK from Study V232-59 who had eligible subjects (i.e. per-protocol subjects) for this study. All 20 centers enrolled subjects to this extension study in accordance with inclusion/exclusion criteria.

PUBLICATION (REFERENCE)

Not applicable

STUDIED PERIOD	06 months	**PHASE OF DEVELOPMENT**
First Visit First Subject:	02 November 2010	Phase 3
Last Visit Last Subject:	12 April 2011	

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OBJECTIVES

PRIMARY OBJECTIVES

1. To describe the seroprotection rate (SPR) at least 2 years following completion of a primary series of modified process RECOMBIVAX HB™ and 1 month following a challenge dose of modified process RECOMBIVAX HB™.
2. To describe the SPR at least 2 years following completion of a primary series of ENGERIX-B™ and 1 month following a challenge dose of modified process RECOMBIVAX HB™.

SECONDARY OBJECTIVE

To describe the safety and tolerability of a challenge dose of modified process RECOMBIVAX HB™ in adults ≥50 years of age.

EXPLORATORY OBJECTIVES

1. To describe the Geometric Mean Titer (GMT) at least 2 years following completion of a primary series of modified process RECOMBIVAX HB™ and 1 month following a challenge dose of modified process RECOMBIVAX HB™.
2. To describe the GMT at least 2 years following completion of a primary series of ENGERIX-B™ and 1 month following a challenge dose of modified process RECOMBIVAX HB™.

METHODOLOGY

This was an open-label, multicenter extension study of V232-059.

Subjects who participated in this extension study received a primary series of 3 doses of modified process RECOMBIVAX HB™ or ENGERIX-B™ following a 0, 1 and 6 months schedule in study V232-059.

A single challenge dose of 10 µg modified process RECOMBIVAX HB™ was administered on Day 1 to all subjects regardless of the primary series they received.

At Day 1, blood samples for detection of the hepatitis B surface antigens (HBsAg), the antibodies against HBsAg (anti-HBs) and against the hepatitis core antigen (anti-HBc) were obtained from eligible subjects prior to the administration of study vaccination. At Day 30, blood samples were collected for detection of anti-HBs.

Safety information was obtained during the 30-day period following vaccination.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED)

296 subjects were eligible, 204 were enrolled.

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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Healthy subjects who had received at ≥50 years of age, 3 doses of either modified process RECOMBIVAX HB™ or ENGERIX-B™ as per protocol for study V232-059 at least 2 years prior to enrolment in this study; no history of hepatitis B infection and no receipt of hepatitis B vaccine beyond what was administered in study V232-059; no known or suspected hypersensitivity to any component of modified process RECOMBIVAX HB™; no known or suspected impairment of immunologic function or recent use of immunomodulatory medications, or immune dysfunction that is caused by a medical condition or other cause; no receipt of hepatitis B immune globulin, serum immune globulin, any other blood-derived product or any investigational drug or vaccine in the past 3 months; no receipt of licensed inactivated or recombinant vaccine in the past 14 days, or of licensed live-virus vaccine in the past 30 days.

TEST VACCINE, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

The injection was administered intramuscularly; the preferred injection site was the deltoid muscle of the upper arm. The batch number was WL00039773.

REFERENCE VACCINE, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Not applicable.

DURATION OF FOLLOW-UP

Approximately 1 month for each subject.

CRITERIA FOR EVALUATION

IMMUNOGENICITY ENDPOINTS

The primary endpoint was the percentage of subjects with anti-HBs ≥10 mIU/mL (i.e. the SPR).

The exploratory endpoints were:

- The anti-HBs GMT
- The percentage of subjects with anti-HBs ≥5 mIU/mL (i.e. quantifiable antibody)
- The percentage of subjects with anti-HBs ≥100 mIU/mL.

SAFETY ENDPOINTS

The endpoints were:

- The solicited injection-site adverse experiences (AE) (i.e. pain, erythema and swelling) and fever (i.e. oral temperature ≥37.8ºC [100ºF]) from Day 1 inclusive to Day 5
- The unsolicited injection-site and systemic AEs and the serious AEs (SAEs) from Day 1 inclusive to Day 15
- The vaccine-related SAEs (considered to be possibly, probably or definitely related to the study vaccine) and deaths at any time during the study.

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STATISTICAL METHODS

IMMUNOGENICITY

The primary immunogenicity analyses and summaries were conducted on the Per Protocol Set (PPS). Subjects who generated positive (or equivocal) anti-HBc or HBsAg tests were excluded from the per-protocol analysis as well as subjects with protocol deviations that may interfere with immune responses.

Analyses were performed according to vaccine received during primary immunization in protocol V232-059 (i.e. modified process RECOMBIVAX HB™ [Group 1] or ENGERIX-B™ [Group 2]).

The number and percentage of subjects with anti-HBs titer ≥5 mIU/mL, ≥10 mIU/mL and ≥100 mIU/mL and the GMT were described for each group. Confidence intervals (CIs) for the percentage of subjects greater than each cut-off were calculated based on the exact method for binomial data. The CIs for the GMTs were based on the natural log-transformed titers and the t-distribution. Additionally, associated reverse cumulative distribution curves for the anti-HBs titers were provided.

Data were summarized at pre and post-challenge timepoints using the methodology described above and provided in each group on the full population and for the following 3 sub-populations:

1. Subjects who were not seroprotected in study V232-059 after receiving the primary vaccination series.
2. Subjects who were seroprotected in study V232-059 after receiving the primary vaccination series and at the pre-challenge follow-up time point.
3. Subjects who were seroprotected in study V232-059 after receiving a primary vaccination series, but had dropped below the seroprotection level at the pre-challenge follow-up time point.

For completeness and exploratory purposes both pre and post-challenge dose data were summarized on the Vaccinated Set (i.e., all subjects vaccinated with the challenge dose regardless of protocol deviations), and for each of the above 3 sub-populations.

SAFETY

All subjects who received a challenge dose in this study and had safety follow-up data were included in the safety and tolerability analysis. All data were summarized regardless of what a subject received for its primary vaccination. All injection-site AEs were considered as related to the study vaccine, while systemic AEs were considered unrelated or vaccine-related according to the investigator assessment.

The number and percentage of subjects reporting the following were described:

- AEs from Day 1 to Day 15
- Injection-site AEs from Day 1 to Day 15 (including those solicited [i.e. pain, erythema and swelling] from Day 1 to Day 5)
- Systemic AEs from Day 1 to Day 15 (including those with an incidence ≥1% in at least one group)

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- Fever (i.e. oral temperature ≥37.8°C [100.0°F]) from Day 1 to Day 5
- SAEs from Day 1 to Day 15
- Death and vaccine-related SAEs during the follow-up period

SUMMARY – CONCLUSIONS

DEMOGRAPHY

Of 296 eligible subjects, 204 were enrolled (68.9%). Of the 204 enrolled subjects, all were vaccinated and 2 (one subject in each group) (1.0%) did not complete the study. One subject was withdrawn at Visit 2 due to the blood draw not being collected, and one was lost to follow-up. The number of subjects excluded from the PPS was small (13 [6.4%]).

The majority of subjects were 50 to 64 years old (128 subjects [62.7%]) with a mean (standard deviation) age of the subjects at enrolment of 63.7 (7.0) years. Generally similar proportions for all demographic characteristics across the two vaccination groups were observed. There were more females (111 [54.4%]) than males (93 [45.6%]) due to an imbalance for those who received ENGERIX-B™ in the primary series vaccination study. The time interval between completion of the primary vaccination series and receipt of the challenge dose was 3.1 to 3.5 years for all subjects.

Prior active conditions in the past 3 years were reported by 182 (89.2%) subjects and were generally similar across both vaccination groups. The most frequently reported (>20% of subjects) were metabolism and nutrition disorders (93 subjects, 45.6%), musculoskeletal and connective tissue disorders (88 subjects, 43.1%), vascular disorders (84 subjects, 41.2%), gastrointestinal disorders (52 subjects, 25.5%) and psychiatric disorders (43 subjects, 21.1%).

Prior medications taken in the past 14 days were reported by 159 (77.9%) subjects and pertained mostly to drug categories linked to the prior active conditions. Prior medications reported by >15% of subjects pertained to the cardiovascular system (104 subjects, 51.0%), nervous system (96 subjects, 47.1%), alimentary tract and metabolism (67 subjects, 32.8%) and musculoskeletal system (36 subjects, 17.6%). A total of 167 (81.9%) subjects reported concomitant medications from Day 1 to Day 15 distributed as follows: cardiovascular system (104 subjects, 51.0%), nervous system (102 subjects, 50.0%), alimentary tract and metabolism (69 subjects, 33.8%) and musculoskeletal system (45 subjects, 22.1%). The rates for both prior and concomitant medications were generally similar in both vaccination groups.

IMMUNOGENICITY RESULTS

Primary Analysis

The percentage of subjects [95% CI] on the PPS who achieved anti-HBs titers ≥10 mIU/mL pre- and one month post-challenge dose was 45.5% [34.8, 56.4] and 85.2% [76.1, 91.9] respectively, in those who received modified process RECOMBIVAX HB™ in the primary vaccination series, and was 58.8% [48.6, 68.5] and 88.3%, [80.5, 93.8], respectively, for those who received ENGERIX-B™.

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Primary Vaccination Received in Study V232-059	Modified Process RECOMBIVAX HB N=88		ENGERIX-B N=103	
Challenge: Modified Process RECOMBIVAX HB	**Pre-Challenge n (%) [95% CI][a]**	**Post-Challenge n (%) [95% CI][a]**	**Pre-Challenge n (%) [95% CI][a]**	**Post-Challenge n (%) [95% CI][a]**
Anti-HBs Titers ≥10 mIU/mL	40 (45.5) [34.8, 56.4]	75 (85.2) [76.1, 91.9]	60 (58.8)[b] [48.6, 68.5]	91 (88.3) [80.5, 93.8]

Anti-HBs: Antibodies against HBsAg; CI: Confidence interval

[a]: 95% CI is computed using the Collett method

[b]: Calculated from 102 subjects due to 1 subject having a missing anti-HBs titer measurement pre-challenge dose

Exploratory Analysis

Full population

The GMT [95% CI] for all subjects on the PPS pre- and one month post-challenge dose was 12.3 mIU/mL [8.3, 18.4] and 957.4 mIU/mL [470.5, 1948.4], respectively, in those who received modified process RECOMBIVAX HB™ in the primary vaccination series, and 24.1 mIU/mL [15.6, 37.3] and 1497.6 mIU/mL [823.8, 2722.5], respectively, for those who received ENGERIX-B™.

Sub-populations

1. For subjects who were not seroprotected after the primary vaccination series, response rates ≥10 mIU/mL [95% CI] were numerically higher for subjects who received modified process RECOMBIVAX HB™ in the primary series (9/18 subjects - 50.0% [26.0, 74.0]) than for those who previously received ENGERIX-B™ (2/12 - 16.7% [2.1, 48.4]).
2. Subjects seroprotected before the challenge dose presented with high mean [95% CI] post-challenge GMT: 14699.1 mIU/mL [9646.2, 22398.7] for the subjects who previously received modified process RECOMBIVAX HB™ and 10097.1 mIU/mL [7291.2, 13982.8] for those who previously received ENGERIX-B™.
3. For subjects who were seroprotected after the primary vaccination series and had a pre-challenge anti-HBs titer <10 mIU/mL, post-challenge GMT and response rates ≥10 mIU/mL [95% CI] were 358.6 mIU/mL [140.9, 912.7] and 87.1% [70.2, 96.4], respectively, for the subjects previously receiving modified process RECOMBIVAX HB™ and 328.6 mIU/mL [152.3, 709.2] and 93.3% [77.9, 99.2], respectively, for those previously receiving ENGERIX-B™.

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Response rates on the Vaccinated Set showed a similar pattern of results to that on the PPS.

SAFETY RESULTS

All subjects received a full dose of modified process RECOMBIVAX HB™ by intramuscular route in the deltoid muscle.

No subjects were withdrawn from the study due to an AE.

A total of 87 (42.9%) subjects reported at least one AE in the 15 days following vaccination, 66 (32.5%) reported at least one injection-site AE and 46 (22.7%) at least one systemic AE. No deaths and no vaccine-related SAEs were reported throughout the study. One systemic SAE of severe bipolar disorder was reported on Day 12 by a 64-year-old female with a medical history of depression since 1975 that resolved in 28 days.

Most of the injection-site AEs were solicited (64 subjects, 31.5%) with injection-site pain being the most frequent (58 subjects, 28.6%) followed by injection-site erythema (11 subjects, 5.4%) and injection-site swelling (10 subjects, 4.9%). Among unsolicited injection-site AEs reported by 7 (3.4%) subjects, only pruritus was reported by ≥1% of subjects (4 subjects, 2.0%). All injection-site AEs reported by ≥1% of subjects were of mild intensity, or had a maximum size of 1 inch (2.5 cm), except 4 cases of pain rated as moderate. No injection-site AEs of severe intensity were reported. Solicited injection-site AEs occurred mostly on the day of vaccination and injection-site pruritus in the first 5 days. All injection-site AEs resolved, with the majority within 3 days.

Overall, 46 subjects (22.7%) reported systemic AEs. Nasopharyngitis was the most frequent with 7 events reported by 7 (3.4%) subjects. Systemic AEs reported by 20 (9.9%) subjects were assessed as vaccine-related by the investigators. Vaccine-related systemic AEs reported by ≥1% of subjects were headache (5 subjects, 2.5%), nasopharyngitis (3 subjects, 1.5%), cough (3 subjects, 1.5%) and back pain, nausea, dizziness, fatigue and oropharyngeal pain by 2 subjects each (1.0%). Systemic AEs were mostly of mild or moderate intensity. Two systemic AEs were reported as severe: an episode of back pain that occurred 4 days following vaccination and resolved in 3 days and the serious AE of bipolar disorder; none of them were assessed as vaccine-related.

Vaccine-related systemic AEs occurred mostly in the first 5 days following vaccination and resolved mostly in 3 days except one case of cough for which information on duration was not provided.

A maximum temperature ≥37.8°C [100°F] was reported by 2 subjects (1.0%) in the 5 days following vaccination: oral temperature of 37.9°C at Day 1 for 1 subject and of 38.5°C at Day 5 for the other.

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CONCLUSION

In subjects primed at ≥50 years of age with 3 doses of either modified process RECOMBIVAX HB™ or ENGERIX-B™ and who received a single challenge dose of 10 µg of modified process RECOMBIVAX HB™ after 3.1 to 3.5 years, the following was observed:

- One month post-challenge the rate of subjects with an anti-HBs titer ≥10 mIU/mL was >85% regardless of the hepatitis B vaccine used for the primary series.
- Pre-challenge GMT and percentages of subjects with anti-HBs titer above pre-defined thresholds were numerically lower in subjects who received a primary series of modified process RECOMBIVAX HB™ compared with those who received ENGERIX-B™.
- One month post-challenge GMT and response rates remained numerically lower in subjects who received a primary series of modified process RECOMBIVAX HB™ compared with those who received ENGERIX-B™ with a reduced difference when compared to before the challenge dose.
- One month post-challenge GMT and response rates were similar regardless of the hepatitis B vaccine used for the primary series in subjects with an anti-HBs titer >10 mIU/mL following the primary series and for which titers fell below the threshold of 10 before the challenge dose.
- The safety of a challenge dose of modified process RECOMBIVAX HB™ is consistent with the current European Summary of Product Characteristics.

DATE OF REPORT 15 February 2012