This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2. Synopsis

MERCK RESEARCH LABORATORIES V232; Hepatitis B Vaccine (Recombinant), Injection 3 x 10 at Months 0, 1, and 6; Vaccination for the Prevention of Hepatitis B Virus Infection	**CLINICAL STUDY REPORT SYNOPSIS**	
PROTOCOL TITLE/NO.: A Study in Healthy Young Adults to Assess the Safety, Tolerability, and Immunogenicity of a Recombinant Hepatitis B Vaccine Manufactured by a Process Upgrade		#054
INVESTIGATOR(S)/STUDY CENTER(S): This study was conducted at 17 sites; 10 in Finland, 3 in Belgium, and 4 in Sweden.		
PRIMARY THERAPY PERIOD: 30-Jun-2005 (first subject in) to 10-May-2006 (last subject out). Last subject completed follow-up: 10-May-2006. All data corrections applied (Frozen File): 27-May-2006.	CLINICAL PHASE:	III
DURATION OF TREATMENT: Three (3) doses of RECOMBIVAX HB™1 (hepatitis B vaccine [recombinant]) vs. recombinant hepatitis B vaccine manufactured by a modified process (hereafter referred to as modified process hepatitis B vaccine) administered as a 1-mL intramuscular injection at Day 1, Month 1, and Month 6 with a 15-day follow-up period after each dose. A Month 7 follow-up visit was required for the final serology sample.		
OBJECTIVE(S): Primary: Among healthy adults who receive the vaccine at 0, 1, and 6 months, to demonstrate that: (1) three lots of modified process hepatitis B vaccine induce similar responses in antibody to hepatitis B surface antigen (anti-HBs), as measured by seroprotection rate (SPR) 1 month after the third dose of vaccine; (2) one month after the third dose of vaccine, the combined modified process hepatitis B vaccine lots will exhibit an adequate seroprotection rate and (3) one month after the third dose of vaccine, the anti-HBs geometric mean titer (GMT) for the modified process hepatitis B vaccine will be improved, or at least non-inferior, when compared with the RECOMBIVAX HB™ (hepatitis B vaccine manufactured by the current process). Secondary: To assess the safety and tolerability of the modified process hepatitis B vaccine in healthy adults.		
STUDY DESIGN: This was a double-blind (operating under in-house blinding procedures), randomized, multicenter study of the safety, tolerability, and immunogenicity of a modified process hepatitis B vaccine and RECOMBIVAX HB™ (manufactured by the current process) in healthy young adults 20 to 35 years of age.		

[1] RECOMBIVAX HB is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

SUBJECT DISPOSITION:

	Modified Process Hepatitis B Vaccine					
	Lot A	Lot B	Lot C	Combined Lots	RECOMBIVAX HB™	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Randomized	217	214	215	646	214	860
Vaccinated						
Visit 1.0	217 (100)	214 (100)	215 (100)	646 (100)	214 (100)	860 (100)
Visit 2.0	214 (98.6)	212 (99.1)	213 (99.1)	639 (98.9)	213 (99.5)	852 (99.1)
Visit 3.0	211 (97.2)	205 (95.8)	206 (95.8)	622 (96.3)	208 (97.2)	830 (96.5)
Completed	209 (96.3)	204 (95.3)	206 (95.8)	619 (95.8)	206 (96.3)	825 (95.9)
Discontinued	8 (3.7)	10 (4.7)	9 (4.2)	27 (4.2)	8 (3.7)	35 (4.1)
Clinical AE	1 (0.5)	0 (0.0)	2 (0.9)	3 (0.5)	1 (0.5)	4 (0.5)
Lost to Follow-up	0 (0.0)	1 (0.5)	2 (0.9)	3 (0.5)	1 (0.5)	4 (0.5)
Subj. Moved	2 (0.9)	1 (0.5)	0 (0.0)	3 (0.5)	1 (0.5)	4 (0.5)
Withdrew Consent	0 (0.0)	2 (0.9)	0 (0.0)	2 (0.3)	1 (0.5)	3 (0.3)
Protocol Deviation	4 (1.8)	6 (2.8)	5 (2.3)	15 (2.3)	4 (1.9)	19 (2.2)
Other	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)

DOSAGE/FORMULATION NOS.: All subjects received a 3-dose regimen of the assigned vaccine on a 0-, 1-, and 6-month schedule, as a 1.0-mL intramuscular injection. The preferable injection site was the deltoid muscle of the upper arm. If other non-study vaccinations were administered at any time during the study, they were not to be administered in the same arm as the study vaccine. Clinical material was supplied in 3-mL vials containing 1 mL of vaccine, which were to be stored at 2 to 8ºC. Freezing of the vaccine was to be avoided.

Clinical Material	Control Number	Formulation Number	Potency per Dose
Recombinant Hepatitis B Vaccine Modified process hepatitis B vaccine, Lot A	[redacted]		10 mcg/mL
Recombinant Hepatitis B Vaccine Modified process hepatitis B vaccine, Lot B			10 mcg/mL
Recombinant Hepatitis B Vaccine Modified process hepatitis B vaccine, Lot C			10 mcg/mL
RECOMBIVAX HB™ (RECOMBIVAX HB Vaccine)			10 mcg/mL

DIAGNOSIS/INCLUSION CRITERIA: Subjects 20 to 35 years of age who were in general good health (based on a medical history taken on Day 1 prior to receiving the first injection of study vaccine); any underlying chronic illness must have been documented to be in stable condition. For all women, a negative urine pregnancy test was obtained just prior to vaccination on Day 1.

EVALUATION CRITERIA: Immunogenicity: Serology samples were obtained on Day 1 prior to the first vaccination and 1 month Postdose 3. These samples were tested for anti-HBs (antibody to hepatitis B surface antigen [HBsAg]) by using the VITROS ECi Immunodiagnostic Anti-HBs assay. Immunogenicity was evaluated at Month 7 (1 month after the final injection for the standard 3-dose regimen) with respect to SPR, defined as the percent of subjects with an anti-HBs titer ≥10 mIU/mL and anti-HBs GMT. Safety: All subjects were required to record any adverse experiences that occurred within 15 days following vaccination. Subjects were instructed to record oral evening temperatures daily for the first 5 days following vaccination.

STATISTICAL PLANNING AND ANALYSIS: Immunogenicity: The primary purpose of this study was to establish similarity among the 3 lots of modified process hepatitis B vaccine, and then to compare the modified process hepatitis B vaccine with RECOMBIVAX HB™. The statistical criterion for consistency was that the anti-HBs SPR would not differ statistically by more than 10 percentage points between any pair of lots. Six (6) pairwise comparisons were performed (2 one-sided tests, or TOST, at the alpha=0.05 level, or correspondingly, 3 two-sided 90% confidence intervals, for each of the 3 pairwise comparisons of the 3 lots) to show the equivalence of each pair of lots. The second primary hypothesis proposed that the combined lots of modified process hepatitis B vaccine would exhibit an adequate immune response. The statistical criterion was that the two-sided 95% confidence interval for the SPR have a lower bound that exceeds 90.0%. The primary endpoint for the comparison of modified process hepatitis B vaccine with RECOMBIVAX HB™ was the Month 7 GMT observed in each group. The primary purpose of the comparison of modified process hepatitis B vaccine with RECOMBIVAX HB™ was to show that the GMT induced by the modified process hepatitis B vaccine was at least non-inferior to and possibly superior to that induced by RECOMBIVAX HB™. The statistical criterion for non-inferiority required that the lower bound of the two-sided 95% confidence interval for the GMT ratio (GMTmodified process hepatitis B vaccine/GMTRECOMBIVAX HB™) exceed 0.67. Confidence intervals were constructed employing an analysis of variance (ANOVA) model with terms for treatment and study center. Conditional on the success of this hypothesis, the criterion for superiority required the lower bound of the confidence interval for the GMT ratio exceed 1.00. Other immunogenicity endpoints of interest were the percentage of subjects with a Month 7 anti-HBs titer ≥5 mIU/mL (quantifiable anti-HBs) and ≥100 mIU/mL. The primary analysis population was per-protocol. Safety: The adverse experience profile following each vaccination and for the entire 3-dose series was described for each group that received the modified process hepatitis B vaccine lots and the group that received RECOMBIVAX HB™. The key safety endpoints were the overall number of subjects reporting injection-site adverse experiences (including erythema, swelling/induration and pain/tenderness/soreness) as well as fever. A risk difference, a 95% confidence interval on the difference, and a probability value on the difference was calculated for comparisons of the combined lots of modified process hepatitis B vaccine and RECOMBIVAX HB™ for the data summarized over all 3 vaccinations for the adverse experiences listed above. Risk differences and a 95% confidence interval on the difference were employed to compare the 2 groups with respect to all adverse experiences reported by ≥1% of subjects in either group.

RESULTS: Immunogenicity: The percentage of subjects seroprotected at Month 7 ranged from 97.8 to 98.9% for the 3 lots of modified process hepatitis B vaccine for a combined SPR of 98.2%. The corresponding SPR for subjects receiving RECOMBIVAX HB™ was 98.5%. None of the bounds of the 90% confidence intervals on the pairwise difference in lots with respect to the SPR exceeded 4.6 percentage points. Therefore, consistency of the modified process hepatitis B vaccine lots was shown. The lower bound of the 95% confidence interval for the combined lots of modified process hepatitis B vaccine was 97.1%. Therefore, the second primary hypothesis regarding an adequate response for SPR was successful. Finally, the GMT response of the combined lots of modified process hepatitis B vaccine was compared with the GMT response for RECOMBIVAX HB™. The estimated GMT response for the combined lots of modified process hepatitis B vaccine was 1761 mIU/mL and the estimated GMT response for RECOMBIVAX HB™ was 1108 mIU/mL. The GMT ratio of modified process hepatitis B vaccine over RECOMBIVAX HB™ was 1.6. The 95% confidence interval for the ratio was 1.2 to 2.1. Therefore, the GMT ratio indicated superiority of the modified process hepatitis B vaccine compared with RECOMBIVAX HB™. Results of the all initially seronegative subjects with serology data set population were similar to those reported above.
Safety: The percentages of subjects reporting any adverse experience, injection-site or systemic adverse experiences were very similar across the 4 vaccination groups in this study. There were no serious vaccine-related adverse experiences in the study. There were 3 serious adverse experiences in the study, all in subjects who received modified process hepatitis B vaccine; however, none of these resulted in discontinuation. There were 2 discontinuations due to vaccine-related adverse experiences in subjects who received the modified process hepatitis B vaccine. No subjects died in this study.

CONCLUSIONS: In healthy young adults 20 to 35 years of age who received 3 doses of 1 of the 3 consistency lots of modified process hepatitis B vaccine or RECOMBIVAX HB™ at 0, 1 and 6 months, the following conclusions may be drawn: 1) The immune responses to modified process hepatitis B vaccine, as measured by the seroprotection rate, are similar among recipients of all 3 consistency lots. 2) The combined results from the consistency lots of modified process hepatitis B vaccine provide an acceptable seroprotection rate. 3) The combined results from the consistency lots of modified process hepatitis B vaccine demonstrate an immune response that is superior to that induced by RECOMBIVAX HB™, as measured by the GMT. 4) In general, the safety and tolerability profiles of all 3 consistency lots of modified process hepatitis B vaccine are comparable to those of RECOMBIVAX HB™. 5) Modified process hepatitis B vaccine and RECOMBIVAX HB™ are generally well tolerated. 6) The incidences of injection-site adverse experiences, systemic adverse experiences, and temperature elevations do not increase following successive vaccinations with modified process hepatitis B vaccine or RECOMBIVAX HB™.

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