2.0 SYNOPSIS

Name of the Sponsor: Dynavax Technologies Corporation	**Individual Study Table Referring to Part of the Dossier:**	**For National Authority Use Only**
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Title of Study: An Observer-Blinded, Randomized Study Comparing the Safety and Immunogenicity of HEPLISAV™ to Licensed Vaccine (Engerix-B®) among Adults (18 to 75 Years of Age) with Chronic Kidney Disease (CKD)

Investigator(s) and Study Center(s): Subjects were enrolled at 59 sites: 47 sites in the United States (US), 3 sites in Canada, and 9 sites in Germany.

Publication(s): None

Study Period: 28 September 2009 through 9 January 2012	**Development Phase:** 3

Objectives:

Primary Objective:

- To demonstrate the noninferiority of the immune response to a 3 single-dose regimen of HEPLISAV compared to the standard 4 double-dose regimen of Engerix-B in subjects with chronic kidney disease (CKD) at 4 weeks after the last dose of study treatment (Week 28) as measured by the seroprotection rate (SPR) defined as the percentage of subjects achieving an antibody level to hepatitis B surface antigen (anti-HBsAg) greater than or equal to 10 mIU/mL

Secondary Objectives:

- Conditional on the demonstration of the above primary objective: To demonstrate the superiority of the immune response to a 3 single-dose regimen of HEPLISAV compared to the standard 4 double-dose regimen of Engerix-B in subjects with CKD at 4 weeks after the last dose of study treatment (Week 28) as measured by the SPR.
- To evaluate the safety of HEPLISAV compared to Engerix-B in subjects with CKD
- To compare the immunogenicity of HEPLISAV to Engerix-B as measured by SPR at Weeks 4, 8, 12, 18, 24, 28, 36, 44, and 52
- To compare the immunogenicity of HEPLISAV to Engerix-B as measured by the percentage of subjects with anti-HBsAg greater than or equal to 100 mIU/mL at Weeks 4, 8, 12, 18, 24, 28, 36, 44, and 52
- To evaluate the immunogenicity of HEPLISAV compared to Engerix-B as measured by the serum anti-HBsAg geometric mean concentration (GMC) at Weeks 4, 8, 12, 18, 24, 28, 36, 44, and 52
- To evaluate the immune response as measured by SPR of subjects with type 2 diabetes mellitus who receive HEPLISAV compared to Engerix-B at 4 weeks after the last dose of study treatment (Week 28)

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Methods:

This was an observer-blinded, randomized study of 521 subjects with chronic kidney disease (CKD). Subjects were randomly assigned 1:1 to receive a 3 single-dose regimen of HEPLISAV (0, 4, and 24 weeks with a placebo at 8 weeks) or a 4 double-dose regimen (total of 8 doses) of the licensed hepatitis B vaccine, Engerix-B (0, 4, 8, and 24 weeks). To maintain the blind, subjects in the HEPLISAV group received an injection of HEPLISAV and a 0.5 mL intramuscular (IM) injection of saline in the deltoid muscle at Weeks 0, 4, and 24, and also received two 0.5-mL IM injections of saline at Week 8 administered in the deltoid muscle in same manner as Engerix-B. Randomization was stratified by glomerular filtration rate (GFR: Less than or equal to 15 mL/min/1.73 m^2, 16 to 30 mL/min/1.73 m^2, and 31 to 45 mL/min/1.73 m^2) and by site. Subjects were recruited from sites in the US, Canada, and Germany. After providing informed consent and meeting eligibility criteria, subjects received study injections at Weeks 0, 4, 8, and 24.

After completing Week 0/Visit 1, all subjects were to return at Weeks 4, 8, 12, 18, 24, 28, 36, 44, and 52 to undergo clinical safety evaluations and to have blood drawn for safety laboratory studies and for measurement of anti-HBsAg levels. Each randomized subject was expected to remain in the study through Week 52, including a 24-week injection period, as noted above, and a 28-week follow-up period after the final dose of study treatment (Weeks 24 through Week 52).

Hemodialysis subjects who were not seroprotected at Weeks 28, 36, or 44 were terminated from the study because they are at high risk for exposure to HBV in the dialysis setting and thus require additional immunizations consistent with national recommendations for hemodialysis patients.

After the Clinical Study Report (CSR) for the study was finalized in June 2012, additional information regarding Good Clinical Practice was found during site audits that required the immunogenicity data, but not the safety analyses data, to be reanalyzed by removing Site 42.

Number of Subjects Planned: Approximately 600 subjects were planned for enrollment.

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Number of Subjects Randomized and Analyzed:

Randomized population: N = 521 (HEPLISAV: n = 258; Engerix-B: n = 263)

Safety population: N = 516 (HEPLISAV: n = 254; Engerix-B: n = 262)

Modified intent-to-treat (mITT) population: N = 491 (HEPLISAV: n = 239; Engerix-B: n = 252)

Note: The size of the mITT population is smaller in this amended clinical study report (CSR) than in the original CSR because of the exclusion of 16 subjects who were treated at Site 42.

Per-Protocol population: N = 339 (HEPLISAV: n = 165; Engerix-B: n = 174)

Note: The size of the PP population is smaller in this amended CSR than in the original CSR for the following reasons:

- Exclusion of 16 subjects (HEPLISAV = 8; Engerix-B = 8) who where treated at Site 42
- Exclusion of 63 subjects (HEPLISAV = 27; Engerix-B = 36) who received vaccine that was not properly stored and who met the criteria for exclusion from the PP population. The number was previously reported as 24 subjects.

Subjects treated at Site 42 or who received improperly stored vaccine were not excluded from the safety analyses.

Diagnosis and Main Criteria for Eligibility:

Eligible subjects were 18 to 75 years of age, clinically stable, with CKD (loss of renal function as defined by a glomerular filtration rate [GFR] less than or equal to 45 mL/min/1.73 m^2). Subjects were required to be hepatitis-B vaccine-naïve; seronegative for hepatitis B surface antigen (HBsAg), anti-HBsAg, antibody against hepatitis B core antigen (anti-HBcAg), hepatitis C virus (HCV), and human immunodeficiency virus (HIV); and have no known history of autoimmune disease.

Test Product, Dose and Mode of Administration, Batch Number:

The test product (HEPLISAV) was 20 mcg recombinant HBsAg subtype *adw* with 3000 mcg 1018 immunostimulatory sequence (ISS) adjuvant manufactured by Rentschler Biotechnologie GmbH in Germany. Subjects in the HEPLISAV group received a single IM injection (0.5 mL) in the right or left deltoid muscle at Weeks 0, 4, and 24 (placebo at Week 8).

Lot Numbers: TDG006, TDG009, and TDG010

Reference Therapy, Dose and Mode of Administration, Batch Number:

The reference therapy was Engerix-B (20 mcg recombinant HBsAg combined with 500 mcg alum adjuvant/mL) manufactured by GlaxoSmithKline Biologicals.

Subjects in the Engerix-B group received 2 IM injections of 1.0 mL each (for a total dose of 40 mcg HBsAg and 1 mg alum) in the right or left deltoid muscle at Weeks 0, 4, 8, and 24.

Lot Numbers: AHBVB678AB, AHBVB734AA, AHBVB798AA, and AHBVB825BE

Placebo:

The placebo was 0.9% sterile saline for injection manufactured by Hospira, Inc.

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To match the number of injections in the Engerix-B group, subjects in the HEPLISAV group received a 0.5 mL IM injection of saline in the deltoid muscle at Weeks 0, 4, and 24. In addition, to maintain the study blind, these subjects also received two 0.5 mL IM injections of saline at Week 8 administered in the deltoid muscle in same manner as Engerix-B.

Lot Numbers: 75-245-DK, 86-167-DK, 90BH223, and 90BK068

Duration of Treatment:

The treatment period was 24 weeks (Week 0 to Week 24), with study injections administered at Weeks 0, 4, 8, and 24. Follow-up for safety and immunogenicity was conducted from Week 24 through Week 52.

Criteria for Evaluation:

Immunogenicity:

Anti-HBsAg serum concentrations were measured using the Ortho Vitros® enhanced chemiluminescence immunoassay.

Safety:

Safety was evaluated on the basis of the incidence, severity, and relationship to study treatment of adverse events (AEs), serious adverse events (SAEs), and potential autoimmune adverse events (AIAEs); incidence and severity of solicited local and systemic post-injection reactions; clinical laboratory tests (serum chemistry, hematology, antinuclear antibody [ANA], antibody to double-stranded DNA [anti-dsDNA]); vital sign measurements; and physical examinations.

Statistical Methods:

Initial analyses were performed to assess the immunogenicity endpoint data and interim safety data (including local and systemic post-injection reactions, AEs, SAEs, and AIAEs) after all subjects completed their Week 28 visit for the primary immunogenicity endpoint assessment. Final analyses were performed following completion of the trial. This report describes the final analyses, including safety data through Week 52 for all subjects.

The primary immunogenicity analysis was based on the mITT population. The mITT population for the immunogenicity analyses comprised all randomized subjects who received at least 1 study injection and had at least 1 post-injection immunogenicity evaluation excluding 16 subjects treated at Site 42.

The PP population for the immunogenicity analyses comprised all randomized subjects who received all study injections, had no major protocol deviations (as specified in the Statistical Analysis Plan and the Protocol Specification Document), and had an immunogenicity evaluation at Week 28.

The safety analysis population comprised all subjects who received at least 1 study injection and had on-study safety data. Subjects who received the wrong study treatment were analyzed *as treated* in the safety analyses, *as randomized* in the mITT analyses, and were excluded from the PP analyses.

All statistical tests were performed at the 2-sided 0.05 level of significance. Post-hoc statistical tests of safety event rates were performed by the 2-tailed Fisher's Exact Test. Nonsignificant *P* values are presented as not statistically significant (NS). No adjustments for multiple testing were made for immunogenicity since there is a single primary endpoint (SPR at Week 28). All tests of noninferiority based on SPR considered HEPLISAV SPR minus Engerix-B

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SPR with a prospectively defined noninferiority margin of -10%.

Summary – Results

Disposition and Demographics:

The percentage of subjects completing the study was the same (83.3%) in both the treatment groups. The most common reasons for early discontinuation from the study were consent withdrawn (4.7% in the HEPLISAV group, 6.1% in the Engerix-B group), other (4.3% in the HEPLISAV group, 4.2% in the Engerix-B group), lost to follow-up (3.1% in the HEPLISAV group, 3.8% in the Engerix-B group), and death (2.7% in the HEPLISAV group, 1.1% in the Engerix-B group).

In the safety population, subjects were predominantly male (61.1%) and white (78.9%), with a mean age of 61.3 years and a mean body mass index (BMI) of 33.1 kg/m^2; 85.1% of subjects had no smoking history; 64.7% had type 2 diabetes mellitus. Demographic variables generally were similar between treatment groups except for the higher percentage of subjects with type 2 diabetes mellitus randomized to HEPLISAV (68.1%) compared with Engerix-B (61.5%).

At the time of enrollment, 18.2% of subjects in the safety population had a GFR less than or equal to 15 mL/min/1.73 m^2, 37.8% of subjects had a GFR between 16 and 30 mL/min/1.73 m^2, and 44.0% of subjects had a GFR between 31 and 45 mL/min/1.73 m^2. A lower proportion of subjects in the HEPLISAV group (15.4%) had a GFR at enrollment less than or equal to 15 mL/min/1.73 m^2 compared with the Engerix-B group (21.0%). At the end of the trial, 13.1% of subjects were on hemodialysis with a similar proportion in each treatment group.

Immunogenicity Results:

In this large trial of CKD subjects, who are known to be hyporesponsive to hepatitis B vaccine, 3 single doses of HEPLISAV induced a superior immune response compared to 4 double doses (8 doses) of Engerix-B by providing superior peak immune responses, earlier seroprotection, and more persistent seroprotection. Peak immune responses were measured by SPR (anti-HBsAg greater than or equal to 10 mIU/mL), the percentage of subjects with anti-HBsAg greater than or equal to 100 mIU/mL, and GMC at the primary endpoint (Week 28). Early immune responses were measured by SPR primarily at Weeks 8 and 12. Persistence of seroprotection was measured by SPR, percentage of subjects with anti-HBsAg greater than or equal to 100 mIU/mL, and GMC at Week 52.

- Superior peak seroprotection was demonstrated at the primary endpoint (Week 28); the SPR in the HEPLISAV group was 89.5% (95% CI, 84.7%, 93.2%), and the SPR in the Engerix-B group was 81.3% (95% CI, 75.7%, 86.1%). The difference between these rates (HEPLISAV minus Engerix-B) was 8.2% (95% CI, 1.7%, 14.7%). The lower limit of the 95% CI was above the prospectively defined noninferiority criterion of -10%; therefore, the immune response of HEPLISAV was noninferior to Engerix-B. Furthermore, the immunogenicity of HEPLISAV was superior to that of Engerix-B because the lower limit of the 95% CI was above 0%.
- At Week 28, the peak percentage of subjects with anti-HBsAg greater than or equal to 100 mIU/mL in the HEPLISAV group (72.6%) was significantly higher than the peak percentage of subjects with anti-HBsAg greater than or equal to 100 mIU/mL in the Engerix-B group (62.1%) with a difference of 10.5% (95% CI, 1.8%, 18.9%).
- The immune response to HEPLISAV provided earlier seroprotection than the immune response to

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Engerix-B. At Week 8, after 2 single doses of HEPLISAV and 2 double doses (4 doses) of Engerix-B, the SPR in the HEPLISAV group (46.8%) was significantly higher than the SPR in the Engerix-B group (20.20%) with a difference between these rates of 26.8% (95% CI, 18.5%, 34.6%). The SPR in the HEPLISAV group at Week 12 (64.3%) was significantly higher than the SPR at Week 12 after 3 double doses of Engerix-B (49.8%) with a difference of 14.6% (95% CI, 5.6%, 23.2%) and was higher than the SPR in the Engerix-B group at Week 24 (61.5%).

- The immune response to HEPLISAV persisted to Week 52 at higher levels than the immune response to Engerix-B. At Week 52 (28 weeks after the last study treatment), 83.7% of subjects who received HEPLISAV maintained seroprotective antibody levels and 76.6% of subjects who received Engerix-B maintained such levels, with the difference of 7.1% (95% CI, -0.5%, 14.5%). At Week 52, significantly more subjects who received HEPLISAV had anti-HBsAg greater than or equal to 100 mIU/mL (65.6%) than those who received Engerix-B (47.7%) with a difference of 17.9% (95% CI, 8.4%, 26.9%). Throughout the trial, GMCs induced by HEPLISAV were significantly higher than those induced by Engerix-B. At Week 52, the GMC induced by HEPLISAV (155.8 mIU/mL) was 3.3-fold higher than that induced by Engerix-B (47.5 mIU/mL).
- HEPLISAV induced earlier seroprotection and a significantly higher immune response than Engerix-B in CKD subjects with and without type 2 diabetes mellitus. At Week 8, the SPR in subjects with type 2 diabetes mellitus who received HEPLISAV (40.3%) was significantly higher than the SPR in those with type 2 diabetes mellitus who received Engerix-B (15.6%) with a difference of 24.7% (95% CI, 14.8%, 33.8%). In addition, at Week 12, the SPR in subjects with type 2 diabetes mellitus who received HEPLISAV (57.7%) was significantly higher than the SPR in those with type 2 diabetes mellitus who received Engerix-B (44.6%) with a difference of 13.1% (95% CI, 1.9%, 23.9%). Also, at Week 28 the percentage of subjects with type 2 diabetes mellitus with anti-HBsAg greater than or equal to 100 mIU/mL who received HEPLISAV (68.7%) was higher than in those who received Engerix-B (59.3%). At Week 28, the GMC in subjects with type 2 diabetes mellitus who received HEPLISAV (397.5 mIU/mL) was significantly higher than the GMC in those with type 2 diabetes mellitus in the Engerix-B group (99.6 mIU/mL) with a ratio of GMCs of 4.0 (95% CI, 1.9, 8.5). At Week 8, the SPR in subjects without type 2 diabetes mellitus who received HEPLISAV (60.8%) was significantly higher than the SPR in those without type 2 diabetes who received Engerix-B (27.1%) with a difference of 33.7% (95% CI, 18.8%, 46.6%). In addition, at Week 12 the SPR in subjects who received HEPLISAV (78.4%) was significantly higher than the SPR in those who received Engerix-B (58.1%) with a difference of 20.3% (95% CI, 6.0%, 33.1%). At Week 28, the GMC in subjects without type 2 diabetes mellitus who received HEPLISAV (932.0 mIU/mL) was significantly higher than the GMC in subjects without type 2 diabetes mellitus who received Engerix-B (257.8 mIU/mL) with a ratio of GMCs of 3.6 (95% CI, .1.4, 9.4).
- HEPLISAV induced earlier seroprotection and a higher immune response than Engerix-B in groups known to have good responses to hepatitis B vaccines (eg, women, white subjects, black subjects) and in groups known to be hyporesponsive to hepatitis B vaccines (eg, older subjects, men, subjects with a BMI greater than or equal to 30 kg/m2). At Weeks 8 and 12, the SPRs in women, men, subjects 56 to 75 years of age, white subjects, black subjects, and subjects with a BMI greater than or equal to 30 kg/m^2 were significantly higher in those who received HEPLISAV than in those who received Engerix-B. For

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example, the SPRs in women who received HEPLISAV (Week 8: 60.5%, Week 12: 77.6%) were significantly higher than the SPRs in women who received Engerix-B (Week 8: 23.2%, Week 12: 61.2%), with differences of 37.2% (95% CI, 23.2%, 49.2%) at Week 8 and 16.4% (95% CI, 3.0%, 28.8%) at Week 12. In subjects 56 to 75 years of age, the SPRs in the HEPLISAV group (Week 8: 44.1%, Week 12: 61.7%) were significantly higher than the SPRs in the Engerix-B group (Week 8: 20.1%, Week 12: 48.9%), with differences of 24.0% (95% CI, 14.5%, 32.9%) at Week 8 and 12.8% (95% CI, 2.5%, 22.6%) at Week 12. At Week 28, in subjects 56 to 75 years of age, the percentage of subjects with anti-HBsAg greater than or equal to 100 mIU/mL was higher in those who received HEPLISAV (70.1%) than in those who received Engerix-B (58.8%). At Week 28, in subjects 56 to 75 years of age, the GMC in subjects who received HEPLISAV was 450.7 mIU/mL and in subjects who received Engerix-B was 128.2 mIU/mL (ratio of GMCs = 3.5; 95% CI, 1.8, 6.9). At Week 28, the GMCs in women, men, subjects 56 to 75 years of age, white subjects, black subjects, and subjects with a BMI greater than or equal to 30 kg/m2 were significantly higher in those who received HEPLISAV than in those who received Engerix-B. For example, at Week 28 the GMC in women who received HEPLISAV was 1510.6 mIU/mL and in women who received Engerix-B was 212.5 mIU/mL (ratio of GMCs = 7.1; 95% CI, 3.0, 16.7).

Safety Results:

- Overall, 46.6% of subjects in the HEPLISAV group and 50.8% of subjects in the Engerix-B group reported a local and/or systemic post-injection reaction. HEPLISAV recipients reported fewer local post-injection reactions than Engerix-B (HEPLISAV: 29.1%; Engerix-B: 34.6%). Injection site pain was the most common local reaction after any active injection (HEPLISAV: 27.9%; Engerix-B: 34.2%). Severe local reactions were infrequent (HEPLISAV: 1.6%; Engerix-B: 0.8%). The frequency of systemic reactions was similar between the HEPLISAV and Engerix-B groups (HEPLISAV: 33.9%; Engerix-B: 35.0%). Fatigue was the most common systemic reaction after any active injection (HEPLISAV: 21.5%; Engerix-B: 25.0%). Severe systemic reactions also were infrequent (HEPLISAV: 4.4%; Engerix-B: 2.7%). Overall reactogenicity tended to decrease with subsequent injections in both treatment groups.
- AEs were reported by most of the subjects in both treatment groups (HEPLISAV: 76.8%; Engerix-B: 75.6%), generally reflecting the comorbidities of the study population. The most common AE was chronic renal failure (HEPLISAV: 7.1%; Engerix-B: 8.8%). A substantial percentage of subjects in both groups experienced a severe AE (HEPLISAV: 23.2%; Engerix-B: 24.4%). The most common severe AE was chronic renal failure (HEPLISAV: 3.9%; Engerix-B: 4.2%). AEs considered by the investigator to be related to study treatment were relatively infrequent in both treatment groups (HEPLISAV: 7.5%; Engerix-B: 9.9%); the most common related AE was injection site erythema (HEPLISAV: 1.2%; Engerix-B: 1.9%).
- Ten deaths occurred during the study (HEPLISAV: n = 7 [2.8%]; Engerix-B: n = 3 [1.1%]; $P = 0.31$). None of the deaths were considered by the investigator to be related to the study treatment.
- SAEs occurred in a similar percentage of subjects in each treatment group (HEPLISAV: 26.8%; Engerix-B: 29.0%). Most SAEs were considered unrelated to the study treatment and reflected the comorbidities of the study population. One SAE was considered by the investigator to be probably related to study treatment: end-stage renal disease in 1 subject in the HEPLISAV group.

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- No confirmed new onset AIAEs occurred during the trial. Potential AIAEs were non-serious and infrequent. One AIAE (hypothyroidism) occurred in the Engerix-B group and was confirmed by the SEAC as autoimmune but not related to study treatment. Subsequent testing of blood from the Week 0 visit for thyroid function demonstrated the hypothyroidism was a pre-existing condition prior to enrollment.
- An additional subject with a potential autoimmune adverse event (AIAE) of hypothyroidism was identified after the trial was completed.
- Safety data were analyzed for a subgroup of 23 subjects inadvertently enrolled with pre-existing autoimmune (PEAI) conditions identified after enrollment. Of these, the 11subjects who received HEPLISAV did not experience exacerbations of their pre-existing disease or have higher rates of AEs or SAEs than the 12 subjects who received Engerix-B.
- No clinically meaningful differences in hematology or serum chemistry laboratory values or laboratory-related AEs were observed between treatment groups. Pre- and post-injection ANA and anti-dsDNA results were similar between treatment groups.

In summary, the 3 single-dose regimen of HEPLISAV demonstrated a safety profile similar to that of the 4 double-dose regimen of Engerix-B. Specifically, HEPLISAV was slightly less reactogenic than Engerix-B, and had similar rates of AEs, SAEs, and potential AIAEs. In those enrolled with pre-existing autoimmune conditions, exacerbation of disease was not observed in either treatment group. There were 7 deaths in the HEPLISAV group and 3 deaths in the Engerix-B group; none were considered by the investigators to be related to the study treatment.

Conclusions:

In this large trial of CKD subjects, a population known to be hyporesponsive to licensed hepatitis B vaccines and at high risk of HBV infection, 3 single doses of HEPLISAV induced a superior immune response to 4 double doses (8 doses) of Engerix-B by providing superior peak seroprotection, earlier seroprotection, and more persistent seroprotection. HEPLISAV generally was well tolerated and had a similar safety profile to Engerix-B. There was no difference in the frequency of autoimmune events in subjects who received HEPLISAV compared with subjects who received Engerix-B.

HEPLISAV is more effective than Engerix-B in providing higher and earlier seroprotection against hepatitis B virus in subjects with CKD.

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