DV2-HBV-24

STUDY PROTOCOL

An Open-label, Single Arm Study, Evaluating the Immunogenicity and Safety of HEPLISAV-B® in Adults With End-Stage Renal Disease Undergoing Hemodialysis

NCT03934736

Amendment 4: 17 April 2020
Amendment 3: 22 July 2019
Amendment 2: 13 February 2019
Amendment 1: 18 December 2018
Original: 20 August 2018

Protocol Title: An Open-label, Single Arm Study, Evaluating the Immunogenicity and Safety of HEPLISAV-B® in Adults With End-Stage Renal Disease Undergoing Hemodialysis

Protocol No.: DV2-HBV-24

Investigational Product: HEPLISAV-B®

US IND Number: IND 12692

Indication: Prevention of Hepatitis B Virus Infection

Study Phase: 1

Sponsor: Dynavax Technologies Corporation
2100 Powell Street, Suite 900
Emeryville, CA 94608
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Medical Monitor: [redacted]

Clinical Operations: [redacted]

Amendment 4: 17 April 2020
Amendment 3: 22 July 2019
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This study will be conducted in accordance with the International Council for Harmonisation (ICH) E6(R2) Good Clinical Practice (GCP) guidelines and applicable local legal and regulatory requirements.

INVESTIGATOR SIGNATURE PAGE

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DECLARATION OF INVESTIGATOR

I confirm that I have read and understood this protocol and agree to conduct the study as outlined in the protocol and other information supplied to me. I agree to conduct the study in accordance with ICH E6(R2) GCP guidelines and applicable local legal and regulatory requirements.

_____ _____
Investigator Signature Date

_____
Investigator Name (Print)

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PROTOCOL SYNOPSIS

Protocol Title: An Open-label, Single Arm Study, Evaluating the Immunogenicity and Safety of HEPLISAV-B® in Adults With End-Stage Renal Disease Undergoing Hemodialysis

Protocol No.: **DV2-HBV-24**

Investigational Medicinal Product: HEPLISAV-B®

Study Phase: 1

No. of Centers: 25

Sample Size: N = Approximately 115 subjects

Study Objectives:

Primary

- To evaluate the safety of HEPLISAV-B with respect to clinically significant adverse events
- To evaluate the immunogenicity induced by HEPLISAV-B at Week 20 as measured by seroprotection rate (SPR)

Secondary

- To evaluate the immunogenicity of HEPLISAV-B as measured by the percentage of subjects with anti-HBs (antibodies against hepatitis B surface antigen) concentration ≥100 mIU/mL
- To evaluate the immunogenicity of HEPLISAV-B as measured by the anti-HBs geometric mean concentration (GMC)
- To evaluate the immunogenicity of HEPLISAV-B at each study visit through 20 weeks after the first dose of study vaccine as measured by the SPR

Study Design: This is an open-label, single arm study design to evaluate HEPLISAV-B in adults with end-stage renal disease (ESRD) who are initiating or undergoing hemodialysis. Eligible subjects will receive HEPLISAV-B at Weeks 0, 4, 8 and 16 and will be followed through Week 68. The study is designed to evaluate the immunogenicity over the 20-week period and safety over the 68-week period.

Subjects will be evaluated for participation in a screening period of up to 4 weeks prior to first dose. Subjects will return to the clinic for periodic

visits as per the schedule of assessments for study specific evaluations including evaluation of immunogenicity and safety.

For subjects who are not seroprotected at the end of Week 20, the investigator will discuss options for obtaining seroprotection.

Study Flow Diagram

	Screening	HEPLISAV-B Treatment				Follow-Up			
Day:	-28	1	29	57	113	141	197	295	477
Week:	-4	0	4	8	16	20	28	42	68
N = approx 115		**X**	**X**	**X**	**X**				

X = study injection

Study Duration: The total duration of study participation is up to 72 weeks, which includes a 4-week screening period, a 16-week injection period, and a 52-week follow-up period.

Study Assessments: The schedule of visits and study assessments is presented in detail in Appendix 1.

Immunogenicity: Anti-HBs will be measured at baseline and then at Weeks 4, 8, 16, and 20.

Safety: Subjects will be monitored for safety until Week 68. Safety evaluations include assessment of:

- The subject's continued eligibility (per eligibility criteria, as relevant) to receive an injection prior to the administration of each study injection
- Medically-attended adverse events (MAEs) occurring from immediately post the first study injection through End-of-Study (EOS) Visit.
- Serious adverse events (SAEs) and deaths occurring from the time the subject signs informed consent through EOS Visit.
- Acute Myocardial Infarctions (AMIs; including ST-segment elevation and non-ST-segment elevation) and adverse events of special interest (AESIs; defined in Appendix 4) occurring from immediately post the

first study injection through EOS Visit. AMIs and AESIs will be reviewed periodically by a Safety Monitoring Committee (SMC).

- Post-injection local and systemic reactions for 7 days after each study injection

Study Treatment: HEPLISAV-B, a licensed, commercially-available hepatitis B vaccine consisting of 20 mcg of HBsAg and 3000 mcg of cytidine phosphoguanosine (CpG) 1018 adjuvant

Dosage and Administration:

- A single dose of 0.5 mL HEPLISAV-B administered intramuscularly in the deltoid muscle at Week 0 (Visit 1), Week 4 (Visit 2), Week 8 (Visit 3), and Week 16 (Visit 4)

Study Population: Adults with ESRD initiating or undergoing hemodialysis who have not previously received a hepatitis B vaccine

Eligibility Criteria: **Inclusion Criteria:**

A subject must meet all of the following criteria to be eligible for the study:

1) Male and female subjects at least 18 years of age
2) Laboratory confirmed negative serology result to hepatitis B virus (HBV) surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), and antibody to hepatitis B core antigen (anti-HBc) prior to first study injection
3) Must be clinically stable and in the opinion of the investigator able to comply with all study procedures
4) Must be able and willing to provide informed consent
5) Receiving hemodialysis or will initiate hemodialysis within 4 weeks of first study injection
6) Women of childbearing potential (WOCBP) must consistently use an acceptable method of contraception or confirm in writing she will abstain from sexual activity from the Screening visit through 4 weeks after the last dose of study injection. Acceptable birth control methods include but are not limited to oral contraceptive medication, an intrauterine device (IUD), an injectable contraceptive (such as medroxyprogesterone acetate or Depo-Provera®), a birth control

patch, or a barrier method (such as condom or diaphragm with spermicide).

Exclusion Criteria:

A subject with any one of the following criteria is not eligible for the study:

1) Previous receipt of any hepatitis B vaccine
2) History of human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection or antibody to HIV or HCV
3) History of sensitivity to any component of HEPLISAV-B vaccine
4) Substance or alcohol abuse that in the opinion of the investigator would interfere with compliance or with interpretation of the study results
5) Recent or ongoing history of febrile illness (within 7 days of the first study injection)
6) Has received any of the following prior to the first study injection:
   - **a) Within 14 days:**
     - i) Any inactivated vaccine
   - **b) Within 28 days:**
     - i) Systemic corticosteroids (more than 3 consecutive days) or other immunomodulatory or immune suppressive medication with the exception of inhaled steroids
     - ii) Any live virus vaccine
     - iii) Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF)
     - iv) Any other investigational medicinal agent
   - **c) Within 90 days:**
     - i) Blood products or immunoglobulin
7) If female and pregnant, nursing, or planning to become pregnant during the study

8) Undergoing chemotherapy or expected to receive chemotherapy during the study period.

9) Has a medical condition considered by the investigator likely to interfere with the subject's compliance or the interpretation of study assessments, including the following laboratory abnormalities which the investigator may consider if severe:

   a) Anemia

   b) Thrombocytopenia

   c) Leukocytosis

   d) Neutropenia

   e) Metabolic acidosis

   f) Increased alanine aminotransferase or aspartate aminotransferase

   g) Hyperkalemia

   h) Hypokalemia

10) Is scheduled to undergo a kidney transplant within 6 months of the first study injection

Statistical Methods

The Safety Population will comprise all subjects who received at least 1 study injection, excluding subjects who have no on-study safety data.

The Per-protocol (PP) Population for the immunogenicity analysis will comprise all subjects who receive all study injections, have no major protocol violations (to be specified in the Statistical Analysis Plan), and have anti-HBs levels obtained within study visit windows at Week 20.

The modified intent-to-treat (mITT) population for the immunogenicity analysis will comprise all subjects who receive at least 1 study injection and have at least 1 post-injection immunogenicity evaluation.

For immunogenicity analysis, the SPR at specified timepoints will be estimated. The associated 2-sided 95% confidence interval will be calculated using the Clopper-Pearson method.

For safety analysis, the incidence and proportion of post-injection reactions and MAEs will be summarized. MAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) System of Organ Class (SOC) and Preferred Term (PT).

The sample size calculation is based on approximately 100 subjects in the per-protocol population. With an expected 15% loss to follow up prior to week 20, approximately 115 subjects will be enrolled. This sample size would allow estimating immunogenicity response at the following accuracy levels depending on the observed immunogenicity responses:

N	If Observed Immunogenicity Response is	Width of the Resulting 95% Confidence Interval	Lower Limit of the Resulting 95% Confidence Interval[a]
100	80.0%	0.165	70.8%
100	86.0%	0.145	77.6%
100	90.0%	0.127	82.4%
100	95.0%	0.096	88.7%

N = number of subjects
[a] Calculation based on exact method (Clopper-Pearson)
Note: Approximately 115 subjects will be enrolled to meet the N of 100 evaluable subjects in the per-protocol population.

A preliminary analysis may be performed to assess the primary immunogenicity objective of the SPR at Week 20 after approximately 50 subjects have completed their Week 20 visit.

1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
AE	adverse event
AESI	adverse event of special interest
AMI	acute myocardial infarction
anti-HBc	antibodies against hepatitis B core antigen
anti-HBs	antibodies against hepatitis B surface antigen
AR	adverse reaction
CFR	Code of Federal Regulations
CKD	chronic kidney disease
CpG	cytidine phosphoguanosine
CRF	case report form
CRO	Contract Research Organization
CSR	Clinical Study Report
DNA	deoxyribonucleic acid
eCRF	electronic case report form
EDC	electronic data capture
EOS	End-of-Study (visit)
ESRD	end-stage renal disease
FDA	United States Food and Drug Administration
FSH	follicle stimulating hormone
GCP	good clinical practice
GMC	geometric mean concentration
HBcAg	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IUD	intrauterine device

Abbreviation or Term	Definition
MAE	medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat (population)
SAE	serious adverse event
SAR	suspected adverse reaction
SMC	Safety Monitoring Committee
SPR	seroprotection rate
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
UNS	unscheduled visit/safety follow-up visit
WOCBP	women of child-bearing potential

2.0 INTRODUCTION AND RATIONALE

2.1 Hepatitis B Infection in Patients With Chronic Kidney Disease

Chronic Kidney Disease (CKD) patients are at increased risk of exposure to hepatitis B virus (HBV) in the hemodialysis setting where prolonged vascular access is required. In an environment where multiple patients receive dialysis concurrently, repeated opportunities exist for person-to-person transmission of infectious agents, directly or indirectly via contaminated devices, equipment and supplies, environmental surfaces, or hands of healthcare personnel.

The Advisory Committee on Immunization Practices recommends that hemodialysis patients receive hepatitis B vaccination (Schillie, Vellozzi et al. 2018). Unlike healthy individuals, in patients with CKD, long-term protection against HBV infection depends on maintenance of anti-HBs (antibodies against HBsAg) because of impaired anamnestic responses (Girndt and Litjens 2010). Long-term maintenance of an anti-HBs level ≥ 10 mIU/mL is desirable since breakthrough infections have occurred in patients with CKD with levels < 10 mIU/mL (Buti, Viladomiu et al. 1992, Miller, Alter et al. 1999), and the duration of protection against HBV depends on the peak post-vaccination antibody level (Jilg, Lorbeer et al. 1984, Floreani, Baldo et al. 2004). Some authors have proposed that an anti-HBs level ≥ 100 mIU/mL is desirable in CKD patients because it correlates better with longer duration of protection than lower levels (Navarro, Teruel et al. 1996, Sezer, Ozdemir et al. 2000, Chaves, Daniels et al. 2011).

At the end of 2015, an estimated 444,337 patients were on chronic hemodialysis in the US with more than 108,826 patients initiating hemodialysis that year, many of whom likely needed hepatitis B vaccination (National Institutes of Health 2017).While the number of HBV infections reported in hemodialysis patients in the US is low, the risk of transmission remains high and dialyzing patients with HBV infection requires special precautions including using dedicated rooms, machines, instruments, medications, supplies, and staff to reduce the risk of infecting other patients (Centers for Disease Control and Prevention 2001, Schillie, Vellozzi et al. 2018).

2.2 Clinical Experience With HEPLISAV-B

A summary of the clinical studies conducted with HEPLISAV-B® in healthy adults is provided in the United States Package Insert (USPI) (Appendix 2) and the Investigator's Brochure.

In the CKD clinical development program, Dynavax completed the following 3 studies to evaluate the use of HEPLISAV-B in patients with CKD, which included patients on hemodialysis:

- DV2-HBV-17, Safety and immunogenicity: 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)
- DV2-HBV-18, Booster: An Open-Label, Randomized, Multi-Center Study Comparing the Safety and Immunogenicity of HEPLISAV™ to Engerix-B® and Fendrix® in Adults on Hemodialysis Who Have Previously Received Hepatitis B Vaccination and Are Not Seroprotected
- DV2-HBV-19, Long-term follow up: An Observational Study Evaluating the Long-Term Safety and Immunogenicity of HEPLISAV™ Compared with Engerix-B® in Adults With Chronic Kidney Disease Who Have Previously Received at Least One Hepatitis B Vaccine Series

Dynavax vaccinated 620 adults with CKD in trials HBV-17 and HBV-18, including 308 subjects who received HEPLISAV-B and 312 subjects who received Engerix-B (HBV-19 was a long-term observational study of subjects who were enrolled in HBV-17).

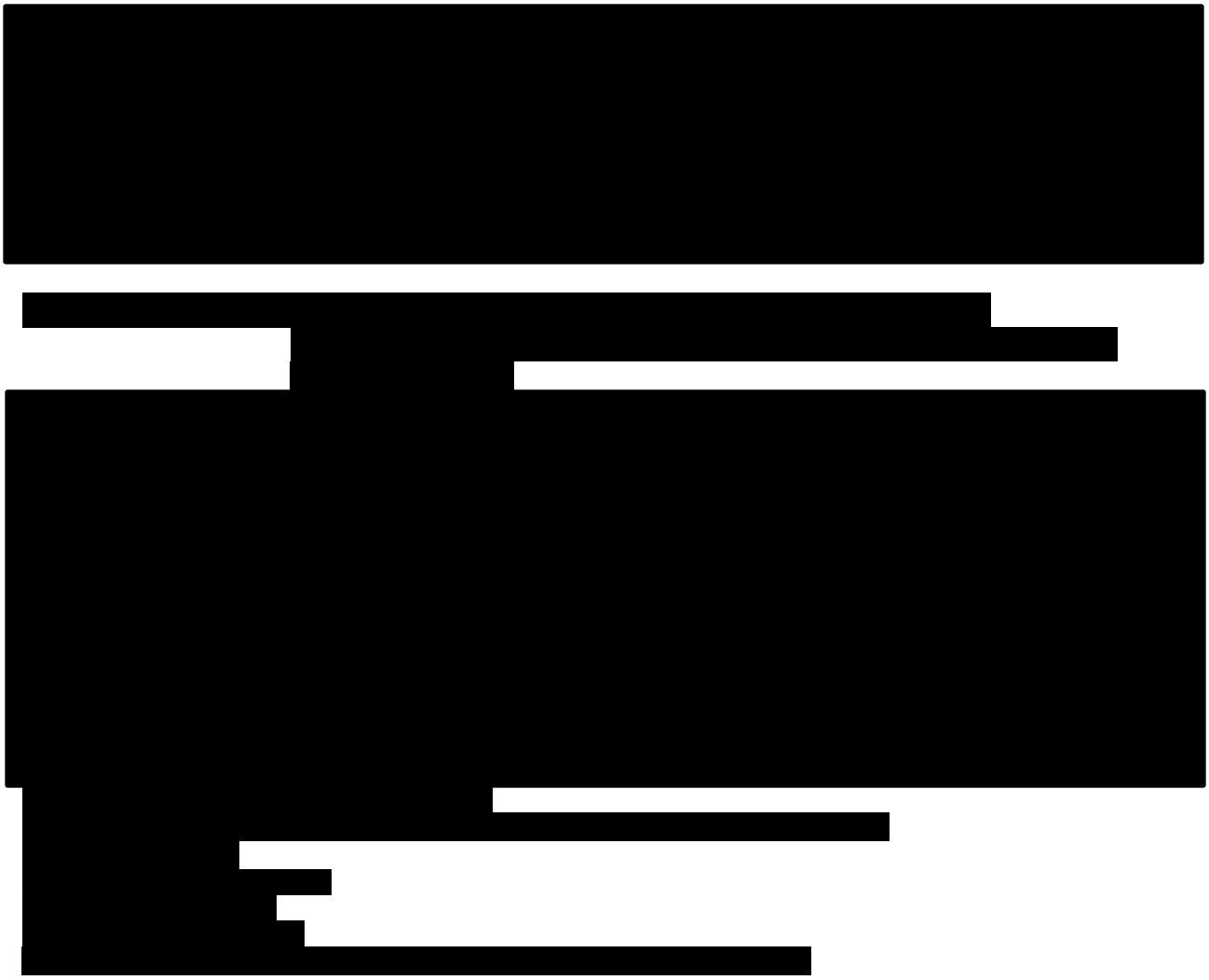
For additional information on experience with CKD, please refer to the Investigator's Brochure.

2.3 Overview of Immunogenicity in CKD Subjects

The HBV-17 study enrolled 521 subjects (HEPLISAV-B: n = 258; Engerix-B: n = 263). Of these, a subset of patients (N = 68, or 13.1%) in study HBV-17 were on hemodialysis either at the start of the study or initiated hemodialysis during the study.

The HBV-17 trial compared the immune response following a 3-injection regimen with HEPLISAV-B administered over a 6-month period (Weeks 0, 4, and 24) versus the standard 8-injection (4 double doses) regimen of Engerix-B, also administered over a 6-month period (Weeks 0, 4, 8, and 24). The primary objective of HBV-17 was to demonstrate the noninferiority of the seroprotection rate (SPR) at 4 weeks after the last active dose of HEPLISAV-B (Week 28) to the SPR at 4 weeks after the last active dose of Engerix-B (Week 28). The noninferiority margin was -10% in the difference in SPRs (HEPLISAV-B minus Engerix-B). Both the primary endpoint of noninferiority and the secondary endpoint of significantly higher immune response, measured by SPR, were demonstrated.

[redacted]



2.4 Study Rationale

In this study, the safety and immunogenicity in patients on hemodialysis will be evaluated further to investigate an optimal dosing regimen for this patient population. An optimal dosing regimen for HEPLISAV-B that induces higher rates of protection, earlier onset of protective immunity, and longer duration of protection in hemodialysis patients would be an important advance in vaccine development given the ongoing risk of HBV infection in the hemodialysis setting and consequences of HBV infection in this highly compromised patient population.

This study will consist of a 4-injection (0.5 mL per injection) regimen of HEPLISAV-B at Weeks 0, 4, 8, and 16. It is anticipated that a fourth dose of HEPLISAV-B will provide improved seroprotection than what was seen in study HBV-17 for hemodialysis patients.

For the primary immunogenicity endpoint, SPR will be evaluated at Week 20, 4 weeks after the last injection, because the peak SPR for hemodialysis subjects in study HBV-17 was observed 4 weeks after the last injection (Week 28).

3.0 STUDY OBJECTIVES

3.1 Primary Objective

- To evaluate the safety of HEPLISAV-B with respect to clinically significant adverse events
- To evaluate the immunogenicity induced by HEPLISAV-B at Week 20 as measured by the seroprotection rate (SPR)

3.2 Secondary Objectives

- To evaluate the immunogenicity of HEPLISAV-B as measured by the percentage of subjects with anti-HBs concentration ≥100 mIU/mL
- To evaluate the immunogenicity of HEPLISAV-B as measured by the anti-HBs geometric mean concentration (GMC)
- To evaluate the immunogenicity of HEPLISAV-B at each study visit through 20 weeks after the first dose of study vaccine as measured by the SPR

4.0 INVESTIGATIONAL PLAN

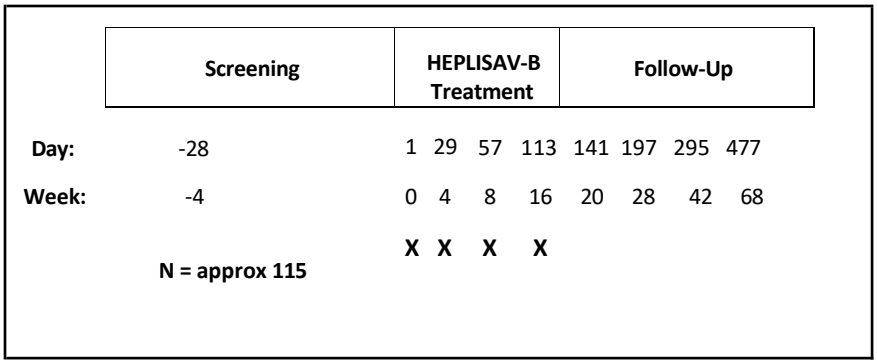
4.1 Study Design

This is an open-label, single arm study design to evaluate HEPLISAV-B in adults with end-stage renal disease (ESRD) who are initiating or undergoing hemodialysis. Eligible subjects will receive HEPLISAV-B at Weeks 0, 4, 8 and 16 and will be followed through Week 68 (Figure 4-1). The study is designed to evaluate the immunogenicity and safety over the 68-week period. Study assessments are outlined in Appendix 1.

Subjects will be evaluated for participation in a screening period of up to 4 weeks prior to first dose. Subjects will return to the clinic for periodic visits as per the schedule of assessments for study specific evaluations including evaluation of immunogenicity and safety (Appendix 1).

For subjects who are not seroprotected at the end of Week 20, the investigator will discuss options for obtaining seroprotection.

Figure 4-1: Study Flow Diagram



X = study injection

4.2 Study Endpoints

4.2.1 Primary Endpoint

- Proportion of subjects with treatment-emergent MAEs
- Proportion of subjects with treatment-emergent SAEs, acute myocardial infarctions (AMIs), or deaths
- Proportion of subjects with treatment-emergent immune-mediated adverse events of special interest (AESIs)
- SPR at Week 20

4.2.2 Secondary Endpoints

- Proportion of subjects with anti-HBs concentration ≥100 mIU/mL
- Anti-HBs geometric mean concentration (GMC)
- SPR at each study visit after the first dose of study vaccine

4.3 Duration of Study

The total duration of study participation is up to 72 weeks, which includes a 4-week screening period, a 16-week injection period, and a 52-week follow-up period.

4.4 Randomization

None of the patients in this study will be randomized.

4.5 Blinding

Blinding will not be performed as this is an open-label study.

4.6 Appropriateness of Measurements

The measures of both immunogenicity and safety in the study are routine clinical and laboratory procedures. The definition of seroprotection used in this study (anti-HBs ≥ 10 mIU/mL) is the same as that upon which the approval of licensed HBV vaccines has been based (Centers for Disease Control and Prevention 1985, Keating and Noble 2003) and is considered the standard in the medical-scientific community.

5.0 SELECTION OF PATIENTS

The study population will include adults with ESRD initiating or undergoing hemodialysis who have not previously received a hepatitis B vaccine and who meet the inclusion and exclusion criteria as described in detail in Sections 5.1 and 5.2.

5.1 Inclusion Criteria

A patient must meet all of the following criteria to be eligible for enrollment (defined as receiving the first study treatment [ie, HEPLISAV-B injection]) in the study:

1) Male and female subjects at least 18 years of age
2) Laboratory confirmed negative serology result to hepatitis B virus (HBV) surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), and antibody to hepatitis B core antigen (anti-HBc) prior to first study injection
3) Must be clinically stable and in the opinion of the investigator able to comply with all study procedures
4) Must be able and willing to provide informed consent
5) Receiving hemodialysis or will initiate hemodialysis within 4 weeks of first study injection
6) Women of childbearing potential (WOCBP) must consistently use an acceptable method of contraception or confirm in writing she will abstain from sexual activity from the Screening visit through 4 weeks after the last dose of study injection. Acceptable birth control methods include but are not limited to oral contraceptive medication, an intrauterine device (IUD), an injectable contraceptive (such as medroxyprogesterone acetate or Depo-Provera®), a birth control patch, or a barrier method (such as condom or diaphragm with spermicide).

5.2 Exclusion Criteria

A subject with any one of the following criteria is not eligible for the study:

1) Previous receipt of any hepatitis B vaccine
2) History of human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection or antibody to HIV or HCV
3) History of sensitivity to any component of HEPLISAV-B vaccine
4) Substance or alcohol abuse that in the opinion of the investigator would interfere with compliance or with interpretation of the study results
5) Recent or ongoing history of febrile illness (within 7 days of the first study injection)
6) Has received any of the following prior to the first study injection:
   a) Within 14 days:
      i) Any inactivated vaccine
   b) Within 28 days:
      i) Systemic corticosteroids (more than 3 consecutive days) or other immunomodulatory or immune suppressive medication with the exception of inhaled steroids
      ii) Any live virus vaccine
      iii) Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF)
      iv) Any other investigational medicinal agent
   c) Within 90 days:
      i) Blood products or immunoglobulin
7) If female and pregnant, nursing, or planning to become pregnant during the study
8) Undergoing chemotherapy or expected to receive chemotherapy during the study period

9) Has a medical condition considered by the investigator likely to interfere with the subject's compliance or the interpretation of study assessments, including the following laboratory abnormalities which the investigator may consider if severe:
   a) Anemia
   b) Thrombocytopenia
   c) Leukocytosis
   d) Neutropenia
   e) Metabolic acidosis
   f) Increased alanine aminotransferase or aspartate aminotransferase
   g) Hyperkalemia
   h) Hypokalemia
10) Is scheduled to undergo a kidney transplant within 6 months of the first study injection

5.2.1 Contraception

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. All female patients are considered to be WOCBP except if they have been postmenopausal (amenorrhea for at least 12 consecutive months or on hormone replacement therapy) for at least 1 year or surgically sterile for at least 1 year.

NOTE:

- Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.

- Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient. Abstinence as a contraceptive method must be documented in writing by the subject.

6.0 STUDY TREATMENT AND SUPPLIES

The identity and instructions for administration, storage, and handling of HEPLISAV-B are described below.

6.1 Study Treatments

The investigational vaccine to be tested is HEPLISAV-B, a licensed, commercially-available hepatitis B vaccine consisting of 20 mcg of HBsAg and 3000 mcg of cytidine phosphoguanosine (CpG) 1018 adjuvant.

HEPLISAV-B [Hepatitis B Vaccine (Recombinant), Adjuvanted] is a sterile solution for intramuscular injection. Each 0.5 mL dose contains HEPLISAV-B in a solution for injection supplied as a single-dose. Additional information for HEPLISAV-B is provided in the USPI (Appendix 2).

6.2 Instructions for Administration

Administer HEPLISAV-B by intramuscular injection in the deltoid muscle region using the pre-filled syringe. HEPLISAV-B administration must be performed prior to the start of dialysis on study visit days.

6.3 Labeling

During the course of the study, HEPLISAV-B labeled for clinical study use will be provided.

At a minimum, HEPLISAV-B will be labeled with the following information: product name, product lot number, contents, volume, concentration, sponsor name, and a statement indicating that the drug is for investigational use only.

6.4 Storage and Handling Instructions

HEPLISAV-B must be stored in a refrigerator at 2°C to 8°C (35°F to 46°F). Do not freeze. If frozen, continue to store the vaccine in the refrigerator but isolate it from other study vaccine and follow the temperature excursion procedures outlined in the Pharmacy Manual. Do not use the vaccine after the expiration date shown on the product label.

The clinical supplies storage area at the site must be monitored closely by the designated site staff for temperature consistency and documentation of temperature monitoring must be maintained. Temperature excursions outside of the recommended storage range may impact product quality and must be reported to Dynavax or its designee per the detailed instructions in the Pharmacy Manual.

6.5 Control and Accountability of Investigational Medicinal Product

All investigational medicinal product must be received by a trained designated person at the study site, handled and stored safely and properly, and kept in a secured location with limited access.

The investigator (or responsible designee) must maintain current and accurate records of the receipt (documentation from shipments of study treatments received), administration (patient-by-patient and overall accounting) and return of study treatments to a Dynavax-specified facility for destruction. All study treatments must be stored in a location with access restricted to authorized personnel only.

A study monitor will be responsible for monitoring the drug accountability at the site. The monitor should be contacted with any questions concerning administration of study treatments.

Records of study treatments accountability, storage, and handling must be made available to the study monitor for the purposes of study treatments accountability. Any discrepancy and/or deficiency must be recorded with an explanation.

The investigator must retain all used product and expired, damaged, and unused study treatments until accountability has been confirmed by the study monitor. Any exceptions to this policy must be specifically permitted by Dynavax.

At the end of the study, or upon request by Dynavax, all unused study treatments must be returned to a Dynavax-specified facility for adequate disposition.

Refer to the Pharmacy Manual for detailed instructions on study treatments.

Study treatments may not be used for any purpose other than that described in the protocol.

6.6 Treatment Compliance

All study injections will be administered by designated personnel only.

7.0 TREATMENT OF SUBJECTS

7.1 Treatments Administered and Treatment Period

Subjects will receive HEPLISAV-B administered intramuscularly in the deltoid muscle at Week 0 (Visit 1), Week 4 (Visit 2), Week 8 (Visit 3), and Week 16 (Visit 4) as outlined in the Schedule of Assessments (Appendix 1). HEPLISAV-B must be administered prior to the start of dialysis on each vaccine administration day.

7.2 Prohibited Treatments or Therapies

The following non-study medications are prohibited:

14 days prior to Injection 1 and through 28 days following each injection:

- any inactivated virus vaccine

28 days prior to Injection 1 and through Week 28:

- Systemic corticosteroids (more than 3 consecutive days) or other immunomodulators or immune suppressive medication, with the exception of inhaled steroids
- Any live virus vaccine
- Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF)

28 days prior to Injection 1 and through Week 68 (unless approved by sponsor):

- Any other investigational medicinal agent (may be allowed after Week 28 [Day 197] upon sponsor approval)

90 days prior to Injection 1 and through Week 28:

- Blood products or immunoglobulin

If a subject requires treatment that is prohibited, the investigator should contact the Dynavax medical monitor or designee to determine whether the subject should receive further study injections. If the subject is not eligible for subsequent study injections, **the subject will not be withdrawn from the study, but** will be followed for safety through End-of-Study (EOS) Visit.

7.3 Permitted Therapy

Use of any permitted medication, including over-the-counter medications or vaccine during the 28 days prior to first injection through Week 28 or Early Discontinuation Visit should be solicited from each subject and recorded in source documents. Use of vitamins and dietary supplements will not be collected unless they are indicated as a concomitant therapy for conditions directly related to undergoing hemodialysis. Medications started prior to first dose, and any medication used in the 28 days prior to first dose but not continued at the time of first dose, will be recorded.

All collected concomitant medications will be recorded in the electronic Case Report Form (eCRF) through Week 28. After Week 28, only prescription medication or over-the-counter drug taken by the subject for the treatment of MAEs, SAEs, AMIs, or AESIs will be recorded on the

eCRF through EOS Visit (further details regarding safety monitoring of AMIs and AESIs are provided in Section 9.4.7.2).

8.0 MANAGEMENT OF STUDY TREATMENT TOXICITIES

8.1 Reasons for Stopping a Subject From Receiving Additional Injections

The investigator will discontinue study treatment and notify the sponsor if any of the following MAEs occur:

- Grade 4 post-injection reaction within 7 days after any study injection
- Clinically significant Grade 3 or higher systemic reaction (eg, angioedema, generalized urticaria) within 7 days after any study injection
- Grade 3 or 4 hypotension within 24 hours of any study injection
- Grade 3 or 4 respiratory reaction or symptoms occurring within 24 hours of any study injection
- Any life-threatening event, regardless of relationship to study drug
- Any AMI (further details regarding safety monitoring of AMIs are provided in Section 9.4.7.2)
- Any confirmed AESI (further details regarding safety monitoring of AESIs are provided in Section 9.4.7.2)

Subjects must also be discontinued from study treatment for any of the following reasons:

- Violation of protocol eligibility criteria
- Prohibited medications
- SAE assessed as a suspected adverse reaction (SAR) or adverse reaction (AR)
- Pregnancy or breastfeeding

Subjects may be discontinued from the study for any of the following reasons:

- Violation of protocol eligibility criteria (only if the subject has not received any study treatment)
- Prohibited medications (only if the subject has not received any study treatment)
- Noncompliance with study procedures as determined by the investigator or sponsor
- The discretion of the investigator

- The sponsor's administrative decision to terminate the study

The investigator or designee must notify Dynavax within 24 hours when a subject has been discontinued from treatment due to an MAE. The subject should not be withdrawn from the study and should continue to be followed for safety (as defined in Section 9.7) through EOS Visit.

8.2 Potential Reasons for Termination of Study

The study will terminate on the date of the last visit of the last participant. However, the sponsor reserves the right to terminate the study at any time. Reasons for termination include but are not limited to:

- Inability to enroll sufficient subjects into the study
- Federal regulations/Good Clinical Practice (GCP) compliance issues that compromise the validity of the study and/or subject safety
- AMIs occurring in ≥ 10% of subjects AND occurring in ≥ 4 subjects (further details regarding safety monitoring of AMIs are provided in Section 9.4.7.2)
- AESIs occurring in ≥ 5% subjects AND occurring in ≥ 3 subjects (further details regarding safety monitoring of AESIs are provided in Section 9.4.7.2)

8.3 Management of Subject Safety

Subjects will be evaluated prior to each study injection to confirm the subject is eligible (per eligibility criteria [Section 5.0], as relevant) to receive an injection.

Injection-site reactions are expected to spontaneously subside. Local pruritus and pain can be treated with oral medications. If significant symptoms of pain and induration persist for more than 12 hours, an ice pack may be applied locally for 30 minutes every 2 hours, as needed. Use of an ice pack prior to 12 hours after the onset of symptoms is discouraged, as it may interfere with the action of the study vaccine. Do not inject into a site if local pain, tenderness, swelling, or pruritus persists from a previous injection or other cause.

Subjects should receive appropriate supportive care measures as deemed necessary by the investigator. The investigator should ensure that adequate medical care is provided to a subject for any MAE, including clinically significant laboratory values, related to the study. For each disorder, attempts should be made to rule out other causes, which might require additional supportive care. The investigator should inform the study medical monitor when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

An unscheduled visit (UNS) should be performed if there are suspected subject safety concerns. All supportive therapies will be recorded in the subject's eCRF.

Subjects who are discontinued from the study will be scheduled for an Early Discontinuation Visit 28 days following their last vaccine administration.

9.0 STUDY PROCEDURES

All tests and evaluations required at specified time points are listed in the Schedule of Assessments (Appendix 1). The results of these tests and evaluations must be entered in the subject's source document and also recorded on the subject's eCRF. Additional evaluations may be done at the discretion of the investigator and with sponsor approval.

9.1 Informed Consent, Screening, and Eligibility

9.1.1 Informed Consent and Screening

The investigator or designee must review the informed consent form (ICF) with each prospective subject to be certain that the prospective subject understands the procedures and risks of the study. Prospective subjects who wish to participate in the study must provide written informed consent by signing the ICF before undergoing any screening procedures. Subjects may undergo study screening tests prior to giving written informed consent provided that these tests are considered part of standard care.

The information from the consent form should be translated and communicated to the subject in language understandable to the subject.

A copy of the signed and dated consent form should be given to the subject before participation in the study. The initial ICF and any subsequent revised written ICF, and written information must receive the Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

The investigator or designee will maintain a log of all subjects who sign the ICF. At a minimum, the log will include a subject identifier, the dates of informed consent and screening procedures, the outcome of the screening, and the reason the subject did not enroll in the study, if applicable.

For screen failures, at a minimum age, sex, ethnicity, race, height, and weight, the reason for screen failure, and any SAEs that occur during the screening period will be collected.

Additional requirements for informed consent are presented in Section 13.3.

9.1.2 Eligibility

After written consent is obtained, screening procedures must be carried out per the Schedule of Assessments (Appendix 1). A subject must meet all of the inclusion criteria and none of the exclusion criteria to be eligible to participate in the study. Documentation of ESRD must be obtained prior to enrollment. Assignment of subject number is described in the Study Reference Manual.

9.1.3 Demographics and Medical and Medication History

Demographic and baseline characteristics of sex, race, ethnicity, age, weight, and height of the subject will be collected. Medical history, defined in Section 9.4.1, will also be recorded.

9.2 Study Visits

Procedures should be performed as close to the scheduled time as possible. The window for study visits is ± 7 days. A detailed outline of all scheduled study procedures is provided in the Schedule of Assessments (Appendix 1). Procedures should be performed at the study center where the subject is being treated, except for Weeks 28 and 42 which will be conducted via telephone call. Subjects who fail screening may be rescreened per approval by the sponsor.

The exact time at which a procedure is performed must be recorded in the subject's study records or appropriate worksheet (if applicable). Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

Blood collections for safety evaluation assume priority over other procedures. Laboratory samples must be collected prior to HEPLISAV-B administration on study injection visit days. Blood collection and HEPLISAV-B administration must be performed prior to the start of dialysis on study visit days.

9.3 Immunogenicity Assessments

Serum sample will be obtained for anti-HBs measurements at baseline and then at Weeks 4, 8, 16, and 20.

9.4 Safety Assessments

The safety assessments are listed below. The Schedule of Assessments is provided in Appendix 1.

9.4.1 Medical and Medication History

Medical history includes clinically significant diseases, surgeries, kidney disease history, autoimmune diseases, and all medications (eg, prescription drugs, over-the-counter drugs) used by the subject within 28 days prior to the Screening Visit.

9.4.2 Physical Examinations

The investigator or qualified designee will conduct physical examinations. A full physical examination (excluding pelvic/genital, rectal, and breast examination) will be conducted at Screening, and a targeted physical examination based on subject-reported symptoms (excluding pelvic/genital, rectal, and breast examination) will be conducted at each study injection visit and End-of-Study (EOS) Visit or Early Discontinuation Visit.

9.4.3 Safety Laboratory Assessments

Laboratory assessments are listed below and will be performed according to the Schedule of Study Assessments (Appendix 1). Sample collections will be prior to injection on vaccination days. Laboratories obtained within 7 days of Day 1 visit do not need to be repeated on Day 1.

- Serum chemistry and hematology will be performed at Screening by a central laboratory.
- Hepatitis and HIV testing at Screening Visit by a central laboratory: serum hepatitis B, hepatitis C, and HIV testing by laboratory tests for HBsAg, anti-HBc, anti-HBs, anti-HCV, and anti-HIV-1/2, respectively
- Reserve serum and plasma aliquot specimens will be collected and stored frozen for possible future testing.
- Additional details for specific tests are provided in the Laboratory Manual.

9.4.4 Pregnancy Testing

All WOCBP (as defined in Section 5.2.1) who are being considered for participation in the study will be tested for pregnancy with a serum test at Screening Visit and a serum or urine β-human chorionic gonadotropin (β-hCG) test within 72 hours prior to taking each dose of study treatment. If the urine test is positive or cannot be confirmed as negative, then a serum test is required which must be negative for the subject to enroll.

9.4.5 Confirmation of Subject Eligibility

Subjects will be evaluated prior to each study injection to confirm the subject is eligible (per eligibility criteria [Section 5.0], as relevant) to receive an injection.

9.4.6 Post-injection Reaction Assessments

Assessments of post-injection reactions will be collected for a minimum of 30 minutes following each of the HEPLISAV-B injections at the clinical site and as reported by the subject in a diary for 7 days. Information about the presence and severity of post-injection local (injection site) reactions (redness, swelling, and pain at or near the injection site) and systemic reactions (malaise, headache, myalgia, and fatigue) that are listed in the subject diary are considered solicited post-injection reactions. Oral temperature is also collected. Solicited post-injection reactions are related to treatment and recorded for 7 days following each study injection, including the day of injection. Post-injection reactions documented by the subject will be collected, reviewed by the study nurse/coordinator with the subject, and recorded on the appropriate eCRF. The grading criteria for post-injection reactions are in Appendix 3. Further information is provided in the Study Reference Manual.

9.4.7 Medically-Attended Adverse Events

All MAEs, as defined in Section 10.2, will be evaluated from immediately after the first study treatment on Day 1 through EOS Visit. (Additionally, if the subject is discontinued early from study treatment, the subject should not be withdrawn from the study and should continue to be followed for safety, as described in Section 9.7, through EOS Visit.)

9.4.7.1 Adverse Events of Special Interest

Subjects who experience signs or symptoms that the investigator or designee considers to be associated with potential AESIs (defined according to a pre-specified list of event terms including autoimmune, autoinflammatory, and hypersensitivity disorders; Appendix 4 provides the full list), as well as any other potentially immune-mediated medical conditions that do not appear in Appendix 4, will be referred for consultation with appropriate experts (eg, rheumatology, immunology) for confirmation.

9.4.7.1.1 Adverse Events of Special Interest Reporting Requirements

All potential AESIs, regardless of seriousness, severity, or relationship to the injection, will be reported to Dynavax or the Dynavax designee. In addition to describing the event on the appropriate eCRFs and in the source documents, Dynavax should be informed within 72 hours by contacting the Dynavax Medical Monitor or designee by submitting a completed Potential Autoimmune Event Report Form (events assessed as serious must be reported to Dynavax or its designee within 24 hours of investigator awareness of the event, as described in Section 10.3.2). Follow-up information should be actively sought and submitted as it becomes available.

Any AESI regardless of relationship to study treatment will be followed as clinically indicated until its resolution or, if non-resolving, until it is considered chronic or stable by the investigator.

Once the site principal investigator refers a subject to an expert evaluation for possible AESI, injections should be discontinued until further notice. If the expert evaluation reveals that the subject did NOT have an AESI, injections can be resumed. If the expert evaluation confirms an AESI, then injections will be permanently discontinued for the subject. In either event, the subject will be followed for safety (as defined in Section 9.7) through EOS Visit.

9.4.7.2 Safety Monitoring Committee

The sponsor will establish a Safety Monitoring Committee (SMC) to evaluate AMI (including ST-segment elevation and non-ST-segment elevation) and AESIs (defined according to a pre-specified list of event terms including autoimmune, autoinflammatory, and hypersensitivity disorders provided in Appendix 4; other potentially immune-mediated medical conditions that do not appear in Appendix 4 are also considered AESIs).

All AMIs and AESIs occurring from immediately after the first study treatment on Day 1 through EOS Visit will be collected and evaluated.

Refer to SMC charter for details on the conduct, membership, and meeting frequency of the SMC.

9.4.8 Serious Adverse Events

All serious adverse events (SAEs), as defined in Section 10.3.1, will be evaluated from the time the consent is signed through EOS Visit. Any SAE must be reported to Dynavax or its designee within 24 hours of the knowledge of the event.

If the SAE is assessed as possibly or probably related to study treatment, it must be followed until it is considered stable or resolved, including beyond EOS Visit.

Any SAE assessed as not related to study treatment will be followed as clinically indicated until its resolution or, if nonresolving, until it is considered chronic or stable, or until study completion.

9.4.9 Concomitant Medications

Any prescription medication or over-the-counter drug taken by the subject from first study injection through Week 28 must be recorded in the eCRF. Use of vitamins and dietary supplements will not be collected unless they are indicated as a concomitant therapy for conditions directly related to undergoing hemodialysis. After Week 28, only prescription

medication or over-the-counter drug taken by the subject for the treatment of MAEs, SAEs, AMIs, or AESIs will be recorded on the eCRF through EOS Visit (further details regarding safety monitoring of AMIs and AESIs are provided in Section 9.4.7.2).

9.5 End of Study

An EOS Visit is required at Week 68 unless the subject is discontinued early from the entire study, in which case an Early Discontinuation Visit is required 28 days after the last dose.

9.6 Unscheduled Visit for Safety

A UNS should be performed if there are suspected subject safety concerns. Procedures for the visit will depend on the reason for visit as determined by the treating principal investigator or sub-investigator. If a UNS is performed because of a safety concern related to study treatments, at a minimum, the following should be performed: a targeted physical examination based on subject-reported symptoms, serum chemistry, and hematology.

If the subject has permanent discontinuation of HEPLISAV-B (ie, discontinues treatment), the subject should continue to be followed for safety (as defined in Section 9.7) through EOS Visit. If the subject permanently discontinues the study, an EOS Visit (Section 9.5) should be scheduled 28 days after the date of last HEPLISAV-B administration.

9.7 Duration of Follow-up

All subjects must be followed through EOS Visit (Section 10.0). If the subject is discontinued early from study treatment, the subject should not be withdrawn from the study and should continue to be followed for safety through EOS Visit. If the subject is discontinued early from the study, an Early Discontinuation Visit is required 28 days after the last dose.

10.0 REPORTING AND DOCUMENTATION OF MEDICALLY-ATTENDED ADVERSE EVENTS

10.1 Post-Injection Reactions

Local and systemic post-injection reactions are to be recorded on the subject diary. If they persist longer than 7 days (ie, 8 days or longer) and are medically attended (ie, subject seeks medical attention), they should also be recorded and reported as MAEs, per protocol Section 10.2. The severity of the post-injection reactions will be graded using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Appendix 3).

Certain local and systemic events are routinely monitored in vaccine clinical trials as indicators of vaccine reactogenicity. It is recognized that each of these events, and particularly those of systemic nature, may under certain circumstances, in an individual subject, have a cause that is unrelated to study vaccine. However, as a matter of convenience and in accordance with common clinical practice, such events occurring within a specified period of time after immunization are herein termed 'post-injection reactions' and will be recorded as related to treatment.

Post-injection reactions documented by the subject via a diary will be collected, reviewed by the study nurse/coordinator with the subject, and recorded on the appropriate eCRF (Section 9.4.6).

Further information is provided in the Study Reference Manual.

10.2 Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug, whether or not considered drug-related. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the study treatment. In this trial, only MAEs, AEs for which a subject seeks medical attention at a doctor's office, clinic, study site, emergency room, or is hospitalized, will be collected.

Medical conditions present at Screening (ie, before informed consent is obtained) or present before the first study treatment (Day 1) are not MAEs and are not recorded on the MAE eCRF. These medical conditions should be adequately documented on the Medical History eCRFs. Any increase in severity or frequency of a medical condition documented as medical history after the first study treatment will be recorded as an MAE and will be captured on the MAE eCRF.

An uncomplicated pregnancy is not an MAE or SAE and should not be reported as an MAE/SAE. Subjects should be followed as described in Section 10.5.

The reporting period for all non-serious MAEs begins at the time of the first study treatment (Day 1) through EOS Visit. All MAEs will be captured on the MAE eCRF.

MAEs should be documented in terms of a single medical diagnosis. When this is not possible, the MAE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject at each study visit.

10.2.1 Overdoses

If an MAE is associated with or resulted from an overdose of HEPLISAV-B (for the purpose of this study defined as more than twice the protocol-specified dose), it will be documented on the MAE eCRF. If it is an SAE, it will also be reported to Dynavax or the Dynavax designee following the SAE reporting process (see Section 10.3.2).

10.2.2 Definition of Adverse Reaction

An AR is defined as any MAE caused by the use of a pharmaceutical product. ARs are a subset of all suspected MAEs for which there is reason to conclude that the pharmaceutical product caused the event.

10.2.3 Definition of Suspected Adverse Reaction

Suspected adverse reaction (SAR) means any MAE for which there is a reasonable possibility that the study treatment caused the MAE. *Reasonable possibility* means there is evidence to suggest a causal relationship between the study treatment and MAE. An SAR implies a lesser degree of certainty about causality than AR, which means an MAE caused by a study treatment.

10.2.4 Definition of Unexpected Medically-Attended Adverse Event or Unexpected Suspected Adverse Reactions

An MAE or SAR is considered *unexpected* if it is not listed in the Investigator's Brochure or USPI or is not listed at the specificity or severity that has been previously observed.

10.3 Serious Adverse Events

10.3.1 Definition of Serious Adverse Events

An MAE is considered an SAE if it meets any of the following criteria:

- Results in death;
- Is life-threatening;

  Note: An MAE or SAR is considered *life-threatening* if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an MAE or SAR that, had it occurred in a more severe form, might have caused death;
- Requires in-patient hospitalization or prolongs existing hospitalization;
- Results in persistent or significant disability or incapacity;

  That is, the event severely or permanently disrupts the subject's ability to perform normal life functions or daily activities.
- Results in a congenital anomaly or birth defect;
- Is medically significant (Important Medical Event);

  Medical and scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject. Examples of such events are allergic bronchospasm requiring treatment in an emergency room, serious blood dyscrasias, or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

10.3.2 Serious Adverse Event Reporting Requirements

Any SAE that occurs from the time the consent is signed through EOS Visit, whether or not the SAE is related to the study treatment, **must be reported to Dynavax or its designee within 24 hours of investigator awareness of the event**. The contact information for reporting SAEs is provided in the Study Reference Manual. General SAE reporting instructions are as follows:

- Submit SAE documents according to instructions in the Study Reference Manual.
- Record all SAEs on the MAE eCRF.
- For SAEs, record the primary event on the MAE eCRF; describe events occurring secondary to that primary event on the SAE form in the narrative description of the case.
- Death is an outcome, not an event. Record the event that resulted in the death as the fatal event on the MAE eCRF.
- For hospitalizations for surgical or diagnostic procedures, record the illness leading to the surgical or diagnostic procedure as the SAE, not the procedure itself. Capture the procedure in the narrative as part of the action taken in response to the illness.
- Elective hospitalizations will not be considered SAEs and do not need to be reported. Complications that prolong elective hospitalizations should be recorded as SAEs. Emergency room visits of less than 24 hours do not meet the criterion of hospitalization for SAE reporting purposes.

The SAE report should contain, at a minimum, the following information:

- Subject identifiers (ie, subject number)
- Suspected medicinal product
- MAE term (must be listed as serious)
- Contact information for person reporting event

The relationship of the SAE to study treatment will be assessed by the investigator (Section 10.4.2). Follow-up information should be actively sought and submitted as it becomes available.

The investigator will assess relationship to study treatment. In addition, the sponsor will assess relationship to study treatment and determine expectedness to HEPLISAV-B based on the current HEPLISAV-B Investigator's Brochure and USPI. The sponsor will report all HEPLISAV-B suspected unexpected serious adverse reactions (SUSARs) to regulatory authorities as expedited reports in accordance with applicable regulatory requirements

(eg, 21 CFR 312.32[c] and 314.80[e] in the US). All other SAEs will be reported as part of regulatory safety updates, as required, such as in annual reports.

10.4 Medically-Attended Adverse Event Severity and Relationship to Study Treatment

10.4.1 Severity Grading of Medically-Attended Adverse Events and Abnormal Laboratory Test Results

The severity of MAEs and laboratory abnormalities will be graded based on the United States Food and Drug Administration's (FDA) Guidance for Industry: Center for Biologics Evaluation and Research (CBER) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials in Appendix 3 (with the exception of malaise, which will be graded per CTCAE v4.03), with the modification that, by convention, all fatal MAEs will be graded as Grade 5 (Fatal).

All MAEs not listed in the CBER toxicity grading scale will be graded as shown in Table 10-1.

Table 10-1: Grading Scale for Medically-Attended Adverse Events Not Included in the CBER Guidance on Toxicity Grading for Healthy Volunteers in Vaccine Clinical Trials

MAE Severity	Definition
Grade 1 – Mild	No interference with activity
Grade 2 – Moderate	Some interference with activity, not requiring medical intervention
Grade 3 – Severe	Prevents daily activity and requires medical intervention
Grade 4 – Potentially life-threatening	Emergency room visit or hospitalization
Grade 5	Death

For all MAEs and SAEs, if there is a change in the severity after onset, the event should be reported as a single entry with the maximum severity grading captured.

10.4.2 Relationship of Medically-Attended Adverse Events to Study Treatment

The investigator will determine the relationship of the MAE to study treatment using the definitions provided in Table 10-2.

Table 10-2 Definitions for Relationship of Medically-Attended Adverse Events to Trial Treatment

Relationship to Trial Treatment	Definition
Not Related	Another cause of the event is most plausible; *or* clinically plausible temporal sequence is inconsistent with the onset of the event and the trial treatment administration; *or* a causal relationship is considered biologically implausible.
Possibly Related	An event that follows a reasonable temporal sequence from administration of the trial treatment or a known or expected response pattern to the suspected drug, but that could readily have been produced by a number of other factors.
Probably Related	An event that follows a reasonable temporal sequence from administration of the trial treatment, *and* there is a biologically plausible mechanism for trial treatment causing or contributing to the MAE, *and* the event could not be reasonably explained by the known characteristics of the subject's clinical state. In addition, the relationship may be confirmed by improvement on stopping the trial treatment and reappearance of the event on repeated exposure.

MAE = medically-attended adverse event.

The investigator will follow all MAEs observed during the study until the MAEs are considered resolved, stabilized, or until the subject has completed the study. The sponsor may request additional follow-up on specific unresolved MAEs.

If the SAE is assessed as possibly or probably related to study treatment, it must be followed until it is considered stable or resolved, including beyond EOS Visit.

Any SAE assessed as not related to study treatment will be followed as clinically indicated until its resolution or, if nonresolving, until it is considered chronic or stable, or until study completion.

The sponsor may request additional follow-up on specific unresolved MAEs.

10.5 Reporting and Documentation of Pregnancy

Any subject who becomes pregnant or begins breastfeeding during the study will be discontinued from all study treatments and will be followed for pregnancy outcome. Follow-up information should be actively sought by the investigator and submitted to Dynavax or designee as soon as it becomes available. The investigator will complete the pregnancy reporting form and all other relevant eCRFs. Uncomplicated pregnancies are not considered an MAE/SAE. A complicated pregnancy or a pregnancy with an adverse outcome may meet criteria for an MAE or SAE and would then also be reported according to the appropriate requirements.

A subject who becomes pregnant will be instructed to report the pregnancy to the study site as soon as possible. The subject should be followed by the investigator through the pregnancy (including beyond EOS) for outcomes. A report of the pregnancy will be completed by the investigator or designee and will document details of the pregnancy, outcome of pregnancy, and details of delivery.

Pregnancies and breastfeeding that occur from Day 1 through the end of the study (Week 68) must be reported by the investigator. The sponsor or designee must be notified as soon as possible once the study site learns of a pregnancy or breastfeeding. Pregnancy report forms provided by the sponsor or designee must be completed and submitted to Dynavax or designee. The contact information for reporting pregnancy is provided in the Study Reference Manual.

11.0 STATISTICAL METHODS

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary or exploratory objectives and/or hypotheses, or to the statistical methods related to those objectives and/or hypotheses, then those changes, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post-hoc exploratory analyses will be clearly identified in the CSR. Handling of missing data, if any, will be outlined in the study Statistical Analysis Plan. Additional details of the statistical analyses to be performed will be provided in the study Statistical Analysis Plan.

11.1 Sample Size Considerations

The sample size calculation is based on approximately 100 subjects in the per-protocol population (Table 11-1). With an expected 15% loss to follow up prior to week 20, approximately 115 subjects will be enrolled. This sample size would allow estimating immunogenicity response at the following accuracy levels depending on the observed immunogenicity responses.

Table 11-1: Sample Size Estimates

N	If Observed Immunogenicity Response is	Width of the Resulting 95% Confidence Interval	Lower Limit of the Resulting 95% Confidence Interval[a]
100	80.0%	0.165	70.8%
100	86.0%	0.145	77.6%
100	90.0%	0.127	82.4%
100	95.0%	0.096	88.7%

N = number of subjects
[a] Calculation based on exact method (Clopper-Pearson)
Note: Approximately 115 subjects will be enrolled to meet the N of 100 evaluable subjects in the per-protocol population.

11.2 Study Analysis Populations

The Safety Population will comprise all subjects who received at least 1 study injection, excluding subjects who have no on-study safety data.

The Per-protocol (PP) Population for the immunogenicity analysis will comprise all subjects who receive all study injections, have no major protocol violations (to be specified in the Statistical Analysis Plan), and have anti-HBs levels obtained within the study visit window at Week 20.

The modified intent-to-treat (mITT) population for the immunogenicity analysis will comprise all subjects who receive at least 1 study injection and have at least 1 post-injection immunogenicity evaluation.

11.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be listed by subject and summarized. Descriptive summary statistics (sample size, mean, median, SD, and range, when appropriate) will be provided for the continuous variables such as age, weight, and height. Count and percentage will be reported for categorical variables such as sex, race, and ethnicity.

11.4 Immunogenicity Analyses

Immunogenicity data will be analyzed based on the PP Population. The SPR at specified timepoints will be estimated. The associated 2-sided 95% confidence interval will be calculated using the Clopper-Pearson method.

11.5 Safety Analyses

Safety data will be analyzed descriptively and will be based on the Safety Population. The most important safety parameters will be presented for all sites combined. Summary statistics will be used to describe the incidence of all post-injection reactions and MAEs (including SAEs, deaths, AMIs, and AESIs; further details regarding safety reporting of AMIs and AESIs are provided in Section 9.4.7.2). The incidence and proportion of injection site reactions and MAEs will be summarized. MAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) System of Organ Class (SOC) and Preferred Term (PT).

The incidence of AMIs and major adverse cardiovascular events will be analyzed in subjects initiating hemodialysis after enrollment in the study and in subjects undergoing hemodialysis at the time of enrollment in the study.

11.6 Interim Analysis

A preliminary analysis may be performed to assess the primary immunogenicity objective of the SPR at Week 20 after approximately 50 subjects have completed their Week 20 visit. Further details will be outlined in the Statistical Analysis Plan.

12.0 DATA QUALITY ASSURANCE

The study sites will be monitored by Dynavax or its designee according to GCP and standard operating procedures. Prior to initiation of the study, representatives from Dynavax or its designee will review with the site personnel information about the investigational product, proper storage of study treatments, protocol requirements, and monitoring requirements. During and after the study, periodic site visits will be made to monitor for compliance, including verification of the accuracy and completeness of data recorded on the eCRFs, source documents, and study treatments accountability records.

13.0 ETHICS

13.1 Institutional Review Board/Independent Ethics Committee

The protocol and informed consent documents must be reviewed and approved by an appropriately composed IRB. The study will not be initiated at a site until appropriate written IRB approval of the protocol, ICF, and all recruiting materials (if applicable) is obtained by the investigator. Copies should be reviewed and approved by Dynavax prior to submission to the IRB. The investigator will submit periodic reports on the progress of the study as required by the IRB, in accordance with applicable governmental regulations, and in agreement with the policy established by Dynavax. In addition, the investigator will inform the IRB of any protocol amendments and administrative changes and will obtain appropriate written IRB approval of all protocol amendments.

13.2 Ethical Conduct of the Study

This study will be conducted in accordance with the International Council for Harmonisation (ICH) E6(R2) GCP guidelines and applicable local legal and regulatory requirements.

The study will be submitted to required clinical trial registries such as www.clinicaltrials.gov.

13.3 Informed Consent

The investigator is responsible for obtaining informed consent from each subject participating in the study in compliance with US CFR Title 21, Part 50, Title 45 Part 46, and ICH and IRB guidelines. Prior to initiation of the study at the site, the ICF, and any other study information to

be provided to the subject must be reviewed and accepted by Dynavax and approved by the governing IRB. The investigator or authorized designee will discuss the purpose and pertinent details of the study with each subject, and the subject must demonstrate understanding, sign, and date the appropriate IRB-approved ICF before undergoing any study-specific procedures. The ICF must be personally signed and dated by the subject and by the person who conducted the informed consent discussion. Additional signature requirements may exist. The original signed and dated ICF will be retained with the subject's study records, and a copy of the signed ICF will be given to the subject. The investigator or designee will maintain a log of all subjects who sign the ICF. At a minimum, the log will include a subject identifier, the dates of informed consent and screening procedures, the outcome of the screening, and the reason the subject did not enroll in the study, if applicable.

13.4 Subject Confidentiality

The investigator is responsible for maintaining the privacy and confidentiality of the subject's medical or health information collected during the study. The investigator is also responsible for ensuring that all use, review and disclosure of subject's medical or health information is in accordance with Health Insurance Portability and Accountability Act (HIPAA) regulations and the ICF approved by the IRB and signed by the subject. Specifically, all data collected about a subject during the study will be identified only by a number and the subject's initials.

14.0 DATA HANDLING AND RECORD KEEPING

14.1 Source Documents

The investigator must maintain detailed records of all study participants who are enrolled in the study or who undergo screening. Source documents include, but are not limited to, subject medical records and investigator's subject study files, as well as all test results.

Data collection is the responsibility of the study site staff under the supervision of that site's investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The following minimum information should be entered into the enrolled subject's source documents:

- The date the subject entered the study and the subject number
- The study protocol number and the name Dynavax
- The date that informed consent was signed
- Evidence that informed consent was obtained before the subject underwent any trial-specific procedures

- Evidence that the subject meets study eligibility requirements (eg, medical history, study procedures, evaluations)
- The dates of all study-related subject visits
- Evidence that study-required procedures and/or evaluations were completed
- Use of any concurrent medications
- Documentation of study treatment accountability
- Occurrence and status of any MAEs
- The date the subject exited the study, and a notation as to whether the subject completed the study or was discontinued early, including the reason for discontinuation
- Any deviations from the protocol

14.2 Direct Access to Source Data/Documents

Qualified individuals designated by Dynavax or its representative will monitor all aspects of the study at regular intervals throughout the study and following study completion. This monitoring is for the purpose of verifying adherence to the protocol including appropriate storage of study treatments, completeness and exactness of the data being entered onto the eCRFs, and compliance with the FDA or other regulatory agency regulations. The investigator and investigator's institution agree to allow these monitors access to all study records, eCRFs, and corresponding portions of the subject's clinical study files; to allow access to the clinical supplies, dispensing, and storage areas; and if requested, to assist the monitors. The investigator further agrees to permit direct access to source data/documents for study-related monitoring, audits, IRB/Independent Ethics Committee (IEC) review, and regulatory inspection(s).

In certain circumstances, a secondary audit may be conducted by members of Dynavax's Quality Assurance group or by Dynavax's designated representative. The investigator will be notified if this is to take place, and advised as to the nature of the audit.

14.3 Case Report Forms

Electronic CRFs (eCRFs) will be used at the clinical study site to collect study data for screen failures and enrolled subjects. When data are available, authorized clinical study site personnel will carefully and accurately record the data on the eCRF. Sites must ensure that all source documents are maintained according to ICH/GCP guidance and support the data that are entered onto the eCRFs.

The eCRF data will be captured in a system validated according to procedures that comply with 21 CFR Part 11 and ICH GCP Guidelines E6 (R2). The eCRFs will be reviewed and signed by

the principal investigator or someone clinically qualified and identified on the delegation log as someone that can sign-off on the eCRF.

14.4 Data Handling

The sponsor may designate a Contract Research Organization (CRO) to perform data management. The CRO will write a data management plan outlining the data management systems, procedures, and agreements between the CRO and sponsor. The plan will be reviewed and signed by a representative of the sponsor's data management department.

Outside the electronic data capture (EDC) system, when appropriate, the CRO will receive FDA 21 CFR 11 compliant external lab data transfers from a validated laboratory information management system. After database lock, the investigator will receive a copy of the subject data for archiving at the study site.

The standard procedures for handling and processing eCRF records including identification of data errors and data clarification process will be followed per Good Clinical Practice (GCP) and the Sponsor's (or designee's) SOPs.

Complete details of data preparation and management will be described in a separate study Data Management Plan.

14.5 Coding of Medically-Attended Adverse Events, Drugs, and Diseases

MAEs and medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded according to the World Health Organization Drug Dictionary.

14.6 Record Retention

The investigator must retain all records relating to the conduct of this study (including subject's study records, receipt and disposition of all investigational materials, subject exclusion logs, signed consent forms, eCRFs, all correspondence, and other supporting documentation) for at least 2 years after a marketing application for this indication is approved; or if an application is not filed or not approved for the drug for this indication, for at least 2 years after clinical development for the drug has been formally discontinued and the appropriate regulatory or health authorities have been notified. However, in certain instances, documents may need to be retained for a longer period if required by regulatory requirements or by an agreement with Dynavax.

The investigator may withdraw from the responsibility of retaining records only after transferring custody of the records to another individual who will accept responsibility for them. A written notice of transfer must be provided to Dynavax prior to or no later than 10 days after transfer.

The investigator must allow representatives of the FDA, the governing IRB, or other regulatory agencies to inspect all study records. If informed of such an inspection, the investigator will notify Dynavax immediately.

The investigator must obtain written approval from Dynavax prior to the destruction of any records relating to the conduct of this study.

15.0 USE OF INFORMATION AND PUBLICATION

It is understood by the investigator that the information generated in this study is the property of Dynavax. It is understood that the investigator is obliged to provide Dynavax with complete test results, all study data, and access to all study records.

All efforts should be made for abstracts and publications to be jointly authored by investigators and Dynavax. Dynavax will be furnished with a copy of any proposed publication. Dynavax's comments shall be given without undue delay, and not later than within 60 days.

Results from the investigation shall not be made available to any third party by the investigators or any of their staff.

It is understood by the investigator that the information generated in this study may be used by Dynavax in connection with the development of the product and therefore may be disclosed to government agencies in various countries.

Dynavax recognizes the importance of communicating medical study data, and therefore encourages their publication in reputable scientific journals and at seminars or conferences.

Any results of medical investigations with Dynavax's products and all publications, lectures, presentations, and manuscripts based thereon shall be exchanged and discussed by the investigators and Dynavax's representatives prior to submission for publication or presentation. Due regard shall be given to Dynavax's legitimate interests, eg, manuscript authorship, obtaining optimal patent protection, coordinating and maintaining the proprietary nature of submissions to health authorities, coordinating with other ongoing studies in the same field, and protecting confidential data and information.

Dynavax will be furnished with a copy of any proposed publication and allowed to make comments. In cases of publications or presentations of material arising from multicenter clinical

investigations, Dynavax is to serve as coordinator and referee. Individual investigators who are part of a multicenter investigation may not publish or present data that are considered common to a multicenter investigation without the consent and the prior review of Dynavax. In case of disagreement among the investigators participating in a multicenter investigation, Dynavax will be the final arbiter. If Dynavax's comments are not accepted, the senior author of the manuscript and Dynavax's representatives shall promptly meet and endeavor to agree mutually on the final wording and disposition of the publication. The above procedure also applies to information on prematurely discontinued and other incomplete studies.

Results from investigations shall not be made available to any third party by the investigating team outside the publication procedure as outlined previously. Dynavax will not quote from publications by investigators in its scientific information or promotional material without full acknowledgment of the source (ie, author and reference).

16.0 REFERENCES

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APPENDIX 1: SCHEDULE OF ASSESSMENTS

Study Period:	**Screening**	**Study Treatment**				**Treatment Follow-up**				**Early Discontinuation[a]**
Visit:	**0**	**1**	**2**	**3**	**4**	**5**	**6[h]**	**7[h]**	**8 End of Study**	
Day:	**-28 to -1**	**1**	**29**	**57**	**113**	**141**	**197**	**295**	**477**	
Week:	**-4**	**0**	**4**	**8**	**16**	**20**	**28[h]**	**42[h]**	**68**	
Visit window (days) from visit date:		**0**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**28+ days after last injection**
Informed consent	X									
Inclusion/Exclusion Criteria	X									
Demographics	X									
Medical and medication history[b]	X	X								
Height and weight[c]	X									
Physical examination[d]	X	X	X	X	X				X	X
Hematology by central laboratory	X									
Serum chemistry by central laboratory	X									
HIV and hepatitis screen (HIV, HBsAg, anti-HBc, anti-HBs, anti-HCV, anti-HIV-1/2)	X									
Serum pregnancy test (for WOCBP)[e]	X									
Serum or urine pregnancy test (for WOCBP)[e,f]		X	X	X	X					

APPENDIX 1: SCHEDULE OF ASSESSMENTS (CONT'D)

Study Period:	**Screening**	**Study Treatment**				**Treatment Follow-up**				**Early Discontinuation[a]**
Visit:	**0**	**1**	**2**	**3**	**4**	**5**	**6[h]**	**7[h]**	**8 End of Study**	
Day:	**-28 to -1**	**1**	**29**	**57**	**113**	**141**	**197**	**295**	**477**	
Week:	**-4**	**0**	**4**	**8**	**16**	**20**	**28[h]**	**42[h]**	**68**	
Visit window (days) from visit date:		**0**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**28+ days after last injection**
Anti-HBs (quantitative) and stored serum and plasma aliquot[g]	X	X	X	X	X	X				X
Confirmation of eligibility prior to each injection		X	X	X	X					
Study injection (HEPLISAV-B®)[i]		X	X	X	X					
30 minute post-injection observation[j]		X	X	X	X					
Instruction to subjects on collection of oral temperature and PIRs[k]		X	X	X	X					
Assessment of SAEs[l]	X	X	X	X	X	X	X	X	X	X
Assessment of MAEs, AESIs, and AMIs[l]		X	X	X	X	X	X	X	X	X
Concomitant medications[m]		X	X	X	X	X	X	X	X	X

MAE = medically-attended adverse event; AESI = adverse event of special interest; AMI = acute myocardial infarction; anti-HBc = antibodies to hepatitis B core antigen; anti-HBs = antibodies to hepatitis B surface antigen; anti-HCV = antibody to hepatitis C virus; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; PIR = post-injection reaction; SAE = serious adverse event; WOCBP = women of child-bearing potential.

APPENDIX 1: SCHEDULE OF ASSESSMENTS (CONT'D)

Footnotes

Early Discontinuation[a]	The assessments at the Early Discontinuation Visit should occur 28 days or more after the last study injection.
Medical and medication history[b]	Medical and medication history are all medical events occurring and medications received by the subject prior to the first study injection.
Height and weight[c]	Height and weight are only collected at Screening.
Physical examinations[d]	A full physical examination (excluding pelvic/genital, rectal, and breast examination) will be conducted at Screening, and a targeted physical examination based on subject-reported symptoms (excluding pelvic/genital, rectal, and breast examination) will be conducted at each study injection visit and End-of-Study (EOS) Visit or Early Discontinuation Visit. If a subject discontinues study treatment, subsequent targeted physical examination is only required at EOS Visit or Early Discontinuation Visit.
Serum pregnancy test (for WOCBP)[e]	All female subjects, regardless of age, are considered to be women of child bearing potential (WOCBP) except if they have been post-menopausal for at least 1 year or surgically sterile for at least 1 year. Samples will be collected prior to study drug injection. All pregnancy test results must be negative prior to injection.
Urine pregnancy test (for WOCBP)[e,f]	All female subjects, regardless of age, are considered to be women of child bearing potential (WOCBP) except if they have been post-menopausal for at least 1 year or surgically sterile for at least 1 year. Samples will be collected prior to study drug injection. All pregnancy test results must be negative prior to injection. Dipstick can be used for urine pregnancy test.
Anti-HBs (quantitative) and stored serum and plasma aliquot[g]	There must be a minimum of 21 days between any study injection and the subsequent anti-HBs sample collection. On treatment days, samples will be collected prior to study injection. Extra aliquots of serum and plasma will be collected and may be stored frozen for future use.
Weeks 28 and 42 [h]	Week 28 and 42 assessments (assessment of SAEs; MAEs, AESIs, AMIs; and concomitant medication) will be completed via telephone call.
Study injection (HEPLISAV-B®)[i]	Blood collection and HEPLISAV-B administration must be performed prior to the start of dialysis on study visit days.
30 minute post-injection observation[j]	May be completed while the subject is receiving dialysis.
Instruction to subjects on collection of oral temperature and PIRs[k]	Subjects will be provided with a diary to record oral temperature and post-injection reactions.
Assessment of MAEs, SAEs, AMIs, and AESIs [l]	SAEs will be collected and followed through EOS Visit. If the SAE is assessed as possibly or probably related to study treatment, it must be followed until it is considered stable or resolved, including beyond EOS Visit. MAEs, AMIs, and AESIs will be collected and followed through EOS Visit. Further details regarding safety monitoring of AMIs and AESIs are provided in Section 9.4.7.2.
Concomitant medications[m]	Concomitant medications are all medications and non-study vaccines received by the subject from the first injection through Week 28 or Early Discontinuation. Use of vitamins and dietary supplements will not be collected unless they are indicated as a concomitant therapy for conditions directly related to undergoing hemodialysis. After Week 28, only prescription medication or over-the-counter drug taken by the subject for the treatment of MAEs, SAEs, AMIs, or AESIs will be recorded on the eCRF through EOS Visit (further details regarding safety monitoring of AMIs and AESIs are provided in Section 9.4.7.2).

APPENDIX 2: HEPLISAV-B® UNITED STATES PACKAGE INSERT

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HEPLISAV-B® safely and effectively. See full prescribing information for HEPLISAV-B.

HEPLISAV-B [Hepatitis B Vaccine (Recombinant), Adjuvanted] Solution for Intramuscular Injection
Initial US Approval: 2017

----------INDICATIONS AND USAGE ----------
HEPLISAV-B is indicated for prevention of infection caused by all known subtypes of hepatitis B virus. HEPLISAV-B is approved for use in adults 18 years of age and older. (1)

---------- DOSAGE AND ADMINISTRATION ----------
For intramuscular administration
Administer two doses (0.5 mL each) of HEPLISAV-B intramuscularly one month apart. (2.1, 2.2)

----------DOSAGE FORMS AND STRENGTHS ----------
HEPLISAV-B is a solution for injection supplied as a single-dose vial and prefilled syringe. A single dose of HEPLISAV-B is 0.5 mL. (3)

----------CONTRAINDICATIONS----------
Severe allergic reaction, such as anaphylaxis, after a previous dose of any hepatitis B vaccine or to any component of HEPLISAV-B, including yeast. (4)

----------ADVERSE REACTIONS ----------
The most common local reaction was injection site pain (23% - 39%). The most common systemic reactions were fatigue (11% - 17%) and headache (8% - 17%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Dynavax at 1-844-889-8753 or VAERS at 1-800-822-7967 and www.vaers.hhs.gov.

----------USE IN SPECIFIC POPULATIONS ----------
A pregnancy registry is available for HEPLISAV-B. Women who receive HEPLISAV-B during pregnancy are encouraged to contact 1-844-443-7734. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

HEPLISAV-B is indicated for prevention of infection caused by all known subtypes of hepatitis B virus. HEPLISAV-B is approved for use in adults 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular administration.

2.1 Dose and Regimen

Administer two doses (0.5 mL each) of HEPLISAV-B one month apart.

2.2 Administration

HEPLISAV-B is a clear to slightly opalescent, colorless to slightly yellow solution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

Administer HEPLISAV-B by intramuscular injection in the deltoid region using a sterile needle and syringe.

3 DOSAGE FORMS AND STRENGTHS

HEPLISAV-B is a sterile solution for injection available in 0.5 mL single-dose vials and prefilled syringes. [see *How Supplied/Storage and Handling* (16.1)].

4 CONTRAINDICATIONS

Do not administer HEPLISAV-B to individuals with a history of severe allergic reaction (e.g. anaphylaxis) after a previous dose of any hepatitis B vaccine or to any component of HEPLISAV-B, including yeast [see *Description* (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of HEPLISAV-B.

5.2 Immunocompromised Individuals

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to HEPLISAV-B.

5.3 Limitations of Vaccine Effectiveness

Hepatitis B has a long incubation period. HEPLISAV-B may not prevent hepatitis B infection in individuals who have an unrecognized hepatitis B infection at the time of vaccine administration.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

A total of 9597 individuals 18 through 70 years of age received at least 1 dose of HEPLISAV-B in 5 clinical trials conducted in the United States, Canada, and Germany. Data from three of these trials are provided below.

Study 1 in Subjects 18 through 55 Years of Age

Study 1 was a randomized, observer-blind, active-controlled, multicenter study in Canada and Germany in which 1810 subjects received at least 1 dose of HEPLISAV-B and 605 subjects received at least 1 dose of Engerix-B® [Hepatitis B Vaccine (Recombinant)]. Enrolled subjects had no history of hepatitis B vaccination or infection. HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months. In the total study population, the mean age was 40 years; 46% of the subjects were men; 93% were white, 2% black, 3% Asian and 3% Hispanic; 26% were obese, 10% had hypertension, 8% had dyslipidemia, and 2% had diabetes mellitus. These demographic and baseline characteristics were similar in both vaccine groups.

Solicited Local and Systemic Adverse Reactions

Subjects were monitored for local and systemic adverse reactions using diary cards for a 7-day period starting on the day of vaccination. The percentages of subjects who reported local and systemic reactions are shown in Table 1.

Table 1
Study 1: Percent of Subjects Who Reported Local or Systemic Reactions Within 7 Days of Vaccination

	HEPLISAV-B %		Engerix-B %		
	Post-Dose*		Post-Dose*		
Reaction	**1**	**2**	**1**	**2**	**3**
Local	N=1810	N=1798	N=605	N=603	N=598
Injection Site Pain	38.5	34.8	33.6	24.7	20.2
Injection Site Redness†	4.1	2.9	0.5	1.0	0.7
Injection Site Swelling†	2.3	1.5	0.7	0.5	0.5
Systemic					
Fatigue	17.4	13.8	16.7	11.9	10.0
Headache	16.9	12.8	19.2	12.3	9.5
Malaise	9.2	7.6	8.9	6.5	6.4
	N=1784	N=1764	N=596	N=590	N=561
Fever‡	1.1	1.5	1.8	1.7	1.8

Note: only subjects having data are included. Clinical trial number: NCT00435812
*HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months
† Redness and swelling ≥ 2.5 cm.
‡ Oral temperature ≥ 100.4°F (38.0°C).

Unsolicited Adverse Events:
Unsolicited adverse events within 28 days following any injection, including placebo, were reported by 42.0% of HEPLISAV-B recipients and 41.3% of Engerix-B recipients.

Serious Adverse Events (SAEs)
Subjects were monitored for serious adverse events for 7 months after the first dose of vaccine. The percentage of subjects reporting serious adverse events was 1.5% in the HEPLISAV-B group and 2.1% in the Engerix-B group. No acute myocardial infarctions were reported. No deaths were reported.

Potentially Immune-mediated Adverse Events
Potentially immune-mediated adverse events that occurred within 7 months of the first dose of vaccine were reported in 0.2% (n = 4) of HEPLISAV-B recipients and 0.7% (n = 4) of Engerix-B recipients. The following events were reported in the HEPLISAV-B group in one subject each: granulomatosis with polyangiitis, lichen planus, Guillain-Barré syndrome, and Grave's disease. The following events were reported in the Engerix-B group in one subject each: Bell's palsy, Raynaud's phenomenon, and Grave's disease. One additional Engerix-B recipient with a history of mixed connective tissue disease had p-ANCA-positive vasculitis.

Study 2 in Subjects 40 through 70 Years of Age

Study 2 was a randomized, observer-blind, active-controlled, multicenter study in Canada and the United States in which 1968 subjects received at least 1 dose of HEPLISAV-B and 481 subjects received at least 1 dose of Engerix-B. HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Enrolled subjects had no history of hepatitis B vaccination or infection. Engerix-B was given at 0, 1, and 6 months. In the total population, the mean age was 54 years; 48% of subjects were men; 82% were white, 15% black, 1% Asian and 6% Hispanic; 44% were obese, 30% had hypertension, 30% had dyslipidemia, and 8% had diabetes mellitus. These demographic and baseline characteristics were similar in both vaccine groups.

Solicited Local and Systemic Adverse Reactions
Subjects were monitored for local and systemic adverse reactions using diary cards for a 7-day period starting on the day of vaccination. The percentages of subjects who experienced local and systemic reactions are shown in Table 2.

Table 2
Study 2: Percent of Subjects Who Reported Local or Systemic Reactions Within 7 Days of Vaccination

	HEPLISAV-B %		Engerix-B %		
	Post-Dose*		Post-Dose*		
Reaction	**1**	**2**	**1**	**2**	**3**
Local	N=1952	N=1905	N=477	N=464	N=448
Injection Site Pain	23.7	22.8	18.4	15.9	13.8
Injection Site Redness†	0.9	0.7	0.6	0.2	0.2
Injection Site Swelling†	0.9	0.6	0.6	0.6	0.2
Systemic					
Fatigue	12.6	10.8	12.8	12.1	9.4
Headache	11.8	8.1	11.9	9.5	8.5
Malaise	7.7	7.0	8.6	7.1	5.1
Myalgia	8.5	6.4	9.6	8.0	4.5
	N=1923	N=1887	N=472	N=459	N=438
Fever‡	0.6	0.6	0.6	0.9	0.7

Note: only subjects having data are included. Clinical Trial Number: NCT01005407
*HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months
† Redness and swelling ≥2.5 cm
‡ Oral temperature ≥ 100.4°F (38.0°C).

Unsolicited Adverse Events:
Unsolicited adverse events within 28 days following any injection, including placebo, were reported by 35.4% of HEPLISAV-B recipients and 36.2% of Engerix-B recipients.

Serious Adverse Events
Subjects were monitored for serious adverse events for 12 months after the first dose of vaccine. The percentage of subjects reporting serious adverse events was 3.9% in the HEPLISAV-B group and 4.8% in the Engerix-B group. Acute myocardial infarction occurred in 0.1% (n=2) of HEPLISAV-B recipients and 0.2% (n=1) of Engerix-B recipients.

Autoimmune Adverse Events
Subjects were monitored for the occurrence of new-onset potentially immune-mediated adverse events for 12 months after the first dose of vaccine. Events were adjudicated as to whether they were autoimmune by an external group of experts blinded to treatment assignment. As determined by the adjudicators, new-onset autoimmune adverse events were reported in 0.2% (n=3) of HEPLISAV-B recipients: two subjects with hypothyroidism and one subject with vitiligo. None of these events was considered related to vaccination by the expert group. No new-onset autoimmune adverse events were reported in the Engerix-B group. Although not referred to the external group of experts, one HEPLISAV-B recipient was determined to have Tolosa-Hunt syndrome which is presumed to have an immune-mediated etiology. This event was not considered related to vaccination.

Deaths
One subject (0.05%) died of a pulmonary embolism in the HEPLISAV-B group and 1 subject (0.2%) died of heart failure in the Engerix-B group. Neither death was considered related to vaccination.

Study 3 in Subjects 18 through 70 Years of Age

Study 3 was a randomized, observer-blind, active-controlled, multicenter study in the United States in which 5587 subjects received at least 1 dose of HEPLISAV-B and 2781 subjects received at least 1 dose of Engerix-B. Enrolled subjects had no history of hepatitis B vaccination or infection. HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months. In the total study population, the mean age was 50 years; 51% were men; 71% were white, 26% black, 1% Asian, and 9% Hispanic; 48% were obese, 36% had hypertension, 32% had dyslipidemia, and 14% had type 2 diabetes mellitus. These demographic and baseline characteristics were similar in both vaccine groups.

Unsolicited Medically-Attended Adverse Events
Subjects were monitored for unsolicited medically-attended adverse events, those for which a subject sought medical care, for 13 months after the first dose of vaccine. Overall, medically-attended adverse events were reported in 46.0% of HEPLISAV-B recipients and 46.2% of Engerix-B recipients. Herpes zoster was reported in 0.7% of HEPLISAV-B recipients and 0.3% of Engerix-B recipients. Unsolicited medically-attended adverse events within 28 days following any injection, including placebo, were reported by 20.1% of both HEPLISAV-B and Engerix-B recipients.

Serious Adverse Events
Subjects were monitored for serious adverse events for 13 months after the first dose of vaccine. The percentage of subjects who reported serious adverse events was 6.2% in the HEPLISAV-B group and 5.3% in the Engerix-B group. Acute myocardial infarction (AMI) was reported in 0.25% (n=14) of HEPLISAV-B recipients and 0.04% (n=1) of Engerix-B recipients. An analysis of serious adverse events likely representing myocardial infarction (MI) was conducted using the standard Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) for MI. This analysis identified a total of 19 HEPLISAV-B subjects (0.3%) and 3 Engerix-B subjects (0.1%) with events included in the SMQ for MI (these events include the 15 reports of AMI). Additional evidence, including information on temporal relationship and baseline risk factors, does not support a causal relationship between HEPLISAV-B administration and AMI. Among the 19 events identified as MI in HEPLISAV-B recipients, three occurred within 14 days, nine occurred within 53-180 days, and seven occurred more than 180 days following any dose of HEPLISAV-B. Among the three events identified as MI in Engerix-B recipients, one each occurred 13, 115, and 203 days following any dose. All 19 HEPLISAV-B recipients and 3 Engerix-B recipients reported one or more baseline risk factors for cardiovascular disease.

Autoimmune Adverse Events
Subjects were monitored for the occurrence of new-onset potentially immune-mediated adverse events for 13 months after the first dose of vaccine. Events were adjudicated as to whether they were autoimmune by an external group of experts who were blinded to treatment assignment. As determined by the adjudicators, new-onset autoimmune adverse events were reported in 0.1% (n=4) of HEPLISAV-B recipients [one each of: alopecia areata, polymyalgia rheumatica, ulcerative colitis, and autoimmune thyroiditis (with concurrent diagnosis of papillary thyroid carcinoma)]. None of these events was considered to be related to vaccination by the external experts. No new-onset autoimmune adverse events were reported in the Engerix-B group.

Deaths
During the study death was reported in 25 subjects (0.4%) in the HEPLISAV-B group and 7 subjects (0.3%) in the Engerix-B group. No death was considered related to vaccination.

7 DRUG INTERACTIONS

7.1 Use with Immune Globulin

There are no data to assess the concomitant use of HEPLISAV-B with immune globulin. When concomitant administration of HEPLISAV-B and immune globulin is required, they should be given with different syringes at different injection sites.

7.2 Interference with Laboratory Tests

Hepatitis B surface antigen (HBsAg) derived from hepatitis B vaccines has been transiently detected in blood samples following vaccination. Serum HBsAg detection may not have diagnostic value within 28 days after receipt of HEPLISAV-B.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to HEPLISAV-B during pregnancy. Women who receive HEPLISAV-B during pregnancy are encouraged to contact 1-844-443-7734.

Risk Summary
All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In clinically recognized pregnancies in the US general population, the estimated background risk of major birth defects is 2% to 4% and of miscarriage is 15% to 20%.

There are no clinical studies of HEPLISAV-B in pregnant women. Available human data on HEPLISAV-B administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

In a developmental toxicity study, 0.3 mL of a vaccine formulation containing 2.5 mcg HBsAg and 3000 mcg cytosine phosphoguanine (CpG) 1018 adjuvant was administered to female rats prior to mating and during gestation. These animal studies revealed no evidence of harm to the fetus due to this vaccine formulation *[see Data]*.

Data
Animal data
Developmental toxicity studies were conducted in female rats. Animals were administered 0.3 mL of a vaccine formulation containing 2.5 mcg HBsAg and 3000 mcg CpG 1018 adjuvant twice prior to mating, and on gestation days 6 and 18 (a single human dose of HEPLISAV-B contains 20 mcg HBsAg and 3000 mcg CpG 1018 adjuvant). No adverse effects on pre-natal and post-natal development up to the time of weaning were observed. There were no vaccine-related fetal malformations or variations observed.

8.2 Lactation
Risk Summary
It is not known whether HEPLISAV-B is excreted in human milk. Data are not available to assess the effects of HEPLISAV-B on the breastfed infant or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HEPLISAV-B and any potential adverse effects on the breastfed child from HEPLISAV-B or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use
Safety and effectiveness of HEPLISAV-B have not been established in individuals less than 18 years of age.

8.5 Geriatric Use
Clinical trials included 909 adults 65 through 70 years of age who received HEPLISAV-B.

Among subjects who received HEPLISAV-B, a seroprotective level of antibody to HBsAg was achieved in 90% of those 65 through 70 years of age compared to 96% of those aged 18 through 64 years of age.

Safety and effectiveness of HEPLISAV-B in adults older than 70 years of age were extrapolated from findings in subjects younger than 70 years of age.

8.6 Adults on Hemodialysis
Safety and effectiveness of HEPLISAV-B have not been established in adults on hemodialysis.

11 DESCRIPTION
HEPLISAV-B [Hepatitis B Vaccine (Recombinant), Adjuvanted] is a sterile solution for intramuscular injection.

The HBsAg is expressed in a recombinant strain of *Hansenula polymorpha* yeast. The fermentation process involves growth of the recombinant *H. polymorpha* on chemically-defined fermentation media containing vitamins and mineral salts.

The HBsAg is expressed intra-cellularly in the yeast cells. It is released from the yeast cells by cell disruption and purified by a series of physicochemical steps. Each dose may contain residual amounts of yeast protein (≤5.0% of total protein), yeast DNA (<20 picogram), and deoxycholate (<0.9 ppm) from the HBsAg manufacturing process.

HEPLISAV-B is prepared by combining the purified HBsAg together with the CpG 1018 adjuvant, a 22-mer phosphorothioate linked oligodeoxynucleotide in a phosphate buffered saline (sodium chloride, 9.0 mg/mL; sodium phosphate, dibasic dodecahydrate, 1.75 mg/mL; sodium phosphate, monobasic dihydrate, 0.48 mg/mL; and polysorbate 80, 0.1 mg/mL).

Each 0.5-mL dose is formulated to contain 20 mcg of HBsAg and 3000 mcg of CpG 1018 adjuvant.

HEPLISAV-B is available in vials and prefilled syringes. The tip caps and stoppers of the prefilled syringes and vial stoppers are not made with natural rubber latex.

HEPLISAV-B is formulated without preservatives. [see *How Supplied/Storage and Handling (16)*].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Infection with hepatitis B virus can have serious consequences including acute massive hepatic necrosis and chronic active hepatitis. Chronically infected persons are at increased risk for cirrhosis and hepatocellular carcinoma.

Antibody concentrations ≥10 mIU/mL against HBsAg are recognized as conferring protection against hepatitis B virus infection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

HEPLISAV-B has not been evaluated for carcinogenicity, mutagenic potential or male infertility in animals. Vaccination of female rats with a vaccine formulation containing 2.5 mcg HBsAg and 3000 mcg CpG 1018 adjuvant had no effect on fertility [see *Use in Specific Populations (8)*].

14 CLINICAL STUDIES

14.1 Evaluation of Seroprotection

The immunogenicity of HEPLISAV-B was evaluated in comparison with a licensed hepatitis B vaccine (Engerix-B) in 3 randomized, active controlled, observer-blinded, multi-center Phase 3 clinical trials of adults. HEPLISAV-B was given as a 2-dose regimen at 0 and 1 months followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months.

The trials compared the seroprotection rates (% with antibody concentration ≥ 10 mIU/mL) induced by HEPLISAV-B and Engerix-B. Noninferiority was met if the lower bound of the 95% confidence interval of the difference in seroprotection rates (HEPLISAV-B minus Engerix-B) was greater than -10%.

Study 1: Seroprotection in Adults 18 through 55 Years of Age

In Study 1, the immunogenicity population comprised 1511 participants who received HEPLISAV-B and 521 who received Engerix-B. The mean age was 40 years for both groups. The primary analysis compared the seroprotection rate at Week 12 for HEPLISAV-B with that at Week 28 for Engerix-B. Non-inferiority of the seroprotection rate induced by HEPLISAV-B compared to Engerix-B was demonstrated (Table 3).

Timepoint	Table 3 Study 1: Seroprotection Rate of HEPLISAV-B and Engerix-B (ages 18 through 55 years)		
	HEPLISAV-B N = 1511	Engerix-B N = 521	Difference in SPRs (HEPLISAV-B minus Engerix-B)
	SPR (95% CI)	SPR (95% CI)	Difference (95% CI)
Week 12 (HEPLISAV-B) Week 28 (Engerix-B)	95% (93.9, 96.1)	81.3% (77.8, 84.6)	13.7% (10.4, 17.5)*

CI = confidence interval; N = number of subjects in the analysis population in the group; SPR = seroprotection rate (% with anti-HBs ≥ 10 mIU/mL).
* Noninferiority was met because the lower bound of the 95% confidence interval of the difference in SPRs was greater than -10%.
Clinical trial number: NCT00435812

Study 2: Seroprotection in Adults 40 through 70 Years of Age

In Study 2, the immunogenicity population comprised 1121 subjects who received HEPLISAV-B and 353 subjects who received Engerix-B. The mean age was 54 years for both groups. The primary analysis compared the seroprotection rate at Week 12 for HEPLISAV-B with that at Week 32 for Engerix-B. Non-inferiority of the seroprotection rate induced by HEPLISAV-B compared to Engerix-B was demonstrated (Table 4).

Timepoint	Table 4 Study 2: Seroprotection Rate of HEPLISAV-B and Engerix-B (ages 40 through 70 years)		
	HEPLISAV-B N = 1121	Engerix-B N = 353	Difference in SPRs (HEPLISAV-B minus Engerix-B)
	SPR (95% CI)	SPR (95% CI)	Difference (95% CI)
Week 12 (HEPLISAV-B) Week 32 (Engerix-B)	90.1% (88.2, 91.8)	70.5% (65.5, 75.2)	19.6% (14.7, 24.8)*

CI = confidence interval; N = number of subjects in the analysis population in the group; SPR = seroprotection rate (% with anti-HBs ≥ 10 mIU/mL).
* Noninferiority was met because the lower bound of the 95% confidence interval of the difference in SPRs was greater than -10%. The SPR following HEPLISAV-B was statistically significantly higher than following Engerix-B (lower bound of the 95% confidence interval of the difference in SPRs was greater than 0%).
Clinical trial number: NCT01005407

Study 3: Seroprotection in Adults 18 through 70 Years of Age Including those with Type 2 Diabetes Mellitus

In Study 3, the immunogenicity population comprised 4537 subjects who received HEPLISAV-B and 2289 subjects who received Engerix-B. The mean age was 51 years and 14% of subjects had type 2 diabetes mellitus (defined as having a clinical diagnosis of type 2 diabetes and taking at least an oral or non-insulin injectable hypoglycemic agent and/or insulin).

The primary analysis compared the seroprotection rate at Week 28 for HEPLISAV-B (n= 640) with that at Week 28 for Engerix-B (n= 321) in subjects with type 2 diabetes mellitus. Non-inferiority of the seroprotection rate induced by HEPLISAV-B compared to Engerix-B was demonstrated (Table 5).

Timepoint	Table 5 Study 3: Seroprotection Rate of HEPLISAV-B and Engerix-B (subjects with type 2 diabetes mellitus ages 18 through 70 years)		
	HEPLISAV-B N = 640	Engerix-B N = 321	Difference in SPRs (HEPLISAV-B minus Engerix-B)
	SPR (95% CI)	SPR (95% CI)	Difference (95% CI)
Week 28	90.0% (87.4, 92.2)	65.1% (59.6, 70.3)	24.9% (19.3, 30.7)*

CI = confidence interval; N = number of subjects in the analysis population in the group; SPR = seroprotection rate (% with anti-HBs ≥ 10 mIU/mL).
* Noninferiority was met because the lower bound of the 95% confidence interval of the difference in SPRs was greater than -10%. The SPR following HEPLISAV-B was statistically significantly higher than following Engerix-B (lower bound of the 95% confidence interval of the difference in SPRs was greater than 0%).
Clinical trial number: NCT02117934

A secondary analysis compared the seroprotection rate at Week 24 for HEPLISAV-B with that at Week 28 for Engerix-B in the total study population. Non-inferiority of the seroprotection rate induced by HEPLISAV-B compared to Engerix-B was demonstrated (Table 6).

Timepoint	Table 6 Study 3: Seroprotection Rate of HEPLISAV-B and Engerix-B (total study population ages 18 through 70 years)		
	HEPLISAV-B N = 4376	Engerix-B N = 2289	Difference in SPRs (HEPLISAV-B minus Engerix-B)
	SPR (95% CI)	SPR (95% CI)	Difference (95% CI)
Week 24 (HEPLISAV-B) Week 28 (Engerix-B)	95.4% (94.8, 96.0)	81.3% (79.6, 82.8)	14.2% (12.5, 15.9)*

CI = confidence interval; N = number of subjects in the analysis population in the group; SPR = seroprotection rate (% with anti-HBs ≥ 10 mIU/mL).
Clinical trial number: NCT02117934
*Noninferiority was met because the lower bound of the 95% confidence interval of the difference in SPRs was greater than -10%. The SPR following HEPLISAV-B was statistically significantly higher than following Engerix-B (lower bound of the 95% confidence interval of the difference in SPRs was greater than 0%.).

Another secondary analysis compared the seroprotection rate at Week 24 for HEPLISAV-B with that at Week 28 for Engerix-B, by age group. For each age stratum non-inferiority of the seroprotection rate induced by HEPLISAV-B compared to Engerix-B was demonstrated (Table 7).

Age (years)	Table 7 Study 3: Seroprotection Rates of HEPLISAV-B and Engerix-B[a] (ages 18 - 70 years)				
	HEPLISAV-B[a]		Engerix-B[a]		Difference in SPRs (HEPLISAV-B minus Engerix-B)
	N	SPR (95% CI)	N	SPR (95% CI)	Difference (95% CI)
18-29	174	100.0% (97.9, 100.0)	99	93.9% (87.3, 97.7)	6.1% (2.8, 12.6)*
30-39	632	98.9% (97.7, 99.6)	326	92.0% (88.5, 94.7)	6.9% (4.2, 10.4)*
40-49	974	97.2% (96.0, 98.2)	518	84.2% (80.7, 87.2)	13.1% (9.9, 16.6)*
50-59	1439	95.2% (94.0, 96.3)	758	79.7% (76.6, 82.5)	15.5% (12.6, 18.7)*
60-70	1157	91.6% (89.9, 93.1)	588	72.6% (68.8, 76.2)	19.0% (15.2, 23.0)*

CI = confidence interval; N = number of subjects in the analysis population in the group; SPR = seroprotection rate (% with anti-HBs ≥ 10 mIU/mL).
[a] Week 24 for HEPLISAV-B and Week 28 for Engerix-B
Clinical trial number: NCT02117934
*Noninferiority was met because the lower bound of the 95% confidence interval of the difference in SPRs was greater than -10%. The SPR following HEPLISAV-B was statistically significantly higher than following Engerix-B (lower bound of the 95% confidence interval of the difference in SPRs was greater than 0%).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

- Vial, 1 dose (0.5 mL) - (NDC number: 43528-002-01)
- Package of 5 single dose vials - (NDC number: 43528-002-05)

- Prefilled syringe, 1 dose (0.5 mL) - (NDC number: 43528-003-01)
- Package of 5 single dose prefilled syringes - (NDC number: 43528-003-05)

The tip caps and stoppers of the prefilled syringes and vial stoppers are not made with natural rubber latex.

16.2 Storage Conditions

Store in a refrigerator at 2°C to 8°C (35°F to 46°F).
Do not freeze; discard if the vaccine has been frozen.
Do not use the vaccine after the expiration date shown on the vial or prefilled syringe label.

17. PATIENT COUNSELING INFORMATION

- Inform vaccine recipient of the potential benefits and risks associated with vaccination, as well as the importance of completing the immunization series.
- Emphasize that HEPLISAV-B contains non-infectious purified HBsAg and cannot cause hepatitis B infection.
- Advise vaccine recipient to report any adverse events to their healthcare provider or to the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967 and www.vaers.hhs.gov.
- Provide the Vaccine Information Statements, which are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

DYNAVAX

Manufactured by:
Dynavax Technologies Corporation
Berkeley, CA 94710 USA

US-18-00-00015

APPENDIX 3: TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Erythema/Redness[a]	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Fever[c] (°C) (°F)	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Malaise	Uneasiness or lack of well being	Uneasiness or lack of well being; limiting instrumental ADL	*A grade is not available*	*A grade is not available*
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant: prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant: prevents daily activity	ER visit or hospitalization

Sources: (Center for Biologics Evaluation and Research 2007, National Cancer Institute 2010).

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

[c] Oral temperature; no recent hot or cold beverages or smoking. Subject should be at rest for vital sign measurements.

APPENDIX 4: LIST OF ADVERSE EVENTS OF SPECIAL INTEREST

Each subject will be assessed for these autoimmune, hypersensitivity, and inflammatory diseases during the trial. The following AESIs[a] will be evaluated and reported to FDA:

Gastrointestinal disorders
- Celiac disease
- Crohn's disease
- Ulcerative colitis
- Ulcerative proctitis

Liver disorders
- Autoimmune cholangitis
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis

Metabolic diseases
- Addison's disease
- Autoimmune thyroiditis (including Hashimoto thyroiditis)
- Diabetes mellitus type 1
- Grave's or Basedow's disease

Musculoskeletal disorders
- Antisynthetase syndrome
- Dermatomyositis
- Juvenile chronic arthritis (including Still's disease)
- Mixed connective tissue disorder
- Polymyalgia rheumatic
- Polymyositis
- Psoriatic arthropathy
- Relapsing polychondritis
- Rheumatoid arthritis
- Scleroderma, including diffuse systemic form and CREST syndrome
- Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis
- Systemic lupus erythematosus
- Systemic sclerosis

Neuroinflammatory disorders

- Acute disseminated encephalomyelitis, including site specific variants: eg, non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis
- Cranial nerve disorders, including paralyses/paresis (eg, Bell's palsy)
- Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
- Tolosa Hunt syndrome[b]
- Immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy)
- Multiple sclerosis
- Myasthenia gravis, including Eaton-Lambert syndrome
- Narcolepsy
- Optic neuritis
- Transverse Myelitis

Skin disorders

- Alopecia areata
- Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis)
- Cutaneous lupus erythematosus
- Erythema nodosum
- Morphoea
- Lichen planus
- Psoriasis
- Rosacea
- Sweet's syndrome
- Vitiligo

Vasculitides

- Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis
- Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis

Others

- Antiphospholipid syndrome
- Autoimmune hemolytic anemia
- Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoprofilerative glomerulonephritis, and masangioproliferative glomerulonephritis
- Autoimmune myocarditis/cardiomyopathy
- Autoimmune thrombocytopenia
- Goodpasture syndrome
- Idiopathic pulmonary fibrosis
- Pernicious anemia
- Raynaud's phenomenon
- Sarcoidosis
- Sjögren's syndrome
- Stevens-johnson syndrome
- Uveitis

[a] List provided to Dynavax Technologies by FDA on 30 January 2019
[b] Added by Dynavax