

MEMORANDUM

**Pharmacovigilance Plan Review
Analytic Epidemiology Branch (AEB)
Division of Epidemiology (DE)
Office of Biostatistics and Epidemiology (OBE)
Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)**

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Subject: Pharmacovigilance Plan Review for the
Biologics License Application of HEPLISAV

Applicant: Dynavax Technologies Corporation

Product: Hepatitis B Vaccine (Recombinant), HEPLISAV

Proposed Indication: Immunization against infection caused by all
known subtypes of hepatitis B virus in adults
18 years of age and older

Current Indication: None

Submission type: Resubmission of BLA 125428

Submission Date: March 15, 2016

PVP Submission Date (if applicable): March 15, 2016

Action Due Date: December 15, 2016

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1. Introduction

1.1 Product description

HEPLISAV™ (hereafter referred to as HEPLISAV) consists of a recombinant yeast cell-derived hepatitis B virus surface antigen (HBsAg, *adw* subtype, 20 mcg) and a proprietary adjuvant, 1018 (3000 mcg), developed by Dynavax Technologies Corporation (Dynavax). The intended biological activity of HBsAg is to generate antibodies to the alpha determinant of the S protein, and the intended biologic activity of 1018, a phosphorothioate oligodeoxyribonucleotide (PS ODN) which uses synthetic immunostimulatory sequences (ISS), is to enhance antibody generation by activating the innate immune system via Toll-like receptor 9 (TLR9). The proposed dosing regimen of HEPLISAV in adults is 20 mcg HBsAg and 3000 mcg 1018 administered by intramuscular (IM) injection at Months 0 and 1.

The aim of the Dynavax hepatitis B vaccine is to induce a significantly higher antibody peak, provide earlier seroprotection, and require fewer doses (2 rather than 3) than currently licensed hepatitis B vaccines. The indication, for which Dynavax is seeking approval, is for immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older.

People thought likely to benefit from vaccination with HEPLISAV are adults at risk of HBV infection. Table 1 summarizes the high risk groups for whom hepatitis B vaccination is recommended by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention.

Table 1. Individuals with Risk Factors for Hepatitis B Infection

Risk Factors for Hepatitis B Infection
Individuals at risk for infection by sexual exposure
Sex partners of HBsAg-positive individuals
Individuals with more than 1 sex partner in the previous 6 months
Men who have sex with men
Individuals with a sexually transmitted disease
Individuals at risk for infection by percutaneous or mucosal exposure to blood
Household contacts of HBsAg-positive individuals
Injection-drug users
Individuals 19 through 59 years of age with diabetes mellitus and individuals greater than or equal to 60 years of age at the discretion of the treating physician
Individuals with end-stage renal disease, including predialysis, hemodialysis, and peritoneal dialysis
Health-care and public safety workers with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids
Residents and staff of facilities for developmentally disabled persons
Others
International travelers to countries with HBsAg prevalence greater than or equal to 2%
Individuals with chronic liver disease
Individuals with HIV infection
All other individuals seeking protection from HBV infection

* Source: Heplisav Risk Management Plan

1.2. Objective of the review

The objective of this review is to identify safety issues that may need to be addressed through post-marketing safety surveillance or studies should the product be licensed. Final determination of the safety profile of the product used in the studies submitted to this BLA is pending final (clinical, statistical and/or product) review.

1.3 Pertinent regulatory history

1.3.1 Prior Licensures

HEPLISAV is not yet approved in any country. This is the first vaccine to use 1018 ISS as an adjuvant in humans.

1.3.2 Original U.S. BLA Review

The original BLA for this product was submitted April 26, 2012 (STN 125428/0.0). The safety data for the BLA drew from 2 pivotal studies (HBV-10 and HBV-16) comprising 3,777 HEPLISAV recipients and seven supportive safety studies (HBV-14, HBV-01, HBV-02, HBV-03, HBV-04, HBV-05, and HBV-08) comprising an additional 648 HEPLISAV recipients for a total of 4,425 HEPLISAV recipients. There were 1,420 subjects in the control groups who received Engerix-B hepatitis B vaccine.

The FDA clinical review, written by Lorie Smith and Alexandra S. Worobec, noted that although HEPLISAV demonstrated a rapid, robust, and sustained seroprotection rate (SPR) against hepatitis B for all study populations evaluated, there were a number of safety concerns. Concerns at that time included:

- A numerical imbalance between the incidence of pulmonary emboli in HEPLISAV and Engerix-B recipients with 5 subjects (0.1%) seen in the HEPLISAV group and 0 subjects in the Engerix-B group. Of note, four of the five events occurred in individuals with underlying predisposition to thrombus. Non-serious thrombotic events occurred with similar frequency between the two groups.
- One case, identified in HBV-10, of new-onset Wegener's granulomatosis in the HEPLISAV treatment arm.
- One case identified in HBV-16 of Tolosa-Hunt syndrome – a granulomatous disorder of the cavernous sinus, which was thought notable because of its potential vasculitis or autoimmune etiology and because reports in the literature suggested this condition could be a limited form or initial presentation of Wegener's granulomatosis in which ANCA testing is often negative.
- One case identified in HBV-16 of narcolepsy in a 43-year-old woman diagnosed 13 days following her second study injection.

- Three cases identified in HBV-16 of new-onset autoimmune disease all occurring in the HEPLISAV arm (two cases of hypothyroidism and one of vitiligo). Of note, the Safety Evaluation and Adjudication Committee (SEAC) thought these to be unrelated to the vaccine. Furthermore, a CBER independent analysis showed thyroid-related adverse events (AEs) to be similar between the two groups.

The safety data were presented to the Vaccines and Related Biologic Products Advisory Committee (VRBPAC) on November 15, 2012. Although the Committee voted 13:1 in support of a sufficient demonstration of vaccine immunogenicity, the committee voted 8:5 (with 1 abstention) that safety data were inadequate to recommend licensure of HEPLISAV at that time. In addition, they were concerned that the studies performed were not adequately balanced in terms of the racial and ethnic groups studied, that the studies were conducted in the general population and did not specifically evaluate safety in high risk populations, and that concomitant administration studies were not done.

The original Pharmacovigilance Plan proposed a phase IV open-label prospective observational study of 5,000 HEPLISAV recipients and 15,000 Engerix-B recipients to assess the incidence of medically significant AEs, including autoimmune disease, for 12 months after the 1st injection. At the VRBPAC, the applicant presented an alternate plan, in which enrollment would ultimately be expanded beyond the initially proposed 5,000 HEPLISAV recipients to include 30,000 HEPLISAV recipients.

The Clinical Review, which incorporated discussion points from the VRBPAC, concluded that the potential for autoimmunity with HEPLISAV immunization, given the case of Wegener's granulomatosis and the possible case of Tolosa-Hunt syndrome in HEPISLAV-vaccinated subjects, required further evaluation in a larger population database and specifically, a closer review of the case of Tolosa-Hunt syndrome by a group of clinical experts. Additionally, the reviewers were concerned about the size of the safety database, the randomization ratios (such that it was difficult to make any conclusion about a 0.5% difference seen in the incidence of potential autoimmune disease between the two groups), and the length of safety follow-up (AEs in HBV-10 and HBV-16 were assessed for 28 weeks following 1st dose). As a result, approval of HEPLISAV for healthy subjects, 18-70 years of age, for the prevention of hepatitis B infection was not recommended by the clinical reviewers.

The Pharmacovigilance/Epidemiology Review deferred a decision as to the adequacy of the Pharmacovigilance Plan (PVP) pending the sponsor's response addressing the concerns of the Clinical Reviewer.

The sponsor received a Complete Response letter from FDA, dated February 22, 2013, with 55 clarifications requested. The clinical Items in the CR included requests for:

- A larger safety database and further clinical evaluation of safety.
- Additional information on several subjects who experienced adverse events including:
 - Subject 32-018, for any medical records related to the diagnosis of narcolepsy
 - Subject 42-320, who was discontinued from the study due to facial swelling and a rash of unknown etiology
 - Subject 21-640, who was referred for medical evaluation of a potential autoimmune event

- Subject 06-174, who suffered a neurological event
- Subjects 22-601, 21-047 and 22-070, for clotting disorder evaluations and serologic markers of autoimmune disease in these three subjects reporting pulmonary emboli
- Radiographic images pertaining to the potential case of Tolosa-Hunt syndrome.

1.3.3. Additional Regulatory History

The European Medicines Agency (EMA), according to a Withdrawal Assessment Report, dated 20 February 2014, did not approve the application for HEPLISAV, and on February 10, 2014, Dynavax officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wished to withdraw its application for a marketing authorization.

Concerns described in the Withdrawal Assessment Report included:

- The quality of the data from trial HBV-17 (a study conducted in patients with chronic kidney disease and not included in the U.S. BLA application), resulting in a recommendation that the data not be used in the evaluation and a “consideration that the data from additional studies may be unreliable given systematic errors in the quality system”;
- A greater proportion of subjects in the HEPLISAV group reporting anemia within 28 days of injection (7 [0.2%] cases vs. 0 cases);
- A greater proportion of subjects reporting ALT and AST increases;
- Continued concern regarding the possibility of exacerbation of preexisting autoimmune diseases;
- The size of the safety database not being considered large enough to adequately assess the theoretical concern of autoimmune disease;
- An assertion that it would be prudent that the class effects (hematologic effects, liver and renal events, activation of the complement system) of PS ODNs be translated into “potential risks” for the Risk Management Plan (RMP); and
- A request that long term effectiveness and safety with concomitant administration of other vaccines be included as an area of important missing information.

According to the Withdrawal Assessment Report, the applicant had revised the pharmacovigilance plan to include a Post-authorisation safety study (PASS) enrolling 120,000 (30,000 to receive HEPLISAV) subjects to investigate both new-onset as well as exacerbations of autoimmune diseases over 2 years, a phase 3 study in generally healthy adults (a request of the FDA), and a pregnancy registry.

1.3.4 Current BLA Application

Dynavax resubmitted a BLA on March 15, 2016, which included new data from an additional pivotal safety study HBV-23 (N=8,374 subjects), as well immunogenicity data from that same study and revised clinical study reports for pivotal studies HBV-10 and HBV-16. The revised BLA describes 3,778 people, rather than 3,777 in studies HBV-10 and HBV-16, as there was a re-analysis of the original 2 trials after the EMA found inconsistencies (per-protocol subjects were included where they should not be and vice versa) and identification of a person who had originally been assigned to the Engerix-B arm but had actually received HEPLISAV. Due to the

substantial amount of clinical data not previously reviewed, a Major Amendment letter was issued on April 18, 2016.

2. Materials Reviewed

2.1 Selected Portions of BLA Submission

- Sequence 0040, 3/15/2016, STN 125428/0.42, Module 1.2 — FDA Complete Response Letter, 22 February 2013
- Sequence 0040, 3/15/2016, STN 125428/0.42, Module 1.11.3 — Clinical Information Amendment Response to CRL Question 1
- Sequence 0040, 3/15/2016, STN 125428/0.42, Module 1.11.3 — Clinical Information Amendment Response to CRL Question 2
- Sequence 0040, 3/15/2016, STN 125428/0.42, Module 1.11.3 — Clinical Information Amendment Response to CRL Question 3
- Sequence 0040, 3/15/2016, STN 125428/0.42, Module 1.16 — Risk Management Plan (Version 2.0)
- Sequence 0040, 3/15/2016, STN 125428/0.42, Module 2.5 — Clinical Overview
- Sequence 0040, 3/15/2016, STN 125428/0.42, Module 2.74 — Summary of Clinical Safety
- Sequence 0040, 3/15/2016, STN 125428/0.42, Module 2.74 — Autoimmune Preferred Terms
- Sequence 0040, 3/15/2016, STN 125428/0.42, Module 2.74 — Summary of Clinical Safety – Narratives
- Sequence 0040, 3/15/2016, STN 125428/0.42, Module 2.74
- Sequence 0040, 3/15/2016, STN 125428/0.42, Module 5.3.5.3 — Integrated Summary of Safety
- Sequence 0063, 10/2/2016, STN 125428/0.65, Module 1.11.3 — Response to Information Request (2) 09 September 2016 (This IR, including the “Evaluation of Acute Myocardial Infarction and Major Adverse Cardiovascular Events in the Phase 3 Heparin Clinical Trials”, was received but will be reviewed as part of a future memo.)
- Sequence 0064, 10/5/2016, STN 125428/0.66, Module 1.11.3 — Response to 28 September 2016 Information Request (This IR was received; a full review will be part of a future memo)

2.2 Input from CBER Clinical and Statistical Reviewers: Of note, the clinical and statistical review is ongoing; final assessment is contingent on responses to a Complete Response Letter.

2.3 Information from original BLA submission

- OBE Pharmacovigilance Review, Manette Niu (supervisor approval 2/6/2013)
- OVR Clinical Review, Lorie Smith, Alexandra S. Worobec (supervisor approval March 22, 2013)
- FDA. Transcript of the 131st Meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC), November 15, 2012.

2.4 European Medicines Agency. Withdrawal Assessment Report: Hepelisav. February 20, 2014. EMA/186212/2014

3. Complete Responses

The sponsor responded to the CR requests from the original BLA application. Specifically, their responses to the 3 clinical questions are as follows:

3.1 CR Question 1

In response to the request for a larger safety database, Dynavax conducted HBV-23 to increase the size of the HEPLISAV safety database. The study enrolled 8,374 subjects (HEPLISAV: n = 5,587; Engerix-B: n = 2,781).

3.2 CR Question 2

In response to requests for additional information pertaining to cases of concern, Dynavax provided the following:

- Subject 32-018, who was diagnosed with narcolepsy 13 days after her second dose of HEPLISAV, was a 42-year-old woman from the U.S. with a history of depression, bipolar disorder, neck and bilateral arm pain, addiction to pain medication, fatigue, and insomnia, on medications including Adderall, temazepam, trazodone, Effexor, aripiprazole, and oxycodone, who on further investigation, reported that narcolepsy symptoms began when she was a teenager (thus were not considered to be new-onset).
- Subject 42-320, who was discontinued from the study due to facial swelling and a rash of unknown etiology, was a 57-year-old woman from the U.S. who developed a rash on the day of her first injection and rash and facial swelling during the months after injection. The subject has refused access to dermatology referral records and states that she has not experienced any recurrence of symptoms or continued to see a dermatologist. The subject had negative anti-ds DNA titers at baseline and end of study. At baseline the ANA titer was <1:40; at Week 52 ANA was 1:40 with a nucleolar pattern.
- Subject 21-640, who was referred for medical evaluation of a potential autoimmune event, was a 68-year-old woman from the U.S. who developed left hand aching and swelling three days after her first injection with HEPLISAV. The diagnosis by the rheumatologist and principal investigator was that this was osteoarthritis without evidence of autoimmune disease.
- Subject 06-174, for which hospital records and neurological outpatient records were requested, was a 55-year-old man from Canada who was hospitalized with dysphasia and left hand numbness over 3 months after his second injection with HEPLISAV. He was evaluated for stroke, but MRI was normal. His symptoms were thought secondary to carpal tunnel syndrome.
- Clotting disorder evaluations were submitted for 3 patients who had pulmonary emboli.

(Reviewer comment: In depth analyses of these cases is deferred to the clinical reviewer. From a pharmacovigilance standpoint, however, it is noted that the potential case of narcolepsy is

thought to have an onset prior to vaccine administration; thus, from the data reviewed by this reviewer, there is no clear reason at this time to include narcolepsy as a specific postmarketing concern.)

3.3 CR Question 3

Additional radiographic material, pertaining to the potential case of Tolosa-Hunt syndrome was submitted. *(Reviewer comment: Evaluation of these results is deferred to the clinical reviewer.)*

4. Pharmacovigilance Plan Review

4.1 Nonclinical Data

Nonclinical studies did not demonstrate severe toxicity in the primary safety study conducted in mice, and all effects were thought to be consistent with the known class effects of structurally similar phosphorothioate oligodeoxynucleotides (PS ODNs) or reflective of the expected immunostimulatory properties of the vaccine components (i.e., injection-site reactions). Toxicities of PS ODNs that are structurally similar to 1018 are described in the PVP and are based largely on animal studies. They include 1) pro-inflammatory effects (e.g., multiorgan lymphohistiocytic cell infiltrates, splenomegaly, and extramedullary hematopoiesis in the spleen and liver; 2) blood-level-dependent effects (increased coagulation times) and activation of complement; 3) transient cytopenias; and 4) changes in target organs (kidney, liver and spleen) especially with repeated administration of high-dose ODN (e.g., presence of basophilic granulation in renal tubular degeneration/regeneration; and Kupffer cell hypertrophy).

A reproductive toxicity study in rats produced no effects on reproductive function of the maternal animals or on the development of the offspring. Pharmacokinetic evaluations of 1018 in rats, and toxicokinetic evaluations in 8-week toxicity studies in rats and monkeys with 1018 doses up to 272-fold the clinical dose on a body-weight basis demonstrated rapid elimination of 1018 from the plasma. In animal studies, 1018 produced histological changes reflecting the TLR9-mediated immunostimulatory activities of 1018. In non-human primates, these changes were not considered significant toxicities even at more than 200 times the dose in HEPLISAV.

4.2 Clinical Safety Database

Reviewer comment: Data presented in this section should be read with the following caveats: (1) The data were drawn from the Risk Management Plan and the Summary of Clinical Safety (Sequence 0040, 3/15/2016, STN 125428/0.42), not the primary data sets. In depth analysis of clinical data is deferred to the clinical review; (2) A determination of the risk-benefit profile for the vaccine was not thought possible by the review team at this time because of incomplete information, including clinical information, and a Complete Response letter, which requested additional clinical information, was issued to the sponsor November 10, 2016.

Study population sizes are displayed in Table 2. In addition to safety data from the trials included in the original BLA submission, this current submission includes data from an additional pivotal trial HBV-23, which enrolled 5,587 and 2,781 subjects in the HEPLISAV and Engerix-B arms respectively, and supportive study HBV-22, which enrolled an additional 25 patients who

received HEPLISAV. The Primary Safety Population (PSP) comprises the subjects in the 3 pivotal phase 3 trials (HBV-10, HBV-16, and HBV-23) who received the intended commercial formulation, dose and number and timing of vaccine doses of HEPLISAV. The Total Safety Population (TSP) comprises safety data from the 3 pivotal trials as well as from an additional 1006 subjects in 8 additional supportive trials (HBV01, HBV-02, HBV-03, HBV-04, HBV-05, HBV-08, HBV-14, HBV-22) who were exposed to the proposed commercial formulation and dosing schedule of HEPLISAV either in 2 open-label trials in which no comparator vaccine was used (HBV-14, HBV-22), or who were exposed to an early formulation or different dosing schedule (HBV0001, HBV-02, HBV-03, HBV-04, HBV-05, HBV-08).

Table 2: Study Population Size*

	HEPLISAV	Engerix-B	Total
Total Safety Population	10,038	4,200	14,238
Primary Safety Population	9,365	3,867	13,232
HBV-10*	1810	605	2415
HBV-16	1968	481	2449
HBV-23***	5587	2781	8368
Supportive Studies	673	333	1,006
HBV0001	48	--	48
HBV-02	30	29	59
HBV-03	48	51	99
HBV-04	206	206	412
HBV-05	48	47	95
HBV-08	61	--	61
HBV-14	207	--	207
HBV-22***	25	--	25

* From Summary of Clinical Safety (SCS) Table 1: Adult Safety Population by Study

** An additional 23 subjects were enrolled in HBV-10 who were under 18 years of age and are not included in this table.

*** These studies provide additional data to that submitted in the original BLA.

4.2.1 Key Inclusion/Exclusion Criteria

Key inclusion/exclusion criteria are described in Table 3. *Reviewer comment: Of note, subjects only up to age 70 were included in the trials; however the indication requested is for immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older. Patients with HIV were excluded from the trials as well, although this is a group that may be at higher risk for becoming infected with hepatitis B and thus be recommended to receive the vaccine, if it should be approved.*

Table 3. Key Inclusion/Exclusion Criteria for the Pivotal Trials (HBV-23, HBV-16, and HBV-10)

	Trial	HBV-23	HBV-16	HBV-10
Criteria				
Inclusion Criteria				
Age (years)		18-70	40-70	11-55
Seronegative for HBsAg, anti-HBs, anti-HBcAg		R	R	R
Seronegative for HIV		R	R	NR
Willing and able to sign IC form and participate in entire study		R	R	R
If a woman, willing to use birth control		R	R	R
Exclusion Criteria				
History of HBV infection		R	R	R
Prior immunization with hepatitis B vaccine (approved or investigational)		R	R	R
Pregnant, breast feeding or planning a pregnancy		R	R	R
Clinically debilitating acute or chronic illness		NR	R	R
Autoimmune disease or history of disease of autoimmune origin		R	R	R
At high risk for exposure to HBV, HCV, or HIV		NR	R	R
Received blood products or immunoglobulin ^a		R	R	R
Ever received injection of DNA plasmids or oligonucleotides		R	R	R
Received vaccine within 4 weeks prior to trial entry		R	R	R
Used systemic corticosteroids (more than 3 consecutive days) ^b		R	R	R
History of sensitivity to any component of study vaccines		R	R	R
Current substance or alcohol abuse or in opinion of investigator unable to comply with study procedures or study results		R	R	R

Data Source: HBV-23, Sections 9.3.1, 9.3.2; HBV-16, Sections 9.3.1, 9.3.2; HBV-10, Sections 9.3.1, 9.3.2.

Anti-HBcAg = antibody against hepatitis B core antigen; anti-HBs = antibody against hepatitis B surface antigen; DNA = deoxyribonucleic acid; HBcAg = hepatitis B virus core antigen; HBsAg = hepatitis B virus surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IC = informed consent; NR = criterion not required in trial protocol; R = required.

^a In previous 3 months or likely to require infusion of blood products throughout the study.

^b Or other immunomodulators or immunosuppressive medications in the last 4 weeks (28 days) prior to trial entry, with the exception of inhaled steroids

4.2.2 Subject Disposition

In HBV-23, HBV-16, and HBV-10, 92.4% of subjects randomized to receive HEPLISAV and 93.2% of subjects randomized to receive Engerix-B completed participation in the trials. Of note, 7 (<0.01%) in the HEPLISAV group and 2 (<0.01%) in the Engerix-B group discontinued the trial because of an adverse event; 163 (1.7%) in the HEPLISAV group and 53 (1.4%) in the Engerix-B group discontinued because of withdrawn consent; and 26 (0.3%) in the HEPLISAV group and 8 (0.2%) in the Engerix-B group discontinued because of death.

4.2.3 Demographic and baseline characteristics

Demographic and baseline characteristics of the safety population groups are displayed in Table 4.

Table 4: Demographics and Baseline Characteristics Primary Safety Population and Total Safety Population (PSP, TSP)

	PSP		TSP	
	HEPLISAV (N = 9365)	Engerix-B (N = 3867)	HEPLISAV (N =10038)	Engerix-B (N =4200)
Age (years)				
N	9365	3867	10038	4200
Mean (SD)	49.1 (11.61)	49.2 (11.65)	48.7 (11.73)	48.8 (11.72)
Median	50.0	50.0	50.0	50.0
Min - Max	18.0, 71.0	18.0, 70.0	18.0, 71.0	18.0, 70.0
Age Subgroup n (%)				
18-70 Years	9365 (100.0%)	3867 (100.0%)	10038 (100.0%)	4200 (100.0%)
≥ 65 Years	909 (9.7%)	372 (9.6%)	926 (9.2%)	380 (9.0%)
Sex n (%)				
Men	4640 (49.5%)	1888 (48.8%)	4893 (48.7%)	2005 (47.7%)
Women	4725 (50.5%)	1979 (51.2%)	5145 (51.3%)	2195 (52.3%)
BMI Stratum n (%)				
< 30 kg/m ²	5306 (56.7%)	2206 (57.0%)	5843 (58.2%)	2501 (59.5%)
≥ 30 kg/m ²	4050 (43.2%)	1657 (42.8%)	4186 (41.7%)	1694 (40.3%)
Race n (%)				
White	7278 (77.7%)	2961 (76.6%)	7664 (76.3%)	3036 (72.3%)
Black or AA	1797 (19.2%)	785 (20.3%)	1818 (18.1%)	786 (18.7%)
Asian	126 (1.3%)	64 (1.7%)	387 (3.9%)	318 (7.6%)
Other	162 (1.7%)	57 (1.5%)	166 (1.7%)	59 (1.4%)
Unknown	2 (<0.1%)	0	3 (<0.1%)	1 (<0.1%)
Ethnicity n (%)				
Hispanic	684 (7.3%)	296 (7.7%)	690 (6.9%)	296 (7.0%)
Non-Hispanic	8675 (92.6%)	3570 (92.3%)	9341 (93.1%)	3902 (92.9%)
Smoking Status n (%)				
Yes ^a	2928 (31.3%)	1251 (32.4%)	3069 (30.6%)	1311 (31.2%)
No	6437 (68.7%)	2616 (67.6%)	6921 (68.9%)	2889 (68.8%)

Data Source: SCS Table 3.1.2.

AA = African American, BMI = body mass index, NA = not applicable, PSP = Primary Safety Population, TSP = Total Safety Population.

^a History of smoking within 1 year prior to enrollment in the trial. Smoking status was not reported in HBV0001.

The populations were similar with regard to age and sex. Both groups had a relatively high proportion of subjects with a BMI ≥ 30 kg/m² and who smoked. The Engerix-B group in the TSP has a higher proportion of Asian subjects than the HEPLISAV group, and in both groups the proportion of Asian subjects was low given the high burden of disease within this population (in the TSP, 3.9% and 7.6% of Heplisav and Engerix-B recipients respectively were Asian).

Populations with limited data, in addition to certain ethnic groups as mentioned above, include subjects <18 years of age (n=11); pregnant women (n=40); persons with a positive test for hepatitis C virus (HCV) infection (n=34); and persons with pre-existing immune-mediated disorders (n=129). Persons in whom HEPLISAV was not studied include persons greater than age 70, immunosuppressed persons, including those with HIV infection or recent cancer (other than

cutaneous) and persons on chemotherapy or immunosuppressive therapy; persons with chronic liver disease other than HCV; persons receiving concomitant immunizations; and persons receiving partial regimens of other hepatitis B vaccines.

4.2.4 Baseline Medical History

Baseline medical conditions are described in Table 5.

Table 5. Medical History Occurring in >5% of Subjects by Preferred Term (DSD)

System Organ Class	HEPLISAV (N=9365) n (%)	Engerix-B (N=3867) n (%)
Subjects with at least one medical history event	8480 (90.5)	3492 (90.3)
Hypertension	2747 (29.3)	1162 (30.0)
Seasonal Allergy	1879 (20.1)	779 (20.1)
Depression	1413 (15.1)	605 (15.6)
Osteoarthritis	1366 (14.6)	582 (15.1)
Gastroesophageal Reflux Disease	1293 (13.8)	542 (14.0)
Back Pain	1160 (12.4)	484 (12.5)
Drug Hypersensitivity	1091 (11.6)	445 (11.5)
Hyperlipidaemia	1019 (10.9)	455 (11.8)
Hysterectomy	969 (10.3)	428 (11.1)
Headache	959 (10.2)	392 (10.1)
Anxiety	952 (10.2)	430 (11.1)
Female Sterilisation	948 (10.1)	388 (10.0)
Type 2 Diabetes Mellitus	870 (9.3)	358 (9.3)
Insomnia	843 (9.0)	341 (8.8)
Obesity	843 (9.0)	342 (8.8)
Postmenopause	797 (8.5)	344 (8.9)
Asthma	727 (7.8)	331 (8.6)
Dyslipidaemia	664 (7.1)	277 (7.2)
Arthralgia	648 (6.9)	277 (7.2)
Migraine	632 (6.7)	281 (7.3)
Myopia	628 (6.7)	192 (5.0)
Tonsillectomy	552 (5.9)	229 (5.9)
Hypercholesterolaemia	494 (5.3)	216 (5.6)

Data source: [SCS Table 4.2](#).

PSP = Primary Safety Population.

The majority of study participants had at least one medical history event, with hypertension, seasonal allergy, and depression being the most common. Also of note, risk factors for cardiovascular disease, including hypertension, hyperlipidemia, and type 2 diabetes mellitus are prevalent in both the treatment and control arms.

4.2.5 Post-injection reactions (PIRs)

In the PSP (except for HBV-23 in which PIRs were not assessed), HEPLISAV had a lower frequency of systemic PIRs including fever and a similar frequency of local PIRs, compared with Engerix-B (Table 6). The most frequent local PIR in both treatment groups was mild to moderate injection-

site pain. The most frequent systemic PIR in both treatment groups was headache and fatigue. PIRs decreased with successive injections in both treatment groups. PIR findings were similar in the supportive trials, except for HBV-22, in which PIRs were not assessed. Analysis comparing PIRs between the HEPLISAV group and comparator Engerix-B group among special populations showed higher proportions of reaction to HEPLISAV among Black subjects and higher proportions of reactions to Engerix-B among Asian subjects and subjects with type 2 diabetes mellitus; however, the numbers are small and, thus, difficult to interpret.

Table 6. Overview of Post-injection Reactions by Treatment Group and Safety Populations

	HBV-16, HBV-10 (T1SP)		HBV-16, HBV-10 and Supportive Trials ^a (T3SP)	
	HEPLISAV (N = 3777)	Engerix-B (N = 1087)	HEPLISAV (N = 4347)	Engerix-B (N = 1344)
Any Post-injection Reaction, n (%)	3762	1084	4332	1341
Subjects with reactions	2071 (55.1)	619 (57.1)	2424 (56.0)	775 (57.8)
Subjects with severe reactions	119 (3.2)	55 (5.1)	134 (3.1)	67 (5.0)
Local Post-injection Reaction, n (%)^b	3762	1084	4332	1341
Subjects with reactions	1612 (42.8)	445 (41.1)	1863 (43.0)	550 (41.0)
Subjects with severe reactions	21 (0.6)	4 (0.4)	21 (0.5)	7 (0.5)
Systemic Post-injection Reaction, n (%)	3762	1084	4332	1339
Subjects with reactions	1215 (32.3)	405 (37.4)	1459 (33.7)	525 (39.2)
Subjects with severe reactions	106 (2.8)	53 (4.9)	121 (2.8)	62 (4.6)

Data Source: ISS Table 3.1.4.3 and ISS Table 3.3.4.

T1SP = Tier 1 Safety Population; T3SP = Tier 3 Safety Population.

^a Excludes supportive trials HBV-02, HBV-05, and HBV-22.

^b Excludes redness and swelling data from HBV-04 in the T3SP.

Note: T3SP includes HBV-16 and HBV-10 and supportive trials HBV0001, HBV-03, HBV-04, HBV-08, and HBV-14.

4.2.6 Safety Events

4.2.6.1 Adverse Events (AEs) and Medically Attended Adverse Events (MAEs)

An overall summary of safety events by treatment group is presented in Table 7.

Table 7. Overall Summary of Safety Events by Treatment Group

	PSP		TSP	
	HEPLISAV (N=9365) n (%)	Engerix-B (N=3867) n (%)	HEPLISAV (N = 10038) n (%)	Engerix-B (N = 4200) n (%)
Number (%) of Subjects With^a:				
Any AE / MAE	4658 (49.7)	1917 (49.6)	5142 (51.2)	2155 (51.3)
Any related AE / MAE	292 (3.1)	110 (2.8)	407 (4.1)	210 (5.0)
Any grade 3 or 4 AE / MAE	1173 (12.5)	528 (13.7)	1283 (12.8)	564 (13.4)
Discontinued study treatment due to AE / MAE	51 (0.5)	19 (0.5)	52 (0.5)	20 (0.5)
Discontinued study treatment due to a related AE / MAE	13 (0.1)	6 (0.2)	14 (0.1)	7 (0.2)
Potential new-onset AESI	30 (0.3)	15 (0.4)	32 (0.3)	16 (0.4)
New-onset AESI	16 (0.2)	5 (0.1)	18 (0.2)	6 (0.1)
Any SAE	449 (4.8)	184 (4.8)	466 (4.6)	200 (4.8)
Any related SAE	4 (<0.1)	5 (0.1)	4 (<0.1)	5 (0.1)
Discontinued study treatment due to SAE	24 (0.3)	7 (0.2)	24 (0.2)	7 (0.2)
Discontinued study treatment due to a related SAE	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Death	26 (0.3)	8 (0.2)	26 (0.3)	8 (0.2)
Related Death	0	0	0	0

Data Source: SCS Tables 5.1.1.2, 5.1.3, 14.1, and 14.1.1.

AESI = adverse event of special interest; PSP = Primary Safety Population; PT = preferred term; SAE = serious adverse event; TSP = Total Safety Population.

^a Rows are counts of subjects with at least one qualifying adverse event.

Adverse events (AEs) collected in HBV-16 and HBV-10 and medically attended adverse events (MAEs) in the TSP were similar in type and frequency between the HEPLISAV and Engerix-B comparator groups (51.2% in the HEPLISAV group and 51.3% in the comparator Engerix-B group). AEs and MAEs considered by investigators to be treatment-related were similar between the two groups (4.1% in the HEPLISAV group and 5.0% in the Engerix-B group). Grade 3 or higher AEs and MAEs were similar in frequency and type between the two treatment groups (12.8% in the HEPLISAV group and 13.4% in the Engerix-B group). The proportion of subjects in the HEPLISAV group who experienced an AE or MAE within 42 days after the last active injection was 16.6% compared to 14.6% in the Engerix-B group. There was a higher incidence in the SOC of blood and lymphatic disorders in the HEPLISAV group in the TSP (n=27, 0.3%) compared with the Engerix-B group (n=3, <0.1%). The most common PTs within that SOC were anemia (HEPLISAV: n=11, 0.1%; Engerix-B: n=2, <0.1%) and leukocytosis (HEPLISAV: n=7, <0.1%; Engerix-B: n=0).

4.2.6.2 AEs/MAEs leading to trial withdrawal

In the TSP, 10 subjects withdrew due to an AE/MAE (7 in the HEPISLAV group [0.1%] and 3 in the Engerix-B group [0.1%]). In the HEPLISAV group, one subject's AE was thought to be treatment-related (migraine). Fifty-two subjects (0.5%) in the HEPLISAV group and 20 subjects (0.5%) in the Engerix-B group discontinued the study treatment after experiencing an AE or an MAE.

4.2.6.3 Venous thrombotic AEs/MAEs

In the TSP, a total of 31 subjects experienced one or more thrombotic or embolic event (Table 8). Fourteen subjects had a deep vein thrombosis, (9 (<0.1%) in the HEPLISAV and 5 (0.1%) in the Engerix-B group) and 10 subjects had a pulmonary embolus (8 (0.1%) in the HEPLISAV group and 2 (0.1%) in the Engerix-B group).

Table 8. Summary of Venous Thrombotic/Thromboembolic Adverse Events and Medically Attended Adverse Events by Standardized MedDRA Query Preferred Term (PSP, TSP)

SMQ Preferred Term	Primary Safety Population		Total Safety Population	
	HEPLISAV (N=9365) n (%)	Engerix-B (N=3867) n (%)	HEPLISAV (N=10038) n (%)	Engerix-B (N=4200) n (%)
Subjects with at least one qualifying adverse event	21 (0.2)	10 (0.3)	21 (0.2)	10 (0.2)
Deep Vein Thrombosis	9 (<0.1)	5 (0.1)	9 (<0.1)	5 (0.1)
Pulmonary Embolism	8 (<0.1)	2 (<0.1)	8 (<0.1)	2 (<0.1)
Phlebitis	2 (<0.1)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Thrombophlebitis Superficial	2 (<0.1)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Phlebitis Superficial	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Venous Thrombosis	1 (<0.1)	0	1 (<0.1)	0
Thrombosis	0	3 (<0.1)	0	3 (<0.1)

Data Source: [SCS Table 12.7](#).

MedDRA = Medical Dictionary for Regulatory Activities; PSP = Primary Safety Population; SMQ = Standardised MedDRA Query; TSP = Total Safety Population.

A laboratory substudy of thrombotic disease was conducted within HBV-23. In this study 207 HEPLISAV recipients and 102 Engerix-B recipients were tested for antiphospholipid antibodies including lupus anticoagulant, anticardiolipin immunoglobulin IgG and IgM, and anti-beta2 glycoprotein 1 IgG and IgM. Overall, new-onset abnormal thrombotic tests occurred in 70 (33.8%) HEPLISAV subjects and 33 (32.4%) Engerix-B subjects. For new-onset anti-beta 2 glycoprotein 1 IgM, there were 19 subjects (9.2%) in the HEPLISAV group and 2 subjects (2.0%) in the Engerix-B group who had normal antibody levels at baseline and had at least one abnormal elevated level at weeks 8, 24, or 56. For new-onset lupus anticoagulant, there were 41 subjects (19.8%) in the HEPLISAV group with an abnormal screen test and 4 subjects (1.9%) with a confirmatory test, compared to 16 subjects (15.7%) in the Engerix-B group with an abnormal screen test and 1 subject (1.0%) with a confirmatory test. Of the subjects with abnormal thrombotic screen tests, one subject in the HEPLISAV group had a venous thrombotic event of pulmonary embolism. *(Reviewer comment: The significance of lab value differences with specific antibodies is deferred to the clinical reviewer.)*

4.2.6.4 Renal AEs/MAEs

In the TSP, 49 subjects (0.5%) with events indicative of acute renal failure received HEPLISAV, and 14 subjects (0.3%) received Engerix-B. According to the SCS, many of these subjects had predisposing comorbidities.

4.2.6.5 Anaphylaxis

Eight events occurred in 6 subjects (HEPLISAV: n = 5; Engerix-B: n = 1). The most frequent AE was type I hypersensitivity.

4.2.6.6 Serious adverse events (SAEs)

SAEs were reported by 466 (4.6%) of subjects in the HEPLISAV group and by 200 (4.8%) of subjects in the Engerix-B group (Table 9).

Table 9. Summary of Serious Adverse Events by System Organ Class and Preferred Term (HEPLISAV >0.1% in the TSP) (PSP, TSP)

System Organ Class	PSP		TSP	
	HEPLISAV (N = 9365) n (%)	Engerix-B (N = 3867) n (%)	HEPLISAV (N = 10038) n (%)	Engerix-B (N = 4200) n (%)
Subjects with at least one treatment-emergent serious adverse event	449 (4.8)	184 (4.8)	466 (4.6)	200 (4.8)
Infections And Infestations	78 (0.8)	35 (0.9)	83 (0.8)	39 (0.9)
Pneumonia	16 (0.2)	8 (0.2)	16 (0.2)	9 (0.2)
Injury, Poisoning And Procedural Complications	64 (0.7)	22 (0.6)	68 (0.7)	25 (0.6)
Cardiac Disorders	59 (0.6)	21 (0.5)	60 (0.6)	22 (0.5)
Acute Myocardial Infarction	16 (0.2)	2 (<0.1)	17 (0.2)	2 (<0.1)
Gastrointestinal Disorders	46 (0.5)	18 (0.5)	47 (0.5)	19 (0.5)
Respiratory, Thoracic And Mediastinal Disorders	45 (0.5)	15 (0.4)	47 (0.5)	16 (0.4)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	46 (0.5)	19 (0.5)	46 (0.5)	21 (0.5)
Nervous System Disorders	42 (0.4)	17 (0.4)	44 (0.4)	19 (0.5)
Musculoskeletal And Connective Tissue Disorders	42 (0.4)	16 (0.4)	44 (0.4)	17 (0.4)
Osteoarthritis	16 (0.2)	5 (0.1)	17 (0.2)	5 (0.1)
Psychiatric Disorders	26 (0.3)	7 (0.2)	26 (0.3)	7 (0.2)
Metabolism And Nutrition Disorders	20 (0.2)	9 (0.2)	22 (0.2)	9 (0.2)
Vascular Disorders	21 (0.2)	9 (0.2)	21 (0.2)	10 (0.2)
General Disorders And Administration Site Conditions	18 (0.2)	11 (0.3)	19 (0.2)	11 (0.3)
Non-Cardiac Chest Pain	12 (0.1)	8 (0.2)	12 (0.1)	8 (0.2)
Hepatobiliary Disorders	16 (0.2)	10 (0.3)	18 (0.2)	10 (0.2)
Renal And Urinary Disorders	14 (0.1)	9 (0.2)	14 (0.1)	10 (0.2)
Reproductive System And Breast Disorders	5 (<0.1)	7 (0.2)	6 (<0.1)	7 (0.2)
Pregnancy, Puerperium And Perinatal Conditions	6 (<0.1)	3 (<0.1)	6 (<0.1)	3 (<0.1)
Blood And Lymphatic System Disorders	4 (<0.1)	3 (<0.1)	4 (<0.1)	3 (<0.1)
Congenital, Familial And Genetic Disorders	3 (<0.1)	1 (<0.1)	3 (<0.1)	1 (<0.1)
Ear And Labyrinth Disorders	3 (<0.1)	1 (<0.1)	3 (<0.1)	1 (<0.1)
Skin And Subcutaneous Tissue Disorders	2 (<0.1)	2 (<0.1)	2 (<0.1)	2 (<0.1)
Investigations	2 (<0.1)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Immune System Disorders	1 (<0.1)	2 (<0.1)	1 (<0.1)	2 (<0.1)
Endocrine Disorders	1 (<0.1)	2 (<0.1)	1 (<0.1)	2 (<0.1)
Social Circumstances	1 (<0.1)	0	1 (<0.1)	0
Surgical And Medical Procedures	0	0	0	2 (<0.1)
Eye Disorders	0	0	0	0

Data Source: SCS Table 10.1.

PSP = Primary Safety Population; SAE = serious adverse event; TSP = Total Safety Population.

Note: All SOC's are included and PT's occurring in $\geq 0.1\%$ of subjects in the HEPLISAV group in the TSP. Table is sorted by SOC from highest to lowest frequency.

An imbalance in SAEs occurred in HEPLISAV subjects with events identified by the preferred term acute myocardial infarction, with (in the TSP) 17 cases (0.2%) in the HEPLISAV group and 2 (<0.1%) in the Engerix-B group ($p=0.08$ by Fisher Exact Test); most of the cases occurred in HBV-23. *Reviewer comment: The sponsor has submitted an analysis related to this in the "Evaluation of Acute Myocardial Infarction and Major Adverse Cardiovascular Events in the Phase 3 Heplisav Clinical Trials." The review of this document will be deferred and will be discussed as part of a potential BLA resubmission.*

4.2.6.7 Treatment-related SAEs

Six SAEs in 4 subjects in the HEPLISAV group and 5 SAEs in 5 subjects in the Engerix-B group were considered by the investigator to be related to study treatment. Subject 120-019 in the HBV-23 trial who received HEPLISAV had 3 related SAEs as a result of her twin pregnancy. Each twin had a related SAE of fetal growth restriction and 1 twin also had a related SAE of Ebstein's anomaly. A female subject who received Engerix-B also had a pregnancy with the outcome of Ebstein's anomaly. One venous thrombotic event considered to be related to study treatment occurred in the HEPLISAV group and 2 occurred in the Engerix-B group. One subject in the HEPLISAV group had a related SAE of granulomatosis with polyangiitis (Wegener's granulomatosis) and 1 subject in the Engerix-B group had a related SAE of bronchial hyperreactivity. One subject in the HEPLISAV group had an abnormal protein electrophoresis, and 1 subject in the Engerix-B group had complex partial seizures that were considered to be related to study treatment. There were no additional SAEs in the 8 supportive trials which were considered by the investigator to be related to study treatment.

Table 10. List of Related Serious Adverse Events by Treatment Group (TSP)

Trial	Subject Number	Age	Sex	MedDRA Preferred Term	Number of Active Injections	Days Since Last Active Dose
HEPLISAV						
HBV-10	24-057	54	F	Granulomatosis With Polyangiitis	2	73
HBV-23	126-234	46	F	Deep Vein Thrombosis	2	78
HBV-23	120-019	24	F	Ebstein's Anomaly	2	240
HBV-23	117-125	66	M	Electrophoresis Protein Abnormal	2	272
HBV-23	120-019	24	F	Foetal Growth Restriction	2	379
				Foetal Growth Restriction	2	379
Engerix-B						
HBV-23	129-290	41	F	Pulmonary Embolism	3	20
HBV-23	126-341	53	M	Deep Vein Thrombosis	2	23
HBV-16	28-352	50	F	Bronchial Hyperreactivity	3	43
HBV-23	118-172	52	F	Complex Partial Seizures	2	61
HBV-23	116-239	35	F	Ebstein's Anomaly	3	276

Data Source: [SCS Listing 4](#).

MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; SOC = system organ class; TSP = Total Safety Population.

4.2.6.8 Deaths

There were 34 deaths in the PSP with no additional deaths occurring in supportive trials of the TSP. No deaths were assessed by the investigators as related to the study treatment. Twenty-six deaths were in the HEPLISAV group (0.26%) and 8 deaths were in the Engerix-B group (0.19%). Twelve deaths were due to drug overdose (psychotropic medications, alcohol, and illicit drugs) and trauma (9 in the HEPLISAV group and 3 in the Engerix-B group). When deaths due to trauma or overdose are excluded, the incidence of deaths in the HEPLISAV and Engerix-B treatment groups was 0.17% (17/10,038) and 0.12% (5/4200) respectively (Table 11).

There was an apparent imbalance in deaths by race (19 (0.25%) in white subjects among the HEPLISAV group and 2 (0.07%) among the Engerix-B group), among smokers (15 (0.49%) in the

HEPLISAV group and 2 (0.15%) in the Engerix-B group, and among women (9 (0.17%) in the HEPLISAV group and 1 (0.05%) in the Engerix-B group. Deaths of note among HEPLISAV recipients include a 46-year-old man with no relevant medical history who died of a pulmonary embolism occurring ^{(b) (6)} days after his second injection of HEPLISAV.

Table 11. Deaths from Causes Other than Traumas or Drug Overdose

Trial	Subject Number	Age (At Study Entry)	Sex	Race	Smoking Status	MedDRA Preferred Term	Number of Active Injections	Days Since Last Active Dose ^a	Relationship to Treatment
HEPLISAV									
HBV-23	130-084	50	M	Black or African American	Nonsmoker	Acute Coronary Syndrome	1	(b) (6)	Not Related
HBV-23	131-049	67	M	White	Nonsmoker	Acute Respiratory Failure	2		Not Related
HBV-23	107-176	68	M	White	Nonsmoker	Hepatic Cirrhosis	2		Not Related
HBV-23	106-407	56	M	White	Smoker	Hepatitis C	2		Not Related
HBV-16	22-003	45	M	White	Nonsmoker	Pulmonary Embolism	2		Not related
HBV-23	131-091	69	M	White	Smoker	Acute Myocardial Infarction	2		Not Related
HBV-23	119-318	61	F	White	Smoker	Death	2		Not Related
HBV-23	112-311	57	M	White	Nonsmoker	Hypertensive Heart Disease	2		Not Related
HBV-23	121-090	61	M	Black or African American	Smoker	Acute Respiratory Distress Syndrome	2		Not Related
HBV-23	132-082	62	M	White	Nonsmoker	Hypertensive Heart Disease	2		Not Related
HBV-23	138-012	58	F	Black or African American	Smoker	Hypertensive Heart Disease	2		Not Related
HBV-23	133-120	70	F	White	Nonsmoker	Cardiac Arrest	2		Not Related
HBV-23	125-113	49	M	White	Nonsmoker	Lung Cancer Metastatic	2		Not Related
HBV-23	122-613	47	M	Black or African American	Nonsmoker	Myocardial Infarction	2		Not Related
HBV-23	104-152	55	F	White	Smoker	Cardio-Respiratory Arrest	2		Not Related
HBV-23	125-139	43	F	White	Smoker	Small Cell Lung Cancer Metastatic	2		Not Related
HBV-23	119-290	51	F	White	Smoker	Death	2		Not Related

Trial	Subject Number	Age (At Study Entry)	Sex	Race	Smoking Status	MedDRA Preferred Term	Number of Active Injections	Days Since Last Active Dose ^a	Relationship to Treatment
Engerix-B									
HBV-23	135-070	52	M	White	Smoker	Myocardial Infarction	1	(b) (6)	Not Related
HBV-23	119-175	48	M	Black or African American	Nonsmoker	Hypertensive Heart Disease	3		Not Related
HBV-16	92-638	64	M	Black or African American	Nonsmoker	Cardiac Failure	2		Not related
HBV-23	130-392	69	M	Black or African American	Nonsmoker	Cardio-Respiratory Arrest	3		Not Related
HBV-23	130-252	67	M	White	Nonsmoker	Pancreatic Carcinoma Metastatic	3		Not Related

Data Source: SCS Listing 1.

F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities.

^a Number of days from the MedDRA Preferred Term event.

4.2.6.9 Adverse Events of Special Interest (AESIs)

AESIs represent autoimmune, inflammatory, and hypersensitivity disorders. AESIs were actively solicited and adjudicated in the pivotal phase 3 trials HBV-23 and HBV-16. Potential new onset AESIs in recipients of HEPLISAV occurred in 0.32% of HEPLISAV recipients and in 0.38% of Engerix-B recipients (see Table 13). After adjudication by a Safety Evaluation and Adjudication Committee (SEAC), 19 (0.19%) were seen in the HEPLISAV group and 6 (0.14%) were seen in the Engerix-B group. Of these, Bell's palsy was seen in 7 (0.07%) in the HEPLISAV group and 2 (0.05%) in the Engerix-B group.

Table 12. Overall Summary of Subjects with Adverse Events of Special Interest (PSP, TSP)

	Primary Safety Population		Total Safety Population	
	HEPLISAV (N=9365) n (%)	Engerix-B (N=3867) n (%)	HEPLISAV (N=10038) n (%)	Engerix-B (N=4200) n (%)
Subjects with at least one potential new-onset AESI	30 (0.32)	15 (0.39)	32 (0.32)	16 (0.38)
- SEAC Adjudicated as Pre-existing	8 (0.09)	10 (0.26)	8 (0.08)	10 (0.24)
- SEAC Adjudicated as not AESI or secondary to other condition	5 (0.05)	0	5 (0.05)	0
New-Onset AESI	17 (0.18)	5 (0.13)	19 (0.19)	6 (0.14)
New-Onset Bell's palsy	6 (0.06)	2 (0.05)	7 (0.07)	2 (0.05)
New-Onset AESI Excluding Bell's Palsy	11 (0.12)	3 (0.08)	12 (0.12)	4 (0.10)

Data Source: [SCS Table 5.9.1](#).

AESI = Adverse Event of Special Interest; PSP = Primary Safety Population; SEAC = Safety Evaluation and Adjudication Committee; TSP = Total Safety Population.

Specific conditions that were thought to be potential AESIs are described in Table 13. *Reviewer comment: the case of Tolosa Hunt is not listed under "Vascular Disorders" but as "Cavernous Sinus Thrombosis" under "Infections and Infestations." Discussion about the cases of Wegener's granulomatosis, Tolosa Hunt, and Takayasu Arteritis are deferred to the clinical review.*

Table 13. Subjects with Potential New Onset Adverse Events of Special Interest by SOC and Preferred Term (PSP and TSP)*

Category/Preferred Term n (%)	PSP		TSP	
	HEPLISAV (N = 9365) n (%)	Engerix-B (N = 3867) n (%)	HEPLISAV (N = 10,038) n (%)	Engerix-B (N = 4200) n (%)
Subjects with at least one potential adverse event of special interest	30 (0.3)	15 (0.4)	32 (0.3)	16 (0.4)
Nervous System Disorders	9 (<0.1)	2 (<0.1)	10 (<0.1)	2 (<0.1)
Guillain-Barre Syndrome	1 (<0.1)	0	1 (<0.1)	0
Vlth Nerve Paralysis	2 (<0.1)	0	2 (<0.1)	0
VIIth Nerve Paralysis	6 (<0.1)	2 (<0.1)	7 (<0.1)	2 (<0.1)
Endocrine Disorders	5 (<0.1)	5 (0.1)	5 (<0.1)	5 (0.1)
Autoimmune Thyroiditis	2 (<0.1)	2 (<0.1)	2 (<0.1)	2 (<0.1)
Basedow's Disease	3 (<0.1)	3 (<0.1)	3 (<0.1)	3 (<0.1)
Skin and Subcutaneous Tissue Disorders	5 (<0.1)	3 (<0.1)	5 (<0.1)	3 (<0.1)
Alopecia Areata	1 (<0.1)	0	1 (<0.1)	0
Cutaneous lupus erythematosus	0	1 (<0.1)	0	1 (<0.1)
Dermatitis Herpetiformis ^a	1 (<0.1)	0	1 (<0.1)	0
Erythema Nodosum	1 (<0.1)	0	1 (<0.1)	0
Lichen Planus	1 (<0.1)	2 (<0.1)	1 (<0.1)	2 (<0.1)
Vitiligo	1 (<0.1)	0	1 (<0.1)	0
Musculoskeletal and Connective Tissue Disorders	4 (<0.1)	2 (<0.1)	4 (<0.1)	3 (<0.1)
Mixed Connective Tissue Disease	0	1 (<0.1)	0	1 (<0.1)
Polymyalgia Rheumatica	1 (<0.1)	0	1 (<0.1)	0
Rheumatoid Arthritis	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Scleroderma	0	1 (<0.1)	0	1 (<0.1)
Sjogren's Syndrome	1 (<0.1)	0	1 (<0.1)	0
Systemic Lupus Erythematosus	1 (<0.1)	0	1 (<0.1)	0
Vascular Disorders	3 (<0.1)	1 (<0.1)	3 (<0.1)	1 (<0.1)
Granulomatosis With Polyangiitis	1 (<0.1)	0	1 (<0.1)	0
Raynaud's Phenomenon	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Takayasu's arteritis ^b	1 (<0.1)	0	1 (<0.1)	0
Gastrointestinal Disorders	2 (<0.1)	2 (<0.1)	2 (<0.1)	2 (<0.1)
Coeliac Disease	0	2 (<0.1)	0	2 (<0.1)
Colitis Ulcerative	2 (<0.1)	0	2 (<0.1)	0
Eye Disorders	0	0	1 (<0.1)	0
Uveitis	0	0	1 (<0.1)	0
Hepatobiliary Disorders	1 (<0.1)	0	1 (<0.1)	0
Biliary Cirrhosis Primary	1 (<0.1)	0	1 (<0.1)	0
Infections and Infestations	1 (<0.1)	0	1 (<0.1)	0
Cavernous Sinus Thrombosis ^c	1 (<0.1)	0	1 (<0.1)	0

* From SCS Table 2.7.4-33

The point estimate for the relative risk (RR) of new-onset AESIs with HEPLISAV compared with Engerix B in the PSP was 1.40 (95% CI: 0.52, 3.80) (Table 14). The point estimate for the RR of HEPLISAV compared with Engerix-B in the TSP, which includes all recipients of 1018, was 1.32 (95% CI: 0.53, 3.32).

Table 14. Relative Risk for New-Onset Adverse Events of Special Interest (PSP, TSP)

	Primary Safety Population			Total Safety Population		
	HEPLISAV (N=9365) n (%)	Engerix-B (N=3867) n (%)	Relative Risk of HEPLISAV Subjects (95% CL)	HEPLISAV (N=10038) n (%)	Engerix-B (N=4200) n (%)	Relative Risk of HEPLISAV Subjects (95% CL)
Potential AESI	30 (0.3)	15 (0.4)	0.83 (0.44, 1.53)	32 (0.3)	16 (0.4)	0.84 (0.46, 1.52)
New-Onset AESI	17 (0.2)	5 (0.1)	1.40 (0.52, 3.80)	19 (0.2)	6 (0.1)	1.32 (0.53, 3.32)
New-Onset Bell's Palsy AESI	6 (<0.1)	2 (<0.1)	1.24 (0.25, 6.13)	7 (<0.1)	2 (<0.1)	1.46 (0.30, 7.05)
New-Onset AESI Excluding Bell's Palsy	11 (0.1)	3 (<0.1)	1.51 (0.42, 5.42)	12 (0.1)	4 (<0.1)	1.26 (0.41, 3.89)

Data Source: SCS Table 5.10.

AE = Adverse Event; AESI = Adverse Event of Special Interest; CL = confidence limit; N = Unique subject/preferred term combinations; PSP = Primary Safety Population; TSP = Total Safety Population.

Presence of an autoimmune disorder was an exclusion criterion in HBV-23, HBV-16, and HBV-10. However, 167 subjects in the TSP (129 subjects (1.3%) in the HEPLISAV group and 38 subjects (0.9%) in the Engerix-B group) were inadvertently enrolled with immune-mediated pre-existing conditions of special interest (PECSIs). After injection with vaccine, 5 subjects with PECSI in the HEPLISAV, and 1 subject with PECSI in the Engerix-B group experienced an exacerbation.

Thyroid adverse events were assessed separately. In the PSP and TSP, the frequency of thyroid events was similar between the treatment groups.

Table 15. Thyroid Adverse Events and Medically Attended Adverse Events by Preferred Term (PSP, TSP)

Preferred Term	Primary Safety Population		Total Safety Population	
	HEPLISAV (N=9365) n (%)	Engerix-B (N=3867) n (%)	HEPLISAV (N=10038) n (%)	Engerix-B (N=4200) n (%)
Subjects with at least one qualifying adverse event	25 (0.3)	11 (0.3)	26 (0.3)	11 (0.3)
Hypothyroidism	18 (0.2)	7 (0.2)	19 (0.2)	7 (0.2)
Hyperthyroidism	5 (<0.1)	0	6 (<0.1)	0
Basedow's Disease	3 (<0.1)	3 (<0.1)	3 (<0.1)	3 (<0.1)
Post Procedural Hypothyroidism	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Primary Hypothyroidism	0	1 (<0.1)	0	1 (<0.1)

Source: SCS Table 12.6

PSP = Primary Safety Population; TSP = Total Safety Population

Thyroid adverse events are identified by the narrow subsets of the MedDRA 17.0 Hypothyroidism and Hyperthyroidism SMQs.

Autoantibodies were assessed in some of the trials. For antinuclear antibody (ANA), 201 subjects (5.5%) in the HEPLISAV group and 54 subjects (5.1%) in the Engerix-B group converted from a negative pre-treatment result to a positive post-treatment result (with a titer of 1:160 considered positive). For anti-double stranded deoxyribonucleic acid antibody (anti-dsDNA), 46 (1.2%) in the HEPLISAV group and 11 (1.0%) in the Engerix-B group converted from a negative pre-treatment result to a positive post-treatment results. Based on the occurrence of an SAE of ANCA-associated vasculitis in a HEPLISAV subject in HBV-10, serum specimens from subjects in HBV-10 and HBV-14 were retrospectively tested for ANCA. No additional events of development of ANCA were identified in either group.

4.2.6.10 Use in pregnancy and lactation

Pregnancy was an exclusion criterion. In total there were 60 pregnancies reported (40 in the HEPLISAV group and 20 in the Engerix-B group). In the HEPLISAV group, 21 subjects had healthy term deliveries, 2 subjects had a healthy premature delivery, 1 subject had a birth with a congenital anomaly, 4 subjects had elective terminations, 3 subjects had spontaneous abortions, 1 subject had a still birth, 3 subjects were status pending at the time of this report, and 5 subjects were lost to follow-up. In the Engerix-B group, 11 subjects had healthy term deliveries, 1 subject had a birth with a congenital anomaly, 4 subjects had an elective termination, 1 subject had a birth with fetal complications leading to SAEs, 2 subjects had spontaneous abortions, and 1 subject was lost to follow-up. The still-birth in the HEPLISAV group occurred at 23 weeks gestational age in a mother with chronic hypertension. The congenital anomaly referred to Ebstein anomaly, which occurred in a twin child whose mother was in the HEPLISAV group as well as a child whose mother was in the Engerix-B group.

4.2.6.11 Additional laboratory data

One phase 3 pivotal trial (HBV-16) included both an Engerix-B comparator arm and laboratory assessments of serum chemistry and hematology. According to the Summary of Clinical Safety, all mean chemistry and hematology values were within the normal range, were comparable across treatment groups, and did not change significantly during the trial. *(Reviewer comment: Further analysis of laboratory values is deferred to the clinical reviewer).*

4.3 Safety Concerns Identified in the Sponsor's Risk Management Plan

4.3.1 Important identified safety issues

- Anaphylaxis due to sensitivity to yeast was identified as an important safety issue, as HEPLISAV may contain yeast protein.
- Deltoid bursitis and vasovagal syncope were identified as an important identified risk.. *(Reviewer comment: In the TSP, there were only 2 subjects with non-serious bursitis in the shoulder on days 4 and 17 post-vaccination and 7 episodes of presyncope and 2 episodes of syncope on the day of vaccination. The sponsor includes these as identified risks not based on data from the trials but because they were thought to represent a class effect for any vaccine that is administered by intramuscular injection).*

4.3.2 Important potential safety risks

- The possibility for development of immune-mediated disease was identified, given a theoretical concern associated with all adjuvants.

4.3.2 Important missing information

- Safety data in persons with chronic liver disease, immunosuppressed persons (i.e. person infected with HIV or who have cancer or on immunosuppressive therapy), and concomitant administration of another vaccine are considered to be important missing information for HEPLISAV.
- Persons receiving partial regimens of other hepatitis B vaccines were also not studied in the pre-approval phase.
- Only limited safety data is available for subject <18 years of age, pregnant women, persons with positive test for hepatitis C infection, and persons with pre-existing immune-mediated disorders.

5. Sponsor's Proposed Actions and Timelines

5.1 Routine Pharmacovigilance

- No risk minimization activities beyond product labeling are considered necessary for HEPISLAV by the sponsor.
- Dynavax will be responsible for overseeing all U.S. pharmacovigilance activities. However, Dynavax will delegate certain pharmacovigilance activities to a third-party contractor.

5.2 Enhanced pharmacovigilance

Dynavax proposes an open-label, post-marketing safety study in adults 18 years of age and older using a large health maintenance organization such as Kaiser Permanente Northern California to further define the safety profile of HEPLISAV. The primary objective of this proposed study will be to assess the incidence of medically significant adverse events, including cardiac, renal, thrombotic, and neurologic events with special attention to immune-mediated disorders following vaccination in HEPLISAV adult recipients compared with adult recipients following vaccination with a control vaccine. It is anticipated that the study design will have a sample size of approximately 40,000 subjects aged 18 years and older, 20,000 recipients of HEPLISAV and 20,000 recipients of a comparator vaccine. Study duration would be approximately 8 years. *(Reviewer comment: Further development of a post-marketing study is needed; however, this is deferred pending further clinical review.)*

6. Postlicensure Safety Review

Not applicable

7. Integrated Risk Assessment

This review focuses on the data as presented in the Risk Management Plan and the Summary of Clinical Safety. Final analysis of clinical data is deferred to the clinical reviewer, and assessment

of an adequate pharmacovigilance plan may change based on the clinical reviewer's findings and on additional information gathered as a result of the CR letter.

Although the addition of data from HBV-23 and clinical information pertaining to specific cases of concern may have allayed some of the concerns raised in the original BLA review, there continue to be safety concerns that, if the product is to be approved, would need to be addressed in a post-marketing safety study. Additional data can contribute to our understanding about preliminary concerns, including imbalances seen in myocardial infarction and deaths, the potential for autoimmune disease (either new-onset or exacerbation of pre-existing conditions), including vasculitides and Bell's Palsy, and the potential class effects of PS-ODNs. These effects may include injection site reactions and systemic flu-like illness, hematologic adverse events (like decreased red cell, neutrophil, and platelet counts and prolongation of aPTT, activation of the alternative complement system, toxic effects on kidney/liver).

Furthermore, it is anticipated that a postmarketing study would need to assess the vaccine in groups for which information is currently missing or limited. Those groups may include such groups as specific ethnic groups, people with HIV, people with hepatitis C and other chronic liver disease, pregnant women, those with concomitant vaccine use, and those having received partial regimens of other hepatitis B vaccines.

8. Recommendations

The decision as to the adequacy of the PVP is deferred pending the sponsor's response addressing the concerns of the FDA Clinical Reviewer, as detailed in the CR letter.

Preliminary anticipated recommendations, which may change based on additional clinical review, include the following:

- Routine pharmacovigilance
- Enhanced pharmacovigilance through a post-marketing study. Additional information on those groups for whom information is missing or limited should be gathered through this study.
- Inclusion of the class effects of PS-ODNs as a potential safety risk in the Risk Management Plan. These effects may include injection site reactions and systemic flu-like illness, hematologic adverse events such as cytopenias and effects on coagulation pathways, activation of the complement system, and toxic effects on kidney or liver.