FDA Advisory Committee Briefing Document

HEPLISAV-B™

[Hepatitis B Vaccine (Recombinant), Adjuvanted]

Vaccines and Related Biological Products
Advisory Committee

Meeting Date: July 28, 2017

Dynavax Technologies Corporation

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Term
1018	Dynavax's proprietary adjuvant used in HEPLISAV-B
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AESI	adverse event of special interest
ANA	antinuclear antibody
ANCA	anti-neutrophil cytoplasmic antibody
anti-HBs	antibody to hepatitis B surface antigen
anti-PR3	antibody to proteinase 3
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
c-ANCA	cytoplasmic staining anti-neutrophil cytoplasmic antibody
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CpG	cytidine-phospho-guanosine
CT	computerized tomography
DNA	deoxyribonucleic acid
dsDNA	double-stranded deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ELISA	enzyme-linked immunosorbent assay
ER	emergency room
GLP	good laboratory practice
GMC	geometric mean concentration
HBsAg	hepatitis B surface antigen
HBV	hepatitis B surface antigen
HIV	human immunodeficiency virus
IFA	immunofluorescence assay
IFN	interferon
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
IM	intramuscular
MACE	major adverse cardiovascular event
MAE	medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
MSM	men who have sex with men
ODN	oligodeoxynucleotide
p-ANCA	perinuclear-staining anti-neutrophil cytoplasmic antibody
pDC	plasmacytoid dendritic cell
PIR	post-injection reaction
PP	Per Protocol
PRR	pattern recognition receptors
PS-ODN	phosphorothioate oligodeoxynucleotide
PSP	Primary Safety Population
PT	preferred term
rHBsAg	recombinant hepatitis B surface antigen
RR	relative risk
SAE	serious adverse event
SEAC	Safety Evaluation and Adjudication Committee
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SPR	seroprotection rate
STD	sexually-transmitted disease
TLR	Toll-like receptor

Key Product Characteristics

- **Product Name:** HEPLISAV-B™ (Hepatitis B Vaccine [Recombinant], Adjuvanted)
- **Proposed Indication for Use:** HEPLISAV-B is indicated for immunization against infection caused by all known subtypes of hepatitis B virus (HBV) in adults 18 years of age and older.
- **Dosage Form:** HEPLISAV-B is a 0.5 mL aqueous mixture of 20 mcg of hepatitis B surface antigen (HBsAg) derived from *Hansenula polymorpha* with 3 mg of 1018, an oligonucleotide adjuvant Toll-like receptor 9 (TLR9) agonist.
- **Administration:** HEPLISAV-B is for intramuscular (IM) injection in a 2-dose regimen given at 0 and 1 month.
- **Manufacturer**: Dynavax Technologies Corporation, Berkeley, CA

1.0 EXECUTIVE SUMMARY

Vaccination against hepatitis B in adults continues to be a problem owing to reduced immune responses to current vaccines that must be administered in 3 doses over 6 months. HEPLISAV-B is a new adult hepatitis B vaccine containing a TLR9 agonist that allows for improved immune responses after only 2 doses including in populations who respond poorly to current vaccines. This document provides a complete review of both immunogenicity and safety, presenting an overall record of statistically significantly higher immunogenicity and acceptable safety. A plan for post-marketing surveillance of safety is included. (This Executive Summary has cross references to the pertinent sections in the document.)

Dynavax Technologies Corporation (Dynavax) originally submitted a Biologics License Application (BLA) for HEPLISAV-B to the Food and Drug Administration (FDA) on 26 April 2012 with a safety database of 5845 adult subjects (HEPLISAV-B: 4425; Engerix-B®: 1420) including 2 pivotal trials. The Vaccines and Related Biological Products Advisory Committee (VRBPAC) met on 15 November 2012 to consider the safety and efficacy of HEPLISAV-B. Based on HEPLISAV-B induced seroprotection rates that were noninferior to and statistically significantly higher than those induced by Engerix-B, the Committee voted 13 to 1 in support of the immunogenicity benefit of HEPLISAV-B. With respect to safety, the Committee voted 8 to 5 (with 1 abstention) that the safety database was insufficient to support approval of HEPLISAV-B. Specific issues raised by the Committee included concerns that:

- The safety database was insufficient to evaluate potential immune-mediated adverse effects of the novel adjuvant in HEPLISAV-B that are relatively infrequent;

- There was a possible association with thyroid diseases and immune-mediated diseases; and

- The clinical studies did not include a racially diverse population reflecting the United States (US) population.

To address these concerns, Dynavax, in consultation with the FDA, developed a protocol for a third phase 3 trial, HBV-23, with the aim to enroll at least 5000 racially diverse adults treated with HEPLISAV-B in the US with safety follow-up of 1 year. After completion of HBV-23, the current HEPLISAV-B safety database for this BLA resubmission comprises 14,238 adult subjects (HEPLISAV-B: 10,038; Engerix-B: 4200).

1.1 Hepatitis B Virus Infection and Recommendations for Vaccination

HBV infection is a serious infectious disease that can result in significant morbidity and mortality (See Section 2.1). In the US, an estimated 4.3% to 5.6% of individuals have been infected with HBV, and 800,000 to 2.2 million individuals are living with chronic HBV infection.[30, 69, 86] An estimated 5000 individuals in the US die from chronic liver disease due to HBV each year.[17]

The first plasma-derived hepatitis B vaccine was approved in 1981 (Heptavax-B®, Merck) and recombinant hepatitis B vaccines were approved in the 1980s (Recombivax®, Merck; Engerix-B, GlaxoSmithKline). These vaccines contain a recombinant HBsAg like that in HEPLISAV-B, are adjuvanted with an aluminum salt, and are administered as a series of 3 doses over 6 months. Hepatitis B vaccines have been recommended by the Advisory Committee on Immunization Practices (ACIP) since 1982 for persons with risk factors for exposure to HBV (Appendix 1).[14, 20, 109] In 2011, the ACIP expanded its recommendations to include routine hepatitis B vaccination of all adults with diabetes mellitus < 60 years of age because of the increased incidence of HBV infection and the increased morbidity due to HBV in persons with diabetes.[103, 109]

1.2 Epidemiology of Hepatitis B Transmission

In 1991, ACIP recommended including hepatitis B vaccine in universal vaccinations for infants and catch-up use in adolescents and reiterated the need for hepatitis B vaccination for adults with risk factors for HBV infection (See Section 2.2).[19] Over the ensuing 2 decades, the incidence of HBV infection in the US decreased 82% from 1990 through 2007.[30, 81] Nonetheless, HBV infection and its consequences continue to be an important public health problem in adults. Approximately 95% of the estimated 21,900 annual new cases of HBV infection in the US occur in adults who did not receive vaccine in childhood vaccination programs. The most recent surveillance data from the Centers for Disease Control and Prevention (CDC) show an increase of 20.7% in reports of acute hepatitis B in adults from 2014 to 2015. [22]

1.3 Unmet Medical Need for an Improved Hepatitis B Vaccine

Most adults today did not receive hepatitis B vaccination as an infant or adolescent (See Section 2.3). The challenge of vaccinating adults against HBV includes 3 major obstacles. First, adults at risk of HBV infection must be accessed and identified through questioning of occupational and sensitive behavioral risk factors. Secondly, the individual must then accept and adhere to the 3-dose 6-month vaccination schedule. Finally, the vaccine must provide high rates of seroprotection. The first obstacle continues to be a challenge to health care providers and public health authorities. The last 2 obstacles can be overcome with a hepatitis B vaccine improved by requiring fewer doses with a shorter administration schedule and inducing a higher rate of seroprotection.

1.3.1 Vaccine Coverage in Adults at Risk of HBV Infection

Successfully vaccinating adults at high risk for HBV is an ongoing challenge due in part to the lack of systematic access to persons at high risk for infection and lack of formal programs for adult immunization (See Section 2.3.1). In a 2011 study, only 34.7% of adults in groups at high risk for hepatitis B had ever received a single dose of hepatitis B vaccine.[1]

1.3.2 Limitations of Current Hepatitis B Vaccines

Even when the currently approved hepatitis B vaccines are administered, they have limitations that reduce their effectiveness that include (See Section 2.3.2):

- Reduced rates of seroprotection from administration of a complete vaccine regimen in adults compared with children,[43] including in populations with known reduced rates of seroprotection: persons with diabetes mellitus, men, older adults, obese individuals, and smokers,[3, 5, 34, 39, 104, 106, 118, 122, 124, 125, 127-129]
- Prolonged time (> 6 months) before achievement of seroprotection because fewer than 50% of adults are protected after receiving 2 doses, and
- Poor adherence to a complete 3-dose vaccination schedule over 6 months.[46, 96]

Such limitations will make it difficult to achieve the March 28, 2017, call by the National Academies of Sciences, Engineering, and Medicine to eliminate viral hepatitis as a public health problem in the US.[95]

1.4 Proposed Mechanism of Action of 1018

1018 is a 22-base synthetic oligonucleotide (ODN) containing immunostimulatory cytidine-phospho-guanosine (CpG) sequence motifs (See Section 3.2 for references and details). 1018 exerts its actions through a single, well-defined cellular receptor, TLR9, which is an important innate immune receptor for sensing the presence of bacterial and viral DNA.[12, 52] TLR9 is expressed on a limited number of cell types, principally plasmacytoid dendritic cells (pDCs) and

memory B cells. When combined with HBsAg in HEPLISAV-B, the principal actions of 1018 in humans include: (1) activating pDCs to secrete interferons (IFNs) and cytokines; (2) converting pDCs into highly efficient antigen-presenting cells that present processed HBsAg peptides to CD4+ T cells; and, (3) promoting T cell differentiation to functional helper T (Th) cells through pDC derived IFNs and cytokines. These antigen-specific Th cells in turn provide multiple signals to B cells specific for intact HBsAg, leading to generation of antibody responses providing protective immunity to HBV. The biological actions of 1018 are exerted locally at the injection site and draining lymph nodes. Their stimulatory actions decline rapidly, with biomarkers of 1018 activity returning to baseline values up to 7 days. At doses administered in HEPLISAV-B, 1018 is cleared from circulation within a few hours and does not reach levels that would lead to systemic TLR9-mediated immune stimulation. Long-lived antibody responses and T and B cell memory constitute the durable effects of immunization with HEPLISAV-B. These responses are highly specific for the HBs antigen itself and, once generated, no longer depend on continuing presence of either the antigen or the 1018 adjuvant.

1.5 Nonclinical Toxicology

The toxicity and potential safety of the HEPLISAV-B vaccine and the 1018 adjuvant have been studied with a series of good laboratory practice (GLP) toxicity studies in mice, rats, baboons, and cynomolgus monkeys (see Section 3.3). The primary safety study of the HEPLISAV-B formulation was performed in mice at 1018 doses 43-fold greater and HBsAg doses 67-fold greater than the human dosage. This dose given intramuscularly for 3 injections was well-tolerated. Target organs affected by these high doses of 1018 were the hematopoietic system, spleen, liver, and injection-site and the findings were all consistent with the known immune stimulatory activity of 1018. These immune-based findings substantially or completely resolved after a 4 week recovery period.

In addition, a study in cynomolgus monkeys was conducted with the 1018 adjuvant alone at doses up to 270-fold greater than clinical dosage administered weekly for 8 weeks. Monkeys are the most relevant species for toxicity evaluation due to their strong similarities with humans in TLR9 distribution and biological responses to CpG-ODN. At the highest doses, findings consistent with TLR9-mediated immune stimulation were observed in the major target organs, liver and spleen, as well as the injection site and draining lymph node. These were mostly to completely reversible after 4 weeks of recovery. Virtually all toxicity observations in monkeys were consistent with known TLR9 biology, except, at the highest dose, for complement activation and increased activated partial thromboplastin time (aPTT), both known sequence-independent ODN class effects. The relative absence of findings attributable to off-target activities is consistent with the complete unresponsiveness of TLR9-deficient mice to high doses of 1018.

1.6 Clinical Development Program

Overall, Dynavax enrolled 14,238 adult subjects in 11 completed clinical trials of HEPLISAV-B (3 pivotal trials and 8 supportive trials), including 10,038 adult subjects who received at least 1 dose of HEPLISAV-B and 4200 adult subjects who received the licensed comparator vaccine, Engerix-B (See Section 4.2).

Engerix-B, is administered at a dose of 20 mcg HBsAg adsorbed on 0.5 mg alum and given at 0, 1, and 6 months. It was chosen as the comparator vaccine because, in adults, it induces the highest immune response,[3] has an acceptable safety profile, and is the most commonly used hepatitis B vaccine in the US.

The clinical development program began with the first phase 1 HEPLISAV-B clinical trial (HBV0001) in December 2000 in Canada. The first phase 3 HEPLISAV-B pivotal study, HBV-10, was initiated in December 2006 in Canada and June 2007 in Germany. In HBV-10, a rare autoimmune event of granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) was reported as a possibly related serious adverse event, resulting in the FDA imposing a clinical hold on the HEPLISAV-B clinical development program. This event and the clinical hold are discussed further in Section 4.2.

After a thorough safety investigation and analysis of autoimmune events, the FDA lifted the clinical hold and the second phase 3 pivotal trial (HBV-16) was conducted in the US and Canada. In this trial, intensive prospective surveillance for immune-mediated disorders was implemented including testing for autoantibodies, expert independent evaluation of suspected immune-mediated events, and establishment of a blinded, independent Safety Evaluation and Adjudication Committee (SEAC) for confirmation of each possible immune-mediated event. In addition, an independent Data and Safety Monitoring Board (DSMB) was used for evaluation of overall safety and study conduct. The DSMB reviewed overall safety, including the blinded adjudications of the SEAC, and had the ability to unblind subjects individually and by treatment group.

The most recent pivotal study, HBV-23, was designed in consultation with FDA and conducted in the US to expand the safety database and further evaluate potential immune-mediated adverse events using the same SEAC and DSMB as in HBV-16. HBV-23 was an observer-blinded, active-controlled trial with a 2:1 randomization ratio (HEPLISAV-B to Engerix-B) that planned to enroll 5000 HEPLISAV-B recipients with safety follow-up for 1 year after the last active vaccine injection. HBV-23 randomized 5592 subjects to HEPLISAV-B and 2782 subjects to Engerix-B; 5092 HEPLISAV-B recipients completed all study visits.

1.6.1 Clinical Trial Design

The primary objective of demonstrating the noninferiority of HEPLISAV-B compared with Engerix-B was assessed in 3 phase 3 pivotal trials: HBV-10, HBV-16, and HBV-23 (See Section

5.1). Immunogenicity and safety data are presented primarily for these 3 pivotal trials. Results from the supportive trials are consistent with those from the pivotal trials.

The pivotal trials were randomized, observer-blinded, active-controlled, parallel-group, multicenter trials that compared immune responses following injection with 2 doses of HEPLISAV-B at 0 and 1 month and 1 dose of placebo at 6 months to 3 doses of Engerix-B at 0, 1, and 6 months.

Eligible subjects in HBV-10 and HBV-16 were generally healthy volunteers. The HBV-23 protocol, however, did not specify that subjects must be generally healthy. Subjects in all 3 pivotal trials were serum negative for HBsAg, anti-HBs, and antibody to hepatitis B core antigen (anti-HBc); had no history of HBV infection; had no prior immunization with any hepatitis B vaccine; had no autoimmune disease; and were not pregnant.

- In HBV-10, 2415 adults 18 to 55 years of age were randomized in a 3:1 ratio to receive HEPLISAV-B or Engerix-B and were followed for 28 weeks after the first injection.
- In HBV-16, 2452 adults 40 to 70 years of age were randomized in a 4:1 ratio to receive HEPLISAV-B or Engerix-B and were followed for 52 weeks after the first injection.
- In HBV-23, 8374 adults 18 to 70 years of age were randomized in a 2:1 ratio to receive HEPLISAV-B or Engerix-B and were followed for 56 weeks after first injection.

1.6.2 Clinical Trial Analyses Population

Immunogenicity analyses were based on the following pre-specified populations:

- The Per-Protocol (PP) Population comprised all randomized subjects who received all study injections, had no major protocol deviations that would affect immunogenicity, and had anti-HBs levels obtained at the primary endpoint. The PP Population was used for the analyses of primary and secondary immunogenicity endpoints.
- The modified Intent-to-Treat (mITT) Population comprised all randomized subjects who received at least 1 study injection and had at least 1 post-injection immunogenicity evaluation. The mITT population was used in immunogenicity analyses in support of the PP immunogenicity analyses.

The PP population was chosen for the primary endpoint analyses in accordance with the FDA guidance on noninferiority trials.[13] In the HEPLISAV-B trials, non-adherence with the third dose would negatively affect the immunogenicity outcomes in the Engerix-B group but have no impact on HEPLISAV-B, thus creating a bias in favor of HEPLISAV-B in the mITT analyses. With these considerations in mind, all primary analyses using the PP Population are supported by sensitivity analyses performed using the mITT Population.

Safety analyses were based on the following pre-specified population:

- The Safety Population for each trial included all subjects who received at least 1 injection of study drug, excluding subjects who had no on-study safety assessment. The Safety Population was used for analyses of adverse events.

Standard safety evaluations included solicited, local and systemic adverse events (AEs; HBV-10 and HBV-16), unsolicited AEs (HBV-10 and HBV-16), and medically-attended adverse events (MAEs; HBV-23). Serious adverse events (SAEs) were collected in all 3 pivotal trials. Immune-mediated adverse events including a list of adverse events of special interest (AESI) provided by FDA for HBV-23 (Appendix 3) were applied retrospectively to HBV-10 and HBV-16. Other autoimmune disorders not on the FDA list were collected in HBV-10, HBV-16, and HBV-23. Laboratory assessments of autoantibodies were conducted in HBV-10 and HBV-16 as well as some early phase trials.

In the 3 pivotal trials, HEPLISAV-B was administered to 9365 subjects 18 years of age and older and Engerix-B was administered to 3867 subjects with an overall subject allocation ratio of 2.4:1. Of these subjects, 8656 (92.4%) HEPLISAV-B subjects and 3606 (93.3%) Engerix-B subjects completed all study visits.

1.7 Immunogenicity

1.7.1 Primary Immunogenicity Endpoints for the Pivotal Trials

The demonstration of seroprotection in the 3 pivotal trials relied on head-to-head comparisons between HEPLISAV-B and Engerix-B (See Section 5.2.2). The trials were powered to demonstrate noninferiority of HEPLISAV-B compared to Engerix-B. The noninferiority margin for each study was an absolute difference of 10% in the SPRs (HEPLISAV-B minus Engerix-B). This margin was based on consideration of historical SPRs of Engerix-B in similar study populations and was accepted by the relevant regulatory authorities. HEPLISAV-B was to be considered noninferior to Engerix-B if the lower bound of the 95% confidence interval (CI) of the difference in SPRs was greater than -10%. The results of the primary immunogenicity analyses are presented in Figure 1-1.

1.7.1.1 HBV-10

The primary immunogenicity objective for HBV-10 was to demonstrate the noninferiority of the SPR at 8 weeks after last active dose (Week 12) of HEPLISAV-B compared to the SPR at 4 weeks after the last active dose (Week 28) for Engerix-B.

The primary immunogenicity objective of demonstrating noninferiority was met (Figure 1-1).

1.7.1.2 HBV-16

The primary immunogenicity objective for HBV-16 was to demonstrate the noninferiority of the immune response to HEPLISAV-B vaccination as measured by the SPR at 8 weeks after the last active dose (Week 12) compared to the SPR for Engerix-B vaccination at 8 weeks after the last active dose (Week 32).

The primary immunogenicity objective of demonstrating noninferiority was met as well as the secondary objective of a statistically significantly higher SPR (lower bound of the 95% CI of the difference in SPRs was greater than 0) (Figure 1-1).

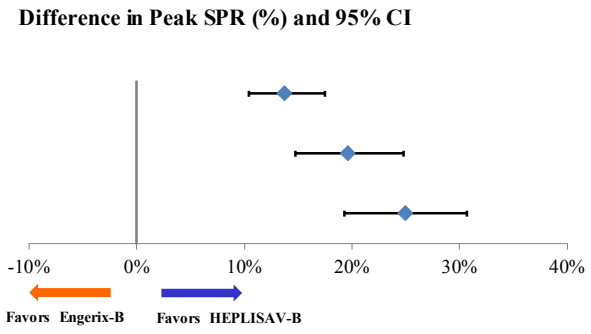
1.7.1.3 HBV-23

The primary immunogenicity objective for HBV-23 was to demonstrate the noninferiority of the SPR induced by HEPLISAV-B compared with the SPR induced by Engerix-B at Week 28 in the subset of subjects with type 2 diabetes mellitus. Type 2 diabetes mellitus was defined by a clinical diagnosis of type 2 diabetes mellitus and taking at least an oral or non-insulin injectable antihyperglycemic agent and/or insulin. Immunogenicity in patients with diabetes was evaluated as the primary outcome because of ACIP recommendations for immunization of adults with diabetes, the high unmet need, and public health risks in this population.

The primary immunogenicity objective in subjects with diabetes mellitus of demonstrating noninferiority was met as well as a secondary objective of a statistically significantly higher SPR (Figure 1-1).

Figure 1-1: SPR at the Primary Immunogenicity Endpoint for Pivotal Trials (Per-Protocol Population)

Study Number	HEPLISAV-B SPR (%)	HEPLISAV-B N	Engerix-B SPR (%)	Engerix-B N	Difference in SPR (95% CI)
HBV-10	95.0	1,511	81.3	521	13.7 (10.4, 17.5)
HBV-16	90.1	1,121	70.5	353	19.6 (14.7, 24.8)
HBV-23	90.0	640	65.1	321	24.9 (19.3, 30.7)



Primary immunogenicity endpoint in HBV-23 was in subjects with diabetes mellitus.
All comparisons: $p < 0.0000001$

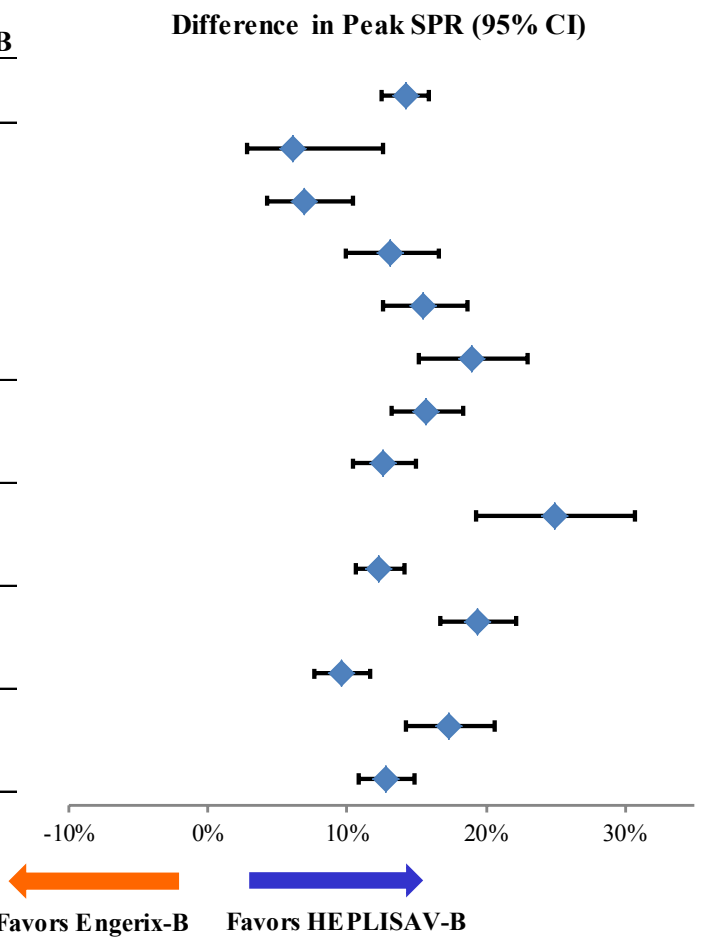
1.7.2 Secondary Immunogenicity Endpoints in HBV-23

In HBV-23, a secondary immunogenicity objective was to demonstrate the noninferiority of the peak immune response to HEPLISAV-B as measured by SPR at Week 24 compared to the peak SPR for Engerix-B at Week 28 in all subjects and in the following subgroups: by age, sex, body mass index (BMI), and smoking status.

The HEPLISAV-B induced peak SPRs were noninferior to and statistically significantly higher than peak SPRs induced by Engerix-B in pre-specified subpopulations known to have reduced SPRs with currently licensed hepatitis B vaccines (older adults, men, subjects with diabetes mellitus, obese subjects, and smokers),[3, 6, 34, 39, 104, 106, 118, 122, 124, 125, 127-129] as well as in subpopulations known to have higher SPRs with licensed vaccines (young adults, women, non-obese subjects, nonsmokers, and subjects without diabetes mellitus) (Figure 1-2).

Figure 1-2: Comparison of Peak SPR in Subjects Who Received HEPLISAV-B (Week 24) With Peak SPR in Subjects Who Received Engerix-B (Week 28) (HBV-23 Per-Protocol Population)

Prespecified Subpopulation	N	Peak SPR (%) HEPLISAV-B	Peak SPR (%) Engerix-B
All Subjects	6665	95.4	81.3
18—29 years	273	100	93.9
30—39 years	958	98.9	92.0
40—49 years	1492	97.2	84.2
50—59 years	2197	95.2	79.7
60—70 years	1745	91.6	72.6
Men	3353	94.5	78.8
Women	3312	96.4	83.8
Diabetes	961	90.0	65.1
No diabetes	5730	96.2	83.9
Obese	3241	94.7	75.4
Non-obese	3420	96.1	86.6
Smoker	2082	95.9	78.6
Non-smoker	4583	95.2	82.4



CI = confidence interval; SPR = seroprotection rate.
Subpopulations are pre-specified in the HBV-23 Protocol. For subjects with type 2 diabetes mellitus, SPR was analyzed at Week 28 for both HEPLISAV-B and Engerix-B.
No multiplicity adjustment was applied.

1.7.3 Exploratory Immunogenicity Endpoint

1.7.3.1 Seroprotection by Race in HBV-23

Immunogenicity by race was an exploratory endpoint in HBV-23. Table 5-5 compares SPRs by race by HEPLISAV-B at Week 24 and Engerix-B at Week 28. The peak SPR in the HEPLISAV-B group was noninferior to and statistically significantly higher than in the Engerix-B group in racial groups except those with small numbers of subjects (See Section 5.2.3).

1.7.3.2 Seroprotection at Early Time Points in HBV-10 and HBV-16

Seroprotection at early time points was assessed in HBV-10 and HBV-16 (Figure 5-1) (See Section 5.2.4):

- At Week 8 in HBV-10, the SPR in the HEPLISAV-B group (88.4%) was not only significantly higher than the SPR in the Engerix-B group at Week 8 (26.7%), but was also higher than the peak SPR in the Engerix-B group at Week 28 (81.2%).
- At Week 8 in HBV-16, the SPR in the HEPLISAV-B group was 76.5% and was not only significantly higher than the SPR in the Engerix-B group at Week 8 (20.4%), but was also higher than the peak SPR in the Engerix-B group at Week 28 (72.9%).

1.7.4 Immunogenicity Summary

The comparison of 2 doses of HEPLISAV-B over 4 weeks to 3 doses of Engerix-B over 24 weeks demonstrated the following

- Noninferior and statistically significantly higher SPRs at the primary endpoints in all 3 pivotal trials;
- Statistically significantly higher peak SPR in all pre-specified populations including subpopulations with reduced SPRs from currently licensed HBV vaccines.
- Seroprotection 5 months earlier for most subjects.

1.8 Safety

Solicited adverse events and unsolicited AEs are integrated for HBV-10 and HBV-16. MAEs are presented for HBV-23. Immune-mediated adverse events, deaths, and SAEs are integrated for the primary safety population (PSP: HBV-10, HBV-16, and HBV-23). The PSP has an overall subject allocation ratio of 2.4:1 (HEPLISAV-B: Engerix-B) (See Section 6.3).

1.8.1 Overview of Safety

The 1018 adjuvant has been evaluated in several other clinical settings in doses up to 100 mg per dose: as a cancer immunotherapeutic by the subcutaneous route, as an asthma immunotherapeutic by the aerosol route, and as an allergy immunotherapeutic conjugated to ragweed by the subcutaneous route. In these programs, 1263 subjects received 1018, including 149 in the cancer and asthma programs who received higher doses (35 mg to 100 mg) and more doses (ranging from 4 to 8 total, given weekly) of 1018. Notably, no maximum tolerated dose was identified in these development programs.

In the HEPLISAV-B studies, the majority of solicited AEs were mild to moderate, self-limited, and did not lead to treatment discontinuation. In HBV-10 and HBV-16, the post-injection reaction profile of HEPLISAV-B included a similar rate of local reactions (HEPLISAV-B: 43%; Engerix-B: 41%) and a lower rate of systemic reactions (HEPLISAV-B: 32%; Engerix-B: 37%) (See Section 6.7.1). The type and frequency of AEs, MAEs, and reasons for treatment withdrawal due to AEs were balanced for subjects who received HEPLISAV-B or Engerix-B (See Sections 6.7.3 and 6.7.4).

Immune-mediated AEs, deaths, and SAEs were balanced between the HEPLISAV-B and Engerix-B groups (Table 1-1) with the exception of differences in events coded to a few Standardized Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs). A higher proportion of subjects in the HEPLISAV-B group died due to illicit or therapeutic drug overdose, and a higher proportion of subjects in the HEPLISAV-B group reported the SAE preferred term of *acute myocardial infarction*. A higher proportion of subjects in the Engerix-B group reported the SAE preferred terms of *prostate cancer* or *dehydration*.

Table 1-1: Summary of Immune-mediated AEs, Deaths, and SAEs (PSP)

Event Type	HEPLISAV-B (N=9365) % (n)	Engerix-B (N=3867) % (n)
Any new-onset immune-mediated AE[a]	0.20 (19)	0.13 (5)
Bell's palsy	0.06 (6)	0.05 (2)
AESI excluding Bell's palsy	0.11 (10)	0.08 (3)
Autoimmune AE not on AESI list[b]	0.03 (3)	0
Death	0.28 (26)	0.21 (8)
Any serious AE	4.8 (449)	4.8 (184)

AE = Adverse event; AESI = Immune-mediated adverse event of special interest; SAE = serious adverse event.
Primary Safety Population: HBV-23, HBV-16, HBV-10.
[a] Comprises AESIs and events not on the AESI list (Appendix 3) that were adjudicated as autoimmune by the Safety Evaluation and Adjudication Committee (SEAC) in HBV-16 and HBV-23.
[b] Comprises 3 events of hypothyroidism not on the AESI list that were adjudicated as new-onset and autoimmune by the SEAC in HBV-16 and HBV-23.

1.8.1.1 Numerical Imbalances in Medically Attended Adverse Events in HBV-23

Assessing whether small numerical differences between treatment arms represent true and clinically meaningful treatment effects or random variation is a consistent challenge in clinical development. MAEs with relative risks (RRs) with 95% CIs that exclude 1 merit further investigation. In addition, the relative risk of other MAEs that occur in a small number of subjects may be fairly large and have wide 95% CIs that include 1 (See Section 6.7.4.1). These also merit further evaluation.

To assess the extent to which any such numerical imbalance discovered post-hoc represents a meaningful clinical effect, observed imbalances in MAEs were comprehensively assessed. As part of the assessment, RRs and 95% CI were calculated for HEPLISAV-B compared with Engerix-B.

Of the 1405 MAEs reported, 10 had a RR with a 95% CI excluding 1 (Table 1-2). Only 1 MAE occurred at a higher frequency in the HEPLISAV-B group: herpes zoster (HZ). As 1018 stimulates TLR9 and Zostavax® is likely to stimulate TLR9,[103, 130] HEPLISAV-B is more likely to protect against HZ than cause it. In contrast, 9 MAEs occurred at a higher frequency in the Engerix-B group. None of these 9 events in the Engerix-B group have been previously known to be associated with Engerix-B, and none have a known biologically plausible explanation.

Of the 1405 MAEs reported, 19 had relatively large RRs with 95% CIs that include 1 (Table 6-10). Five MAEs with a variety of etiologies occurred at a higher frequency in the HEPLISAV-B group: *wound, excoriation, lipoma, acute myocardial infarction,* and *bipolar I disorder*. Because of the clinical importance of the term, *acute myocardial infarction*, it was extensively investigated (See Section 6.7.11). Fourteen other MAEs with a variety of etiologies occurred with a higher frequency in the Engerix-B group including: *coronary artery arteriosclerosis, irritable bowel syndrome, acute cholecystitis,* and *oral herpes*. None of these 14 MAEs have been previously known to be associated with Engerix-B and none have a known biologically plausible explanation.

From a statistical perspective, given the large number of events observed in this study, it is expected that a small number of events will reach a threshold that excludes 1 even though there is no true treatment effect. This situation may be expected to arise when very few events are reported for the vast majority of AE terms.

Table 1-2: MAE Preferred Terms With Relative Risks With 95% Confidence Intervals That Exclude 1 (HBV-23 Safety Population)

Preferred Term	HEPLISAV-B (N=5587) % (n)	Engerix-B (N=2781) % (n)	Relative Risk (HEPLISAV-B/Engerix-B) 95% CI
Herpes Zoster	0.7 (38)	0.3 (9)	2.10 (1.02 - 4.34)
Tooth Infection	0.3 (17)	0.6 (17)	0.50 (0.25 - 0.97)
Inguinal Hernia	<0.1 (5)	0.3 (8)	0.31 (0.10 - 0.95)
Impaired Glucose Tolerance	<0.1 (4)	0.3 (7)	0.28 (0.08 - 0.97)
Exostosis	0.1 (6)	0.5 (14)	0.21 (0.08 - 0.55)
Positional Vertigo	<0.1 (3)	0.2 (6)	0.25 (0.06 - 0.99)
Arthropod Sting	<0.1 (3)	0.3 (8)	0.19 (0.05 - 0.70)
Hypomagnesaemia	<0.1 (2)	0.2 (6)	0.17 (0.03 - 0.82)
Pleurisy	<0.1 (2)	0.3 (7)	0.14 (0.03 - 0.68)
Thyroid Neoplasm	0	0.2 (5)	0.05 (0 - 0.82)

CI = confidence interval.
Note: Relative risks and asymptotic 95% CIs were calculated using the Wald method if both treatment groups had one or more AEs. Otherwise the Wald Modified method was used to calculate continuity corrected RRs and asymptotic 95% CIs.

1.8.1.2 Immune-Mediated Adverse Events

Safety findings related to immune-mediated disease were analyzed extensively (See Sections 6.2.2 and 6.7.6). Immune-mediated AESIs were actively solicited and adjudicated by an independent SEAC in the pivotal phase 3 trials HBV-16 and HBV-23. The frequency of new-onset immune-mediated AEs in the PSP (Table 1-1) was balanced between treatment groups.

In the PSP, Bell's palsy was reported by similar proportions of subjects who received HEPLISAV-B or Engerix-B. New-onset AESIs excluding Bell's palsy also occurred in similar proportions of subjects who received HEPLISAV-B or Engerix-B. No AESI other than Bell's palsy occurred in more than 1 recipient of HEPLISAV-B.

In the PSP with a subject allocation ratio of 2.4:1 (HEPLISAV-B:Engerix-B), 3 rare, serious autoimmune events occurred in the HEPLISAV-B group: granulomatosis with polyangiitis, Guillain-Barré syndrome (5 days after an influenza vaccination), and cavernous sinus syndrome (presumed to be Tolosa Hunt syndrome), and 1 event in the Engerix-B group, ANCA-positive vasculitis.

New-onset AESIs occurred with variable time to onset, in a variety of organ systems, and by a variety of mechanisms (Table 6-15) confirming no consistent pattern of immune-related AEs in the HEPLISAV-B group.

Three events of hypothyroidism that were not on the list of AESIs were adjudicated as autoimmune by the SEAC in HBV-16 and HBV-23. All occurred in women in the HEPLISAV-B group at a rate lower than background. One of these events was considered to be related to

papillary thyroid carcinoma. Other thyroid events were balanced between the treatment groups (Table 6-16).

In the PSP in subjects with pre-existing AESIs, exacerbations were similar between HEPLISAV-B and Engerix-B.

In trials in which autoantibodies were tested (HBV-10, HBV-16 and supportive trials), rates of development of common autoantibodies were similar between recipients of HEPLISAV-B and recipients of Engerix-B, including ANA (HEPLISAV-B: 5.5%; Engerix-B: 5.1%) and anti-dsDNA (HEPLISAV-B: 1.2%; Engerix-B: 1.0%). Based on the occurrence of an SAE of ANCA-associated vasculitis (granulomatosis with polyangiitis) in a HEPLISAV-B subject in HBV-10, retrospective testing for ANCA was performed among 2568 subjects. One Engerix-B subject also had an ANCA-positive vasculitis. There were no additional subjects with ANCA-positive results in either treatment group.

In HBV-23, a subset of 309 subjects was also tested for antiphospholipid antibodies which have been associated with an increased risk of thrombosis. The frequency of new-onset antiphospholipid antibodies was similar in both groups for anticardiolipin immunoglobulin G (IgG) and immunoglobulin M (IgM), anti-beta 2 glycoprotein 1 IgG, and lupus anticoagulant confirmatory/screen ratio. One nonspecific antiphospholipid autoantibody (beta 2 glycoprotein 1 IgM) was transiently increased at Week 8 in a higher proportion of subjects who received HEPLISAV-B (7.7%) than subjects who received Engerix-B (1.0%). The transient increase in beta 2 glycoprotein 1 IgM levels was not associated with thrombotic or thromboembolic events, was not diagnostic of antiphospholipid syndrome, and has been previously reported following Engerix-B administration as well as following viral and bacterial infections.[32, 80, 89]

1.8.1.3 Deaths

Most deaths occurred in subjects with significant pre-existing disease, comorbidities, or contributory social circumstances (See Section 6.7.9). The only imbalance between the treatment groups was in deaths due to illicit or therapeutic drug overdose documented at autopsy (HEPLISAV-B: n = 6 [0.06%]; Engerix-B: n = 1 [0.03%]). Excluding overdose deaths, there were 20 (0.21%) deaths in subjects who received HEPLISAV-B and 7 (0.18%) in subjects who received Engerix-B.

1.8.1.4 Serious Adverse Events

SAEs were generally balanced between treatment groups in type and frequency in the PSP and were commensurate with common morbidities in the general adult population (See Section 6.7.10). In the PSP, differences between treatment groups with a higher proportion in the Engerix-B group in 2 PTs (*prostate cancer* and *dehydration)* had 95% CIs that excluded 1. All events with a higher proportion of subjects in the HEPLISAV-B group had 95% CIs that included 1.

The most frequent treatment emergent SAEs in the PSP by preferred term were *pneumonia, osteoarthritis*, *acute myocardial infarction*, and *noncardiac chest pain*. The proportion of subjects reporting these events was similar between vaccine groups except for an unexpected numerical imbalance in the single preferred term of *acute myocardial infarction* (See Section 6.7.11.1). The imbalance in *acute myocardial infarction* was the result of a numerical imbalance in a single study, HBV-23 (HEPLISAV-B: 0.25% [n = 14]; Engerix-B: 0.04% [n = 1]; RR = 6.97; 95% CI: 0.92, 52.97). Of note, in HBV-23, *acute myocardial infarctions* occurred in 0.26% (n = 2) of 762 subjects with diabetes who received HEPLISAV-B and in 0.26% (n = 1) of 381 subjects with diabetes who received Engerix-B. Among the small number of *acute myocardial infarction* events in HBV-16, the proportion of subjects with an *acute myocardial infarction* was lower in the HEPLISAV-B group (HEPLISAV-B: 0.10% [n = 2]; Engerix-B: 0.21% [n = 1]; RR = 0.49; 95% CI: 0.04, 5.38). No *acute myocardial infarctions* were reported in HBV-10.

1.8.1.5 Major Adverse Cardiovascular Events

The numerical imbalance in *acute myocardial infarctions* in HBV-23 was an unexpected finding. It was not observed in nonclinical studies or in previous clinical trials and there is no known plausible association between cardiovascular disease and 1018, other CpG ODNs, or other hepatitis B vaccines (See Section 6.7.11). Cardiovascular endpoints were not prospectively evaluated in any HEPLISAV-B trial including HBV-23. Thus, the evaluation of the numerical imbalance was post-hoc with no formal hypothesis testing.

A comprehensive strategy to assess whether the numerical imbalance in *acute myocardial infarctions* in HBV-23 could be associated with treatment was developed in collaboration and consultation with Darren McGuire, MD, MHSc (University of Texas Southwestern Medical Center) (Table 1-3). Dr. McGuire is a cardiologist with extensive clinical trial and regulatory experience in the cardiovascular area.

Table 1-3: Strategy for Assessing the Numerical Imbalance in *Acute Myocardial Infarction*

This systematic strategy included:

1. Performing blinded review of clinical annotations and cardiac catheterization data by Dr. McGuire for all reported acute myocardial infarction events;

2. Broadly searching for other possibly missed acute myocardial infarctions or strokes using the Standardized MedDRA Query (SMQ) (Section 6.7.11.3) a strategy that augments capture of all potential myocardial infarction and stroke events;

3. Engaging the Cleveland Clinic C5 Research Center (Section 6.7.11.4.1) to perform post-hoc, blinded, central adjudication of all deaths and all potential myocardial infarctions and strokes identified by preferred term/SMQs using standardized processes and case definitions for events commonly used in clinical development of cardiovascular therapeutics;[51]

4. Conducting analyses of the reported acute myocardial infarction events and analyses of the composite outcome of adjudication-confirmed major adverse cardiovascular events (MACE) comprising cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, and analysis of each independent component of the composite. Analysis of this 3-point MACE composite outcome is the gold standard for cardiovascular outcomes assessment of atherosclerotic vascular diseases that share a common underlying pathophysiology and represent a continuum of the natural history of atherosclerotic vascular disease and its acute complications;[110]

5. Using confirmed MACE outcomes to examine:
   a. Baseline characteristics of subjects who experienced events,
   b. Timing of events relative to vaccination, and
   c. Observed rates of events with expected background rates modeled using population-based databases and risk prediction methods commonly used in clinical practice;

6. Evaluating possible vaccine-induced immunological etiologies of myocardial infarction and MACE:
   a. Mimicking an acute systemic infection (that increases the risk of myocardial infarction and MACE shortly after diagnosis);
   b. Vasculitis;
   c. Myocarditis; or
   d. Hypercoagulable state.

Based on this systematic evaluation, we found myocardial infarctions and MACE outcomes occurred:

- In persons in whom they would be expected, who had a high burden of cardiovascular risk factors with advanced and often multi-vessel obstructive coronary artery disease;
- With no evidence by clinical annotations and cardiac catheterization data for inflammatory/immune-mediated vasculitides or myocarditis;
- With no evidence of a hypercoagulable state based as other venous or arterial thrombotic/thromboembolic events were balanced and;
- Without close temporal relationship to vaccine administration;
- At rates in the HEPLISAV-B group that were similar to or lower than background.

Based on this comprehensive assessment, the observed numerical difference between treatment groups in the occurrence of events coded to the MedDRA preferred term *acute myocardial infarction* in HBV-23 is an isolated finding in the HEPLISAV-B database that appears most likely explained by random variation resulting in an unexpectedly low number of events observed in the Engerix-B group in HBV-23.

1.8.1.5.1 Cardiac Catheterization Results

Clinical annotations and cardiac catheterization results were available for each *acute myocardial infarction* event (See Section 6.7.11.1.1 and narratives are presented in Appendix 6). Dr. McGuire reviewed the reports and the case summaries blinded to investigational product assignment. In each case, Dr. McGuire determined that the clinical presentation was most consistent with a typical acute coronary syndrome event, and for the majority with catheterization data, there were consistent descriptions of typical acute "culprit" lesions in the setting of advanced, multi-vessel obstructive coronary artery disease. Importantly, the catheterization reports rule out atypical causes for acute myocardial infarction that could be mediated by inflammation or immune mechanisms, such as coronary vasculitis, aneurysmal disease, coronary dissection, vasospasm, embolism/*in situ* thrombosis, or myocarditis masquerading as an acute myocardial infarction. These clinical annotations and catheterization reports also exclude "type 2 myocardial infarctions"-that is, myocardial infarction due to myocardial supply demand mismatch often driven by acute stressors such as sepsis, shock, anemia, hypertensive crisis, heart failure decompensation, hypoxia, acute kidney failure, etc.

1.8.1.5.2 Analysis of 3-Point MACE

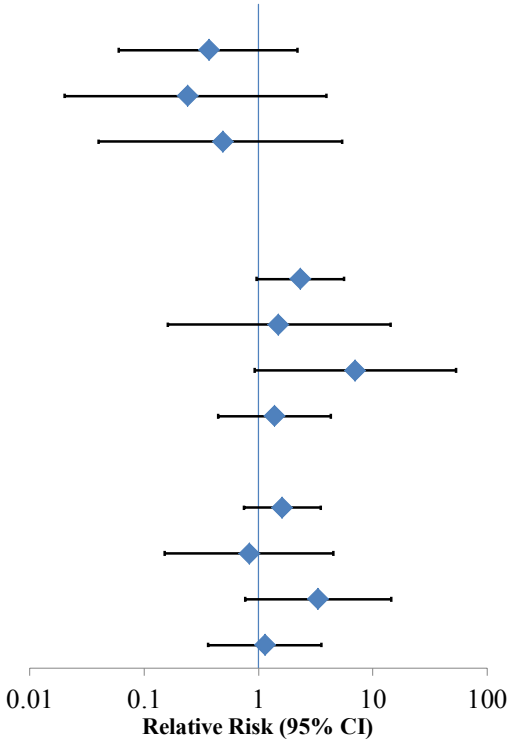
The first question we asked was what were the events of interest?

All deaths as well as all potential myocardial infarction and stroke events ascertained by adverse event reporting and identified by SMQ were submitted to Cleveland Clinic C5 Research for blinded adjudication of major adverse cardiovascular events (See Section 6.7.11.4.1). Figure 1-3 presents the analysis of confirmed 3-point MACE outcomes by trial and in the PSP. In all analyses, the 95% CI included 1.

In the PSP, a numerical imbalance was observed only in myocardial infarction attributable to the imbalance observed in the single trial, HBV-23; death due to cardiovascular cause and stroke were balanced between groups. Removing adjudication-confirmed myocardial infarction events observed in HBV-23 from the PSP, 0.18% (n = 17) of subjects in the HEPLISAV-B group and 0.18% (n = 7) of subjects in the Engerix-B group experienced a MACE outcome. The difference between treatment groups is thus driven entirely by the imbalance in myocardial infarctions in HBV-23.

Figure 1-3: Subjects With Adjudication-Confirmed 3-point MACE by Treatment Group (Primary Safety Population)

MACE	HEPLISAV-B	Engerix-B	Relative Risk (95% CI)
	N=1968	**N=481**	
HBV-16	**n (%)**	**n (%)**	
Composite 3-point MACE events	3 (0.15)	2 (0.42)	0.37 (0.06, 2.19)
Death from cardiovascular cause	1 (0.05)	1 (0.21)	0.24 (0.02, 3.9)
Myocardial infarction	2 (0.10)	1 (0.21)	0.49 (0.04, 5.38)
Stroke	0	0	N/A N/A
	N=5587	**N=2781**	
HBV-23	**n (%)**	**n (%)**	
Composite 3-point MACE events	28 (0.50)	6 (0.22)	2.32 (0.96, 5.60)
Death from cardiovascular cause	3 (0.05)	1 (0.04)	1.49 (0.16, 14.35)
Myocardial infarction	14 (0.25)	1 (0.04)	6.97 (0.92, 52.97)
Stroke	11 (0.20)	4 (0.14)	1.37 (0.44, 4.30)
	N=9365	**N=3867**	
PSP (HBV-10, HBV-16, and HBV-23)	**n (%)**	**n (%)**	
Composite 3-point MACE events	31 (0.33)	8 (0.21)	1.6 (0.74, 3.48)
Death from cardiovascular cause	4 (0.04)	2 (0.05)	0.83 (0.15, 4.51)
Myocardial infarction	16 (0.17)	2 (0.05)	3.3 (0.76, 14.36)
Stroke	11 (0.12)	4 (0.10)	1.14 (0.36, 3.56)



CI = confidence interval; MACE = Major Adverse Cardiovascular Events. Composite 3-point MACE comprises death from cardiovascular cause, non-fatal myocardial infarction, and non-fatal stroke; N/A= not applicable
Note: Subjects with multiple MACE outcomes are counted once in the composite endpoints.

1.8.1.5.3 Baseline Cardiovascular Risk Factors in Subjects with a MACE

Next we asked, in whom did these events occur?

The subjects who had MACE outcomes were older and had a 2-fold or higher prevalence of hypertension, diabetes, and hyperlipidemia at enrollment than in the PSP (See Section 6.7.11.4.3 and Table 1-4). Every subject who had a MACE outcome in the HEPLISAV-B trials had 1 or more of these cardiovascular risk factors and/or prior cardiovascular disease. Thus, MACE outcomes occurred in subjects in whom they would be expected to occur.

Table 1-4: Baseline Cardiovascular Risk Factors in Subjects Who Had an Adjudication-Confirmed MACE Outcome Compared With the Primary Safety Population

Risk Factor	Confirmed MACE (N = 39)	HEPLISAV-B (N = 9365)	Engerix-B (N = 3867)
Age: median in years (range)	60 (39 – 70)	49.1 (18 – 70)	49.2 (18 – 70)
Medical Condition	**% (n)**	**% (n)**	**% (n)**
Hypertension	74.4 (29)	29.8 (2792)	30.5 (1178)
Hyperlipidemia	25.6 (10)	10.9 (1019)	11.8 (455)
Obesity	46.2 (18)	43.2 (4050)	42.8 (1657)
Diabetes mellitus	20.5 (8)	10.3 (961)	11.0 (425)
Smoking	28.2 (11)	31.3 (2928)	32.4 (1251)

MACE = Major Adverse Cardiovascular Events.

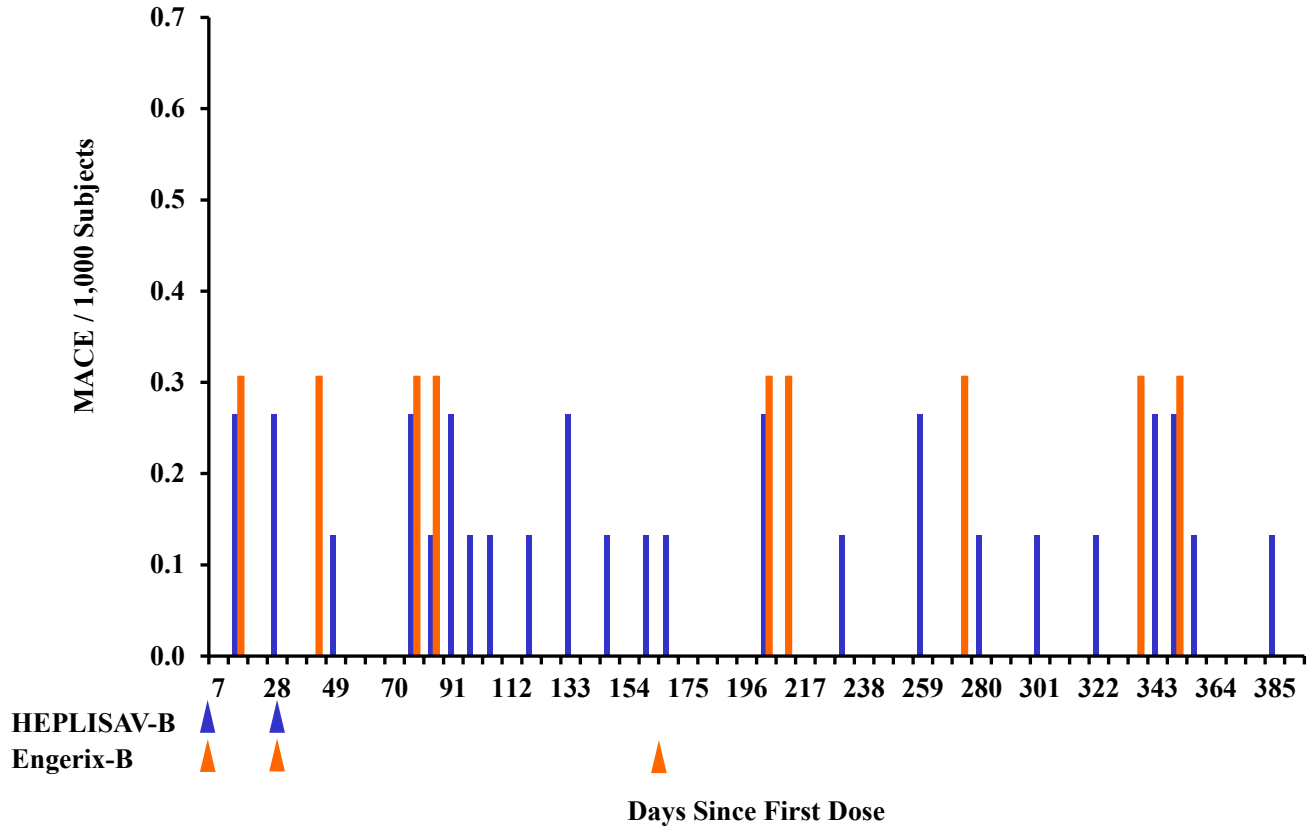
1.8.1.5.4 Temporal Distribution of MACE Outcomes

We then asked, when did the events occur?

Figure 1-4 presents the time of occurrence of MACE outcomes per 1000 subjects in the PSP.

MACE outcomes occurred over the entire duration of the trials without clear evidence of a cluster of events at any time including immediately following vaccine administration (Figure 1-5).

Figure 1-4: Temporal Distribution of MACE (Primary Safety Population)

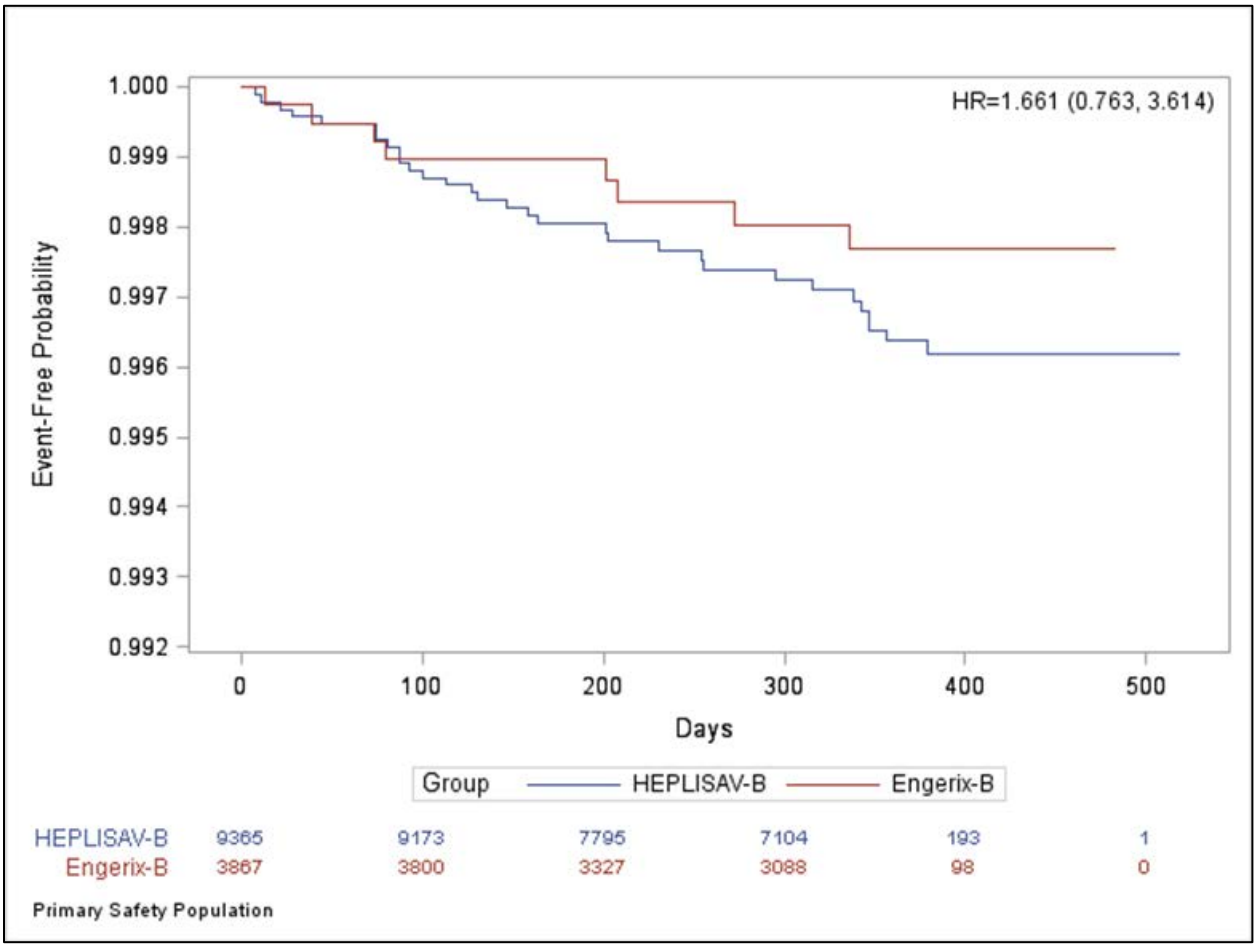


The arrows represent vaccine injections.

1.8.1.5.4.1 Time to Onset of MACE

Analyses of the temporal association between HEPLISAV-B or Engerix-B injection and MACE show that there is no imbalance between treatment groups through at least 28 days after the second injection (Study Day 56) (HEPLISAV-B: 0.05% [n = 5]; Engerix-B: 0.05% [n = 2]). Instead, the imbalance in MACE outcomes occurred late in the studies, beginning after Study Day 100 (Figure 1-5). Of note, the incidence in the HEPLISAV-B group in the first 100 days (4.3/1000 person years) was similar to the last 100 days (4.6/1000 person years).

Figure 1-5: Kaplan-Meier Curve for MACE From First Injection



HR = Hazard Ratio; MACE = Major Adverse Cardiovascular Events.

1.8.1.5.5 Comparison of Observed versus Expected Incidence Rates of MACE

Then we asked how did the incidence of observed events compare with what would be expected in the HEPLISAV-B studies based on characteristics of the enrolled cohort?

We estimated the age-, sex-, and race-adjusted expected frequency of MACE outcomes in the trial populations using population-based data published from studies in the US that were most comparable to the HEPLISAV-B study populations and data collection methods.[92] The population-based databases were used to estimate the expected rate (Table 1-5) and number of events in 35 to 70 year-old whites and blacks in HBV-16 and HBV-23 (Table 6-31) to make the study population as comparable to the population-based databases as possible. We also estimated expected rates incorporating baseline risk factors using other well-validated risk prediction models for the US.

Using population-based databases in HBV-23, in the HEPLISAV-B group, age-, sex-, and race-adjusted incidence rates of observed composite MACE outcomes and cardiovascular deaths were lower than expected, and myocardial infarction and strokes were similar to expected. In the Engerix-B group, observed composite MACE outcomes, deaths, myocardial infarctions, and strokes were each lower than expected. Notably, in HBV-23, the observed rate of myocardial infarction in the Engerix-B group was 6.8-fold lower than expected.

In the PSP, rates of MACE outcomes adjusted by age, sex, and race (but not for other cardiovascular risk factors) in the HEPLISAV-B group were similar to or lower than expected. In the Engerix-B group, rates were lower than expected. Accounting for other cardiovascular risk factors using validated population-based risk prediction models commonly used in routine clinical practice increased the expected number of events over the age-, sex-, and race-adjusted estimates (Table 6-31). This analysis suggests that the imbalance in events coded to the single preferred term of *acute myocardial infarction* is likely a lower than expected rate of events in the Engerix-B group rather than an increased rate in the HEPLISAV-B group.

Table 1-5: Comparison of Observed With Expected Incidence Rates of MACE in 35 to 70 Year-old Whites and Blacks in HBV-16 and HBV-23 (Safety Populations)

HBV-16 and HBV-23 Safety Populations		HBV-16		HBV-23		Pooled HBV-16 and HBV-23	
		HEPLISAV-B (N = 1830 person years)	Engerix-B (N = 451 person years)	HEPLISAV-B (N = 4893 person years)	Engerix-B (N = 2453 person years)	HEPLISAV-B (N = 6724 person years)	Engerix-B (N = 2903 person years)
MACE	Expected rate	6.1/1000 p-y		6.7/1000 p-y		6.5/1000 p-y	
	Observed rate /1000 p-y (n)	1.6 (3)	4.4 (2)	5.7 (28)	2.4 (6)	4.6 (31)	2.8 (8)
Cardio-vascular Deaths	Expected rate	1.5/1000 p-y		1.6/1000 p-y		1.6/1000 p-y	
	Observed rate/1000 p-y (n)	0.5 (1)	2.2 (1)	0.6 (3)	0.4 (1)	0.6 (4)	0.7 (2)
MI	Expected rate	2.5/1000 p-y		2.7/1000 p-y		2.6/1000 p-y	
	Observed rate/1000 p-y (n)	1.1 (2)	2.2 (1)	2.9 (14)	0.4 (1)	2.4 (16)	0.7 (2)
Stroke	Expected rate	2.1/1000 p-y		2.4/1000 p-y		2.3/1000 p-y	
	Observed rate/1000 p-y (n)	0	0	2.2 (11)	1.6 (4)	1.6 (11)	1.4 (4)

MACE = Major Adverse Cardiovascular Events; MI = myocardial infarction; p-y = person-year.
NOTE: All MACE outcomes occurred in white and black subjects. There were no MACE outcomes in HBV-10. Population-based estimates were based on incidence of events in whites and blacks in the US: 1) Vital Statistics surveillance for deaths [23]; 2) the Atherosclerosis Risk in Communities Surveillance for myocardial infarction; and 3) the Greater Cincinnati/Northern Kentucky Stroke Study for strokes.[92,64]

1.8.1.5.6 Possible Immunologic Etiologies of Major Adverse Cardiovascular Events

Finally we asked, what possible vaccine-associated etiologies could explain the MACE outcomes in subjects at risk for cardiovascular events?

We identified 4 mechanisms by which TLR9 stimulation or HEPLISAV-B immunization might theoretically cause myocardial infarction: 1) mimicking an acute systemic infection (that increases risk of myocardial infarction; 2) vasculitis; 3) myocarditis; and 4) hypercoagulable state (See Section 6.7.11.4.6).

Inflammatory stimuli may trigger acute coronary and cerebrovascular events. Acute respiratory and urinary tract infections have been associated with an increased risk of both myocardial infarction and stroke shortly after diagnosis. The increased incidence of myocardial infarction is greatest in the first 1 to 3 days after infection is diagnosed (up to 4.95-fold higher), declines substantially by 28 days, and approaches baseline values between 28 and 91 days.[26, 27, 123, 107, 112, 113] Importantly, no increased risk has been observed following influenza, tetanus, or pneumococcal vaccination. In the PSP comparing HEPLISAV-B and Engerix-B, however, there was no imbalance between treatment groups in the occurrence of myocardial infarction or MACE outcomes during these time periods following vaccine administration. The imbalance in events emerged gradually and at later times, beginning after 100 days (72 days after last HEPLISAV-B administration). The risk of stroke is likewise elevated after infection[113], however no imbalance in stroke events was observed between vaccine groups in HBV-23 or in the PSP.

Cardiologist review of clinical synopses and catheterization data that were available for all but one of the confirmed acute myocardial infarction events excluded inflammatory vasculitides and myocarditis. In all cases, typical clinical presentations were reported for acute myocardial infarction and were accompanied by catheterization data reporting typical culprit lesions in the setting of advanced obstructive coronary artery disease.

Evaluation of clinical events that may reflect a hypercoagulable state for arterial and venous thrombosis and embolism revealed no imbalance beyond myocardial infarction. Stroke, deep vein thrombosis, and pulmonary embolism were infrequent and were balanced between groups in HBV-23 and in the overall PSP analysis. In the HEPLISAV-B group, 0.22% (n = 21) of subjects had thrombotic/thromboembolic events compared with 0.26% (n = 10) of subjects in the Engerix-B group.

The role of inflammation in the development of atherosclerotic lesions is now well established. However, substantial evidence suggests that lesion development is a gradual process requiring chronic inflammation occurring over decades, rather than a process triggered by a transient inflammatory insult.[48, 74, 76] The possibility that 2 local injections of the 1018 adjuvant stimulate chronic, systemic inflammation lacks plausibility for multiple reasons. 1018 is removed rapidly from circulation and is degraded with an estimated half-life of 3 to 4 days. The direct, systemically measurable effects of 1018 on the immune system return to baseline within 7 days

after injection (Section 2.0). C-reactive protein (CRP) is a sensitive and widely-used marker of systemic inflammation; elevated CRP is associated with an increased risk of myocardial infarction.[29, 100] In HBV-10, 3.3% of 1620 subjects who received HEPLISAV-B and 5.0% of 533 subjects who received Engerix-B had normal CRP results at baseline and elevated at 8 weeks post-second injection. These data do not indicate a pattern of increased serum CRP resulting from either HEPLISAV-B or Engerix-B treatment.

With regard to the potential induction of an autoimmune condition, there are few autoimmune causes of myocardial infarction, except in persons with specific systemic autoimmune disease, such as lupus erythematosus. The primary autoimmune considerations are coronary vasculitis and antiphospholipid syndrome. By review of cardiac catheterization data, there was no evidence for coronary vasculitis. There was also no evidence of antiphospholipid syndrome or other hypercoagulable conditions as summarized above. In HBV-23, a laboratory substudy assessing antiphospholipid antibodies was conducted in a random subset of patients. A transient increase in the nonspecific anti-beta2 glycoprotein 1 IgM was observed in the HEPLISAV-B group and compared with the Engerix-B group but in no subject was it associated with a thrombotic event or antiphospholipid syndrome. There was no difference between treatment groups in anticardiolipin antibodies, anti-beta2 glycoprotein 1 IgG, or lupus anticoagulant (Section 6.7.8.4).

1.8.1.5.7 Conclusions Regarding Myocardial Infarction and Major Adverse Cardiovascular Events

From these assessments we conclude that myocardial infarctions as well as MACE:

- Were unexpected based on nonclinical data (See Section 6.7.11.4.6);
- Occurred in subjects in whom such events would be expected based on their high prevalence of baseline cardiovascular risk factors. Myocardial infarctions occurred in patients with prevalent, often multi-vessel, obstructive coronary disease, and in most cases, with a clear culprit lesion;
- Occurred randomly throughout the duration of the trials with no temporal relationship to time of vaccine administration;
- In the HEPLISAV-B group occurred at incidence rates similar to or lower than expected and in the Engerix-B group lower than expected; and
- Were not related to a persistent inflammatory state or an autoimmune condition causing myocardial infarction including coronary vasculitis or antiphospholipid syndrome.

Therefore, the events appear to represent background incidence of acute myocardial infarctions and MACE in an at-risk adult patient population.

If the events are background and we ruled out possible vaccine-induced immune etiologies, *why was there an imbalance between the groups*? Only 1 myocardial infarction occurred in 2781 subjects who received Engerix-B in HBV-23. In contrast, 6 such events would have been expected based on estimated age-, sex-, and race-adjusted background rates (Table 6-29). This unexpectedly low number of events in the Engerix-B group was observed only in HBV-23 in which subjects in both treatment groups carried a similar and substantial level of cardiovascular risk.

Such an imbalance in a preferred term is expected in analyses of very small numbers of subjects reporting events, particularly in the context of testing 1405 MAE preferred terms in HBV-23. These very small proportions provide inherently unreliable estimates that may not be reproducible upon repeated testing.

Due to the absence of any supportive evidence or scientific rationale for the numerical imbalance to be associated with vaccine, the most reasonable conclusion is the imbalance is due to random variation. Our systematic evaluation of the myocardial infarction and extended cardiovascular event data cannot prove the imbalance in myocardial infarctions is due to random variation. Therefore, a large observational post-marketing surveillance study is proposed to rapidly confirm the lack of association of HEPLISAV-B with myocardial infarction and cardiovascular outcomes (See Section 7.0).

1.8.1.6 Anaphylaxis

No vaccine-associated events of anaphylaxis were observed (See Section 6.7.12).

1.8.2 Overall Summary of Safety

In summary, the safety data demonstrate that HEPLISAV-B was well tolerated with an overall safety profile similar to that of Engerix-B.

1.9 Proposed Post-Marketing Surveillance Study

To confirm the safety of HEPLISAV-B in medical practice as quickly as possible, a large observational post-marketing vaccine surveillance study is the most feasible and appropriate design (See Section 7.0). The post-marketing study in adults 18 years of age and older will determine the incidence of cardiovascular, immune-mediated, and other medical events. Dynavax proposes this observational electronic medical record review be conducted in an integrated health system/health maintenance organization (HMO) setting such as Kaiser Permanente Northern California (KPNC) and another Kaiser site. They have extensive experience in conducting vaccine safety studies. The study design will be finalized in consultation with FDA.

For the analysis of MACE:

- A comparison of event rates between 20,000 HEPLISAV-B recipients and 20,000 recipients of other hepatitis B vaccines.

- A sample size of 20,000 patients per group will provide > 99% power to rule out a 2-fold increase in the incidence of MACE if the background incidence rate is 6 per 1000 person years.

For the analysis of immune-mediated events:

- A comparison of rates of pre-specified immune-mediated events between 20,000 HEPLISAV-B recipients and 20,000 recipients of other hepatitis B vaccines.

- A sample size of 20,000 patients per group will provide approximately 87% power to detect a 2.5-fold increase in the incidence of immune-mediated diseases using a one-sided test at a level of significance of 0.025 if the background incidence rate is 1 per 1000 person years.

It is anticipated that 20,000 patients will receive HEPLISAV-B and an equivalent number will receive another hepatitis B vaccine within 1 year of first use of HEPLISAV-B if the study is conducted at Kaiser or another similarly sized HMO. An interim analysis of all MACE outcomes as well as all immune-mediated AEs will be reviewed by an independent safety data monitoring committee to ensure that no major adverse safety differences emerge during the conduct of the study. Depending upon the rate of uptake, we estimate the first interim analysis will be conducted 12 months following initiation of the study.

1.10 Benefit/Risk

HEPLISAV-B has a favorable benefit/risk profile for the vaccination of adults 18 years of age or older (See Section 8.0):

- While there may be a perception that hepatitis B is no longer a problem in the US, each year more than 20,000 adults are becoming infected with a recent 20.7% increase in reported cases, and more than 5000 persons are dying. In addition, the number of persons at risk with diabetes is growing each year. The unmet need for a new hepatitis B vaccine for adults is also defined by the limitations of currently approved vaccines: 1) lower rates of seroprotection in adults, particularly in individuals with diabetes mellitus; 2) prolonged time to seroprotection due to the 3 dose, 6 month schedule; and, 3) poor adherence rates in adults.

- Inducing SPRs greater than 90% in all adult populations studied, HEPLISAV-B consistently provides a clinically and statistically significantly higher proportion of adults with seroprotection compared with Engerix-B. In subjects with diabetes the SPR was 90.0% in the HEPLISAV-B group and 65.1% in the Engerix-B group.

- Protection from hepatitis B infection is achieved with 2 doses over 1 month.

- Completing the 3-dose schedule of Engerix-B over 6 months is challenging for some adults who are at very high risk for HBV infection. Extrapolating from data from 18 to 39 year-old men who have sex with men (MSM) attending an sexually transmitted disease (STD) clinic,[46] the difference seroprotection between HEPLISAV-B and Engerix-B increases nearly 3-fold, from 11.0% in men who receive all 3 doses of vaccine in clinical trials to 28.9% in projected actual use.

- A particular benefit of HEPLISAV-B over Engerix-B is likely in persons with diabetes mellitus; notably, a population in whom the small number of myocardial infarction events was balanced between the HEPLISAV-B and Engerix-B groups. Poor implementation of the ACIP recommendation for routine hepatitis B vaccination of individuals with diabetes is aggravated by the limitations of Engerix-B. We modeled the use of HEPLISAV-B instead of using Engerix-B in an extrapolation of a hypothetical, 1-time vaccination program of adults diagnosed with diabetes (528,047 individuals) described by CDC[109] to 5,000,000 persons with diabetes, approximately half of those ≤ age 60 years who are unvaccinated (Table 8-1). Use of HEPLISAV-B would be expected to lead to a further 72% decrease in hepatitis-B related health outcomes compared with Engerix-B.

- Overall, HEPLISAV-B was well tolerated. A comprehensive analysis of immune-mediated events showed similar rates in the HEPLISAV-B and Engerix-B groups. Other AEs were balanced between treatment groups with the exception of the single preferred term of *acute myocardial infarction*, in which there was an unexpected imbalance for HEPLISAV-B only in HBV-23. A comprehensive evaluation found:

    - Myocardial infarctions and MACE outcomes occurred in subjects in whom they would be expected at rates at or below background;

    - No evidence for theoretically plausible vaccine-induced immune etiologies of the events;

    - The most reasonable conclusion is the numerical imbalance is likely due to random variation in small numbers of events; and

    - A large, observational, post-marketing surveillance study is proposed as the most feasible and appropriate design to confirm the safety of HEPLISAV-B with respect to MACE and immune-mediated conditions.

Although current hepatitis B vaccines have addressed a medical need in infants and adolescents, there remains a large unmet need in adults. A 2-dose hepatitis B vaccine with an acceptable safety profile should provide improved seroprotection and a significant public health benefit to adults 18 years of age or older.

2.0 UNMET NEED

Summary of Unmet Need

Hepatitis B is a serious infectious disease with significant morbidity and mortality

- Once infected, 5% to 20% of adults and 45% to 59% of older adults will develop a chronic infection
- 800,000 to 2.2 million people in the US are living with chronic HBV infection, of which 5000 die each year with a cost of care estimated $1.2 billion in 2006 and likely higher today

Hepatitis B vaccination programs

- Recombinant hepatitis B vaccines were developed in the 1980s as a 3 dose series over 6 months
- Since 1982, ACIP recommends routine immunization of all children as well as adults at risk from sexual, percutaneous or occupational exposure
- In 2011 ACIP recommended routine hepatitis B vaccination of all adults with diabetes mellitus < 60 years of age because of the increased incidence of HBV infection and the increased morbidity

Current epidemiology of hepatitis B in the United States

- Since 2000, steady decreases in new HBV infections in 0-19 and 20-29 year olds owing to successful childhood immunization, but rates in adults aged 30-39, 40-49, and 50-59 are trending upwards
- 95% of the estimated 21,900 annual new cases of HBV infection in the US occur in adults
- 20.7% increase in reports of acute hepatitis B illness nationwide from 2014 to 2015
- 114% increase in acute hepatitis B in the Appalachian region related to the escalating opioid epidemic and related injection drug use

Limitations of Current Hepatitis B Vaccines

- Reduced Seroprotection – rates in adults with a complete regimen are lower than in children. The proportion of adults protected by 3 doses of the current vaccines drops off notably after 40 years of age and is less than 75% by age 60. Rates are also reduced in men, smokers, obese people and those with diabetes.
- Delayed Seroprotection – 50% to 80% of persons do not achieve seroprotection until after the third dose at 6 months leaving unprotected individuals at risk of imminent exposure to HBV such as health care workers, injection-drug users, and travelers
- Difficulty with Adherence to the Current 3-dose Vaccination Regimen in Adults – Vaccine Safety Datalink data show only 54% received all 3 doses within 1 year and only 43% of MSM at an STD clinic received all 3 doses of a vaccine even when administered on an accelerated 0, 1, 4 month schedule

2.1 Hepatitis B Virus Infection and Recommendations for Vaccination

HBV infection is a serious infectious disease that can result in significant morbidity and mortality. After infection, 5% to 20% of adults and 45% to 59% of older adults will develop chronic hepatitis B infection;[66, 101] and up to 40% of chronically infected individuals will develop cirrhosis, liver failure, or hepatocellular carcinoma. Once infected, adults 40 years of age or older with symptomatic, acute HBV infection have higher mortality than younger persons with a case fatality rate of 1.6% to 4.4%.[30] In the US, an estimated 4.3% to 5.6% of individuals have been infected with HBV, and 800,000 to 2.2 million individuals are living with chronic HBV infection.[30, 56, 69] An estimated 5000 individuals in the US die from chronic liver disease due to HBV each year.[17] The cost of care for individuals with chronic HBV infection was an estimated $1.2 billion in 2006 and is likely to be higher today.[63]

The first plasma-derived hepatitis B vaccine was approved in 1981, and recombinant hepatitis B vaccines were approved in the 1980s (Recombivax,® Merck; Engerix-B, GlaxoSmithKline). These vaccines contain a recombinant HBsAg like that in HEPLISAV-B, are adjuvanted with an aluminum salt, and are administered as a series of 3 doses over 6 months. Hepatitis B vaccines have been recommended by ACIP since 1982 for persons with risk factors for exposure to HBV, including: (1) persons at risk through sexual exposure, including MSM, persons with more than 1 sex partner in the previous 6 months, and persons with an STD; (2) persons at risk through percutaneous or mucosal exposure including injection-drug users, patients with chronic kidney disease, and health-care workers and others who could be exposed to blood or body fluids at work; and (3) other persons who are at high risk for HBV infection such as travelers to countries with a high prevalence of HBV infection and those with hepatitis C or human immunodeficiency virus infection (Appendix 1).[14, 20, 109] In 2011, the ACIP expanded its recommendations to include routine hepatitis B vaccination of all adults with diabetes mellitus < 60 years of age because of the increased incidence of HBV infection and the increased morbidity due to HBV in persons with diabetes.[103, 109]

2.2 Hepatitis B Transmission

2.2.1 Epidemiology

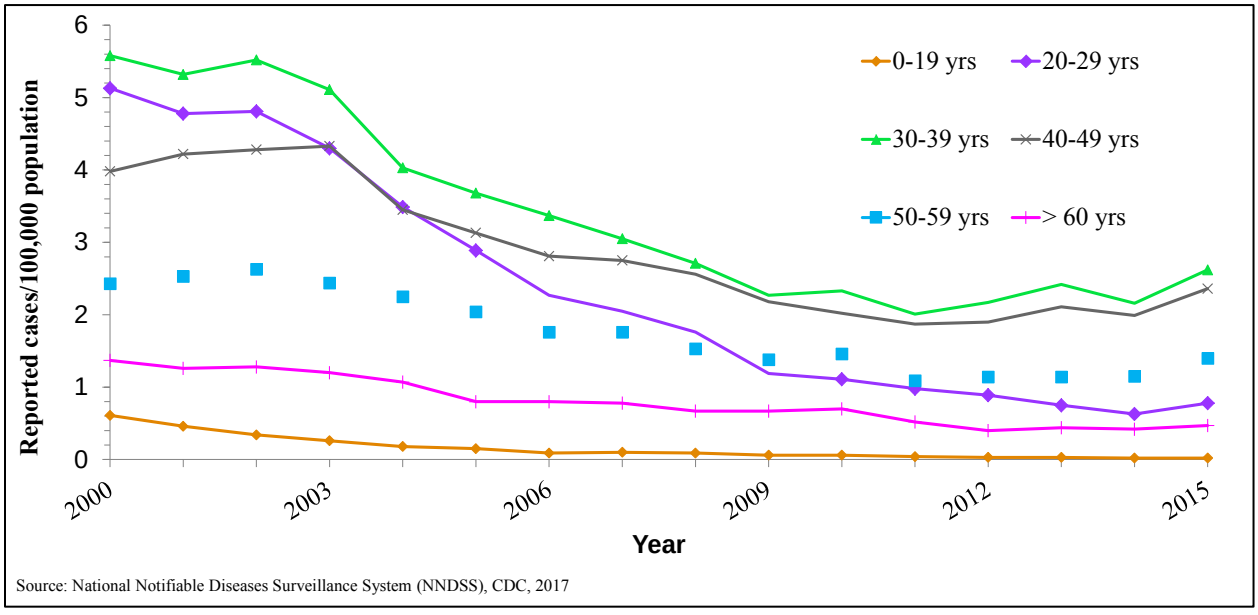
In 1991, ACIP recommended including hepatitis B vaccine in universal vaccinations for infants and catch-up use in adolescents, and reiterated the need for hepatitis B vaccination for adults with risk factors for HBV infection.[19] Over the ensuing 2 decades, the incidence of HBV infection in the US decreased 82% from 1990 through 2007.[30, 81]

The universal childhood hepatitis B immunization program in the US has been very successful due to a well-established immunization infrastructure and that nearly all infants and children develop a seroprotective antibody response to hepatitis B vaccine.[44] Nonetheless in adults, HBV infection and its consequences continue to be an important public health problem. Approximately 95% of the estimated 21,900 (95% CI: 12,500, 53,600) annual new cases of HBV illness in the US occur in adults who did not receive vaccine in childhood vaccination programs.

The most recent CDC surveillance data show an increase of 20.7% in reports of acute hepatitis B from 2014 to 2015.[22] According to the most recent CDC estimates, the annual incidence of HBV infection is highest in men 30 to 45 years of age (38.9 per 100,000 population). Among racial groups, it is highest in blacks (17.6 per 100,000 population) and lowest among Asian/Pacific Islanders (3.3 per 100,000 population). There is a 2-fold increased risk for persons with diabetes mellitus (18.9 per 100,000 population).[16, 30]

Figure 2-1 presents the reported rates of new acute cases of hepatitis B by age and year in the United States since 2000. CDC acknowledges that national public health reporting of acute cases of hepatitis B underestimates new infections when compared with datasets comprising more systematic surveillance. The success of the infant/childhood/adolescent hepatitis B vaccination program is shown in the 0 to 19 year age group. The age group 20 to 29 years shows a progressive reduction in incidence over time, thought to be a consequence of well-immunized adolescents progressively aging. In contrast, previously stable rates in the age groups 30 to 39, 40 to 49, and 50 to 59 years have recently trended upwards. At least some of the recent increase in HBV transmission is likely due to the increase in the misuse of prescription opioids and associated intravenous heroin use among persons who inject drugs. In Kentucky, Tennessee, and West Virginia in the Appalachian region, acute hepatitis B increased 114% from 2006-2013.[24]

Figure 2-1: Annual Incidence of Acute Hepatitis B Reported to CDC, by Age Group — United States, 2000–2015



2.2.2 Healthcare-associated Outbreaks of HBV

Healthcare-associated outbreaks of HBV remain a problem in the US. Ninety-three percent (93%) of healthcare-associated outbreaks in 2008 to 2015 reported to CDC were in non-hospital settings, such as skilled nursing facilities or assisted living facilities. There were 23 outbreaks

reported to CDC, with 175 outbreak-associated acute HBV cases, and more than 10,700 persons notified for screening.[18] Fourteen (82%) of 17 reported outbreaks occurred in persons with diabetes because of misuse of devices for monitoring blood glucose.

2.3 Unmet Medical Need for an Improved Hepatitis B Vaccine

Most adults today did not receive hepatitis B vaccination as an infant or adolescent. The challenge of vaccinating adults against HBV includes 3 major obstacles. First, adults at risk of HBV infection must be accessed and identified through questioning of occupational and sensitive behavioral risk factors. Secondly, the individual must then accept and adhere to the 3-dose 6-month vaccination schedule. And finally, the vaccine must provide high rates of seroprotection. The first obstacle continues to be a challenge to health care providers and public health authorities. The last 2 obstacles can be overcome with a hepatitis B vaccine improved by fewer doses over a shorter administration schedule and inducing a higher rate of seroprotection.

2.3.1 Vaccine Coverage in Adults at Risk of HBV Infection

Successfully vaccinating adults at high risk for HBV is an ongoing challenge due in part to the lack of systematic access to persons at high risk for infection and lack of formal programs for adult immunization. In a 2011 study, only 34.7% of adults in groups at high risk for hepatitis B had ever received a single dose of hepatitis B vaccine.[1] Of note, the US Department of Health and Human Services recently published a "National Viral Hepatitis Action Plan 2017-2020" with a goal to prevent new viral hepatitis infections including a strategy to achieve universal vaccination of adults at risk of HBV infection.[43]

In 2010, an estimated 77.2% of 14 million individuals with diabetes 59 years of age and younger (10.8 million individuals) had not received 3 doses of HBV vaccine.[15] In 2015, an estimated 75.6% of such persons had not been vaccinated.[126]

2.3.2 Limitations of Current Hepatitis B Vaccines

Even when the currently approved hepatitis B vaccines (Engerix-B and Recombivax) are administered, they have limitations that reduce their effectiveness that include:

- Reduced rates of seroprotection from administration of a complete vaccine regimen in adults compared with children, [43] including in populations with known reduced rates of seroprotection: individuals with diabetes mellitus, men, older adults, obese individuals, and smokers,[3, 5, 34, 39, 104, 106, 118, 122, 124, 125, 127-129]
- Prolonged time (> 6 months) before achievement of seroprotection, because fewer than 50% of individuals are protected after receiving 2 doses, and
- Poor adherence to a complete 3-dose vaccination schedule over 6 months. [46, 96]

Such limitations will make it difficult to achieve the March 28, 2017, call by the National Academies of Sciences, Engineering, and Medicine for eliminating viral hepatitis as a public health problem in the United States.[95]

2.3.2.1 Reduced Seroprotection Rates in Adults

Vaccines against HBV induce antibodies to hepatitis B surface antigen (anti-HBs). An anti-HBs level greater than or equal to 10 mIU/mL has been shown to correlate with protection against HBV infection.[20, 21, 40, 58, 116] Healthy individuals who develop anti-HBs concentrations greater than or equal to 10 mIU/mL after vaccination are considered to be protected against symptomatic HBV infection for decades even if their anti-HBs concentrations decline to less than 10 mIU/mL.[73, 83, 87] Thus, the HEPLISAV-B clinical development program, like previous clinical development programs for hepatitis B vaccines,[88, 114] has used seroprotection, defined as serum concentrations of anti-HBs greater than or equal to 10 mIU/mL, as the indicator of clinical efficacy and the basis for regulatory approval. Immunogenicity of hepatitis B vaccines is typically expressed in terms of the seroprotection rate (SPR), or the proportion of individuals achieving an anti-HBs concentration greater than or equal to 10 mIU/mL after vaccination.[58, 78]

Many adults do not respond adequately to the currently licensed hepatitis B vaccines. While 99% to 100% of children develop seroprotective antibody levels, the proportion of adults who are protected by 3 doses of the currently licensed vaccines is less than in children, and is particularly notable after 40 years of age. By age 60 years seroprotection develops in less than 75% of those vaccinated.[3]

One important challenge is that some populations with high HBV incidence rates also have reduced seroprotection rates. For example, men have a higher incidence of HBV infection than women and have reduced immune responses to currently licensed hepatitis B vaccines.[5, 16, 106, 125, 129] Individuals with diabetes mellitus also have an increased risk of contracting HBV infection and also have reduced rates of seroprotection.

2.3.2.2 Delayed Seroprotection

In addition to the variable antibody response in many adults with the currently licensed vaccines, 50% to 80% of persons do not achieve seroprotection until after the third dose at 6 months. Because of this lengthy time required for full immunization, most individuals remain at risk for HBV infection until after receiving the third dose.[60, 82] This prolonged time period needed to achieve seroprotection can be a particular issue for individuals at risk of imminent exposure to HBV such as health care workers, injection-drug users, or travelers.

2.3.2.3 Difficulty with Adherence to the Current 3-Dose Vaccination Regimen in Adults

Not all individuals receive the complete 3-dose regimen, leaving many susceptible to HBV infection. In a large retrospective Vaccine Safety Datalink study of more than 88,000 adult hepatitis B vaccine recipients, only 54% received all 3 doses within 1 year and only 64% of those vaccinated received all 3 doses of vaccine during an 8-year study period.[96] In Italy, passive surveillance of acute hepatitis B cases reported that 3.2% of new infections occurred in persons who had received vaccine, 81.9% of whom had not completed their vaccine regimen.[119] Adherence is even more challenging in high risk populations. For example, in a study of an STD clinic population of MSM, only 43% of the men received all 3 doses of a vaccine even when administered on an accelerated 0, 1, 4 month schedule.[46]

3.0 SCIENTIFIC RATIONALE

Summary of Scientific Rationale

HEPLISAV-B: recombinant HBsAg antigen plus 1018 adjuvant

- HBsAg is a yeast recombinant product similar to recombinant HBsAg in Engerix-B and Recombivax - intended to generate protective antibodies to the conserved "a" determinant of the S protein
- Principal difference is the 1018 adjuvant in HEPLISAV-B vs. the alum adjuvant in current vaccines

1018 Adjuvant: Therapeutic Rationale

- 1018 is highly specific and provides more uniform enhancement of antibody responses to HBsAg, particularly in populations with reduced seroprotection rates to the licensed, alum-adjuvanted vaccines
- 1018 helps achieve high rates of seroprotection with 2, rather than 3 injections

1018 Adjuvant: Mechanism of Action

- 1018 is a synthetic 22-base DNA oligonucleotide with immunostimulatory CpG motifs
  - Activates single innate immune receptor, TLR9, mimicking the natural ligand microbial DNA
  - TLR9 has limited cellular distribution; primary targets for adjuvant activity of 1018 are plasmacytoid dendritic cells
- Alum adjuvants, in contrast, activate multiple inflammatory pathways in a broad range of cell types by inducing membrane disruption and cell stress - with no specific cellular receptor for alum
- The actions of 1018 are transient and localized to the injection site and draining lymph nodes
  - 1018 is detected systemically 1-4 hours after injection and substantially below active levels
  - Biological responses to HEPLISAV-B injection peak 1 day after injection and return to baseline within 7 days
- Long-lived effects of 1018 action are components of the adaptive immune response
  - These include antigen-specific antibodies and T- and B-cell memory
    - Long-lived adaptive responses do not require the presence of 1018 or TLR9 signaling

1018 Adjuvant: Toxicity

- Repeat-dose toxicity study of HBsAg + 1018 in mice produced expected findings, primarily reflecting TLR9-mediated immune stimulation
  - Principal affected organs were the hematopoietic system, spleen, liver, and injection-site
  - Complete resolution of findings after recovery period.
- Toxicity of 1018 in cynomolgus monkeys studies at doses up to a 270-fold excess weekly for 8 weeks.
  - Monkeys are the most relevant species for toxicity evaluation due to the strong similarities with humans in TLR9 cellular distribution and biological responses to CpG-ODN
  - Dose-dependent immune activation observed in the liver and spleen, both major target organs for

ODN uptake, were observed at the 54- and 270-fold excess dose given SQ for 8 weeks
  - Findings were completely or substantially resolved after 4 weeks of non-dosing recovery
- Cardiac toxicity
  - The heart is not a target organ for oligonucleotide accumulation
  - Repeat-dose studies with 1018 in mice, rats and monkeys, showing no treatment-related findings of heart pathology with >200-fold excess dosing regimens up to 8-weeks duration

HEPLISAV-B is composed of 20 mcg of recombinant HBsAg and 3 mg of 1018 adjuvant as a sterile, preservative-free, phosphate buffered aqueous 0.5 mL mixture for IM injection. The HBsAg in HEPLISAV-B is a 22-nm particle that is produced in *Hansenula polymorpha* yeast cells that contain the hepatitis B virus S protein. This particle resembles the noninfectious particles secreted by human hepatocytes during natural HBV infection[121] and is similar to the yeast recombinant HBsAg in Engerix-B and Recombivax. The desired biological activity of HBsAg in both HEPLISAV-B and the 2 licensed vaccines is to generate protective antibodies to the "a" determinant of the S protein. The adjuvant, 1018, is a synthetic oligonucleotide containing stimulatory CpG motifs recognized by TLR9. This contrasts with the alum adjuvant used in Engerix-B and Recombivax. The rationale for using 1018 instead of alum as the adjuvant is to:

- provide more uniform enhancement of antibody responses to HBsAg, particularly in populations with reduced seroprotection rates to the licensed, alum-adjuvanted vaccines, and
- achieve high rates of seroprotection with 2, rather than 3 injections.

3.1 Background

It has long been recognized that production of antibody responses to protein antigens requires recognition of the intact antigen by B cells and recognition by helper T (Th) cells of peptide fragments of the antigen displayed on antigen-presenting cells. Over the past 20 years it has become clear that a third type of signal is required for optimal antibody responses, activation of antigen-presenting cells by engagement of the innate immune system.[57] Bacteria and viruses express many molecules that are ligands for the broadly-specific pattern recognition receptors (PRR) that activate innate immune responses in antigen-presenting cells such as macrophages and dendritic cells. While some vaccines can efficiently activate these PRR, especially vaccines based on whole bacteria or viruses, many vaccines require addition of an adjuvant to fully engage innate responses and optimize protective antibody responses.

One of the best studied PRR families is the TLR family composed of 10 transmembrane signaling molecules that play a key role in the initiation of innate immune responses and the enhancement of subsequent antigen-specific adaptive immune response.[120] Six of these TLRs are expressed on the cell surface, whereas 4 are expressed in the endosomal compartment of the cell, where pathogens are engulfed and degraded. All endosomal TLRs recognize nucleic acids,

including TLR9 which preferentially recognizes bacterial and viral DNA. The basis for this preferential recognition is the fact that the CpG dinucleotide is substantially under-represented in mammalian DNA relative to viral or bacterial DNA. 1018 is a synthetic 22-base CpG oligonucleotide that specifically activates TLR9 and mimics the innate activation signal of microbial DNA.[52] A number of CpG-ODNs, including 1018 have been evaluated clinically, not only as vaccine adjuvants, but in cancer, viral infections and allergic diseases.[28, 61]

3.2 1018 Adjuvant: Mechanism of Action and Therapeutic Rationale

1018 acts by stimulating a single, well-defined cellular receptor, TLR9.[12, 52] TLR9 is a transmembrane receptor present in the endosomal membrane, with the DNA-binding domain exposed to the lumen of the endosomes.[62] The distribution of cell types that express TLR9 is more restricted than for most other TLR, especially in humans and non-human primates.[12] In humans, TLR9 expression by antigen-presenting cells is limited to plasmacytoid dendritic cells (pDCs) and memory B cells.[53, 59] In mice, TLR9 stimulation of dendritic cells, but not B cells is essential for the adjuvant activity of 1018, and this is likely true in humans as well.[54]

Stimulation of pDCs by 1018 produces 2 distinct responses. The first is the rapid and transient production of type 1 IFNs.[35] This is followed by maturation of pDCs into efficient antigen-presenting cells, with increased expression of CD40, CD86, MHC-I, and MHC-II,[49] and production of cytokines, especially interleukin (IL)-12, which guide the differentiation of naïve T cells.[2, 35] 1018 induces relatively modest IFN responses compared to many other CpG-ODN sequences, however it is a very efficient inducer of pDC maturation. [35, 79]

In contrast, alum, the adjuvant used in the currently licensed hepatitis B vaccines, does not bind to a specific PRR. Alum causes membrane destabilization, leading to activation of multiple pathways of the innate response to cellular damage and stress, including the NALP3 inflammasome.[37, 67, 111] In contrast to TLR9, NALP3 is also expressed in a wide range of other immune and nonimmune cells, including T cells, neutrophils, macrophages, endothelial cells, and epithelial cells.[7, 38, 72, 84] The role of specific cell types and signaling pathways in the adjuvant activity of alum has not been clearly defined.

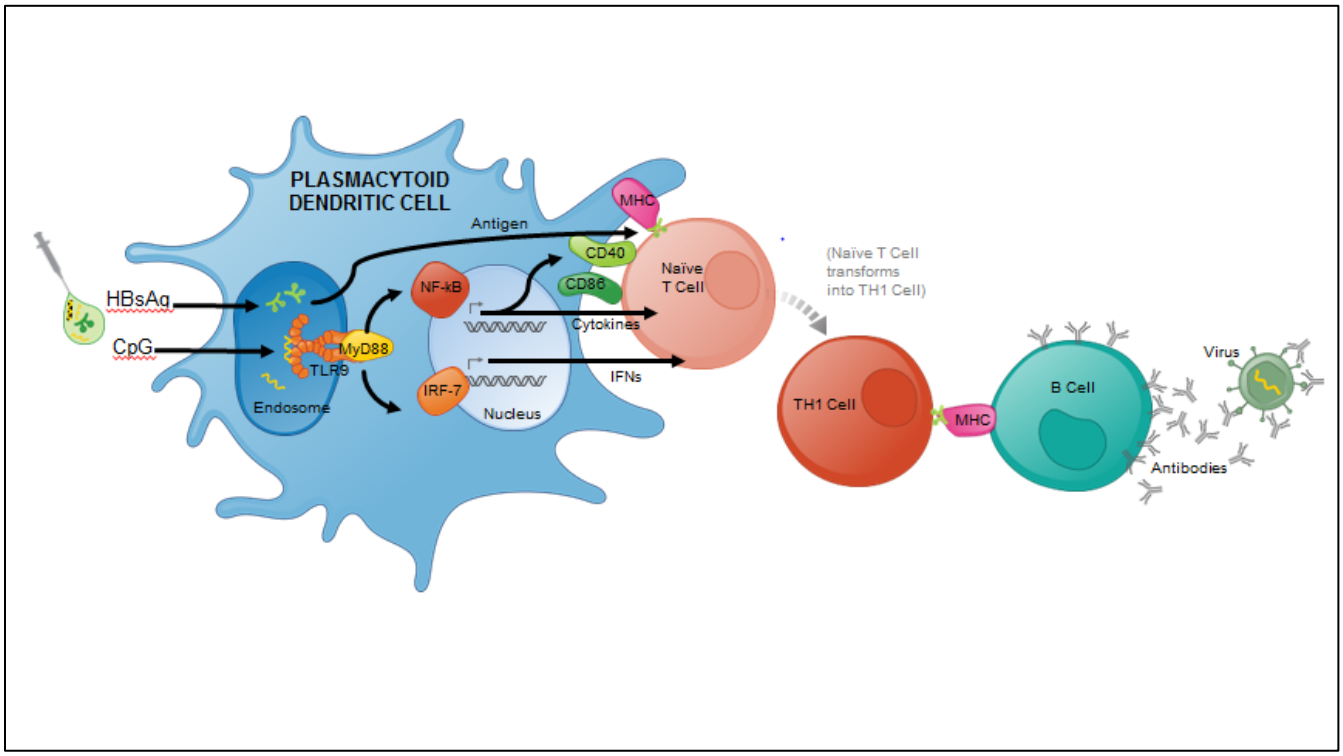
1018 co-administered with HBsAg as HEPLISAV-B, is thought to have the following actions:

- In the first 1 to 2 days, pDCs at the injection site are activated by 1018, take up and process HBsAg in their endosomes and migrate to the draining lymph nodes.
- Activated pDCs present HBsAg peptides, in association with MHC-II to CD4+ T cells, which differentiate into functional helper T cells
- These Th cells, in turn, activate HBsAg-specific B cells, leading to their development into antibody-producing plasma cells that subsequently migrate from the lymph node.

These key steps in the development of antibody responses to HBsAg occur predominantly in the lymph nodes draining the site of injection, where the highest concentrations of both the antigen and 1018 adjuvant occur. These steps summarize the contribution of the transient, adjuvant-

mediated innate response to the subsequent adaptive response composed of antibodies and memory T and B cells. In contrast to innate immune responses, adaptive responses are long-lived and exquisitely specific for the immunizing vaccine antigen. illustrates the proposed mechanism of action for 1018. A portion of the 1018 enters the blood stream, where it is rapidly diluted to concentrations well below those expected to cause stimulation and cannot be detected more than 4 hours after injection. The evidence that stimulation by an injected CpG-ODN is confined to the injection sites and relevant lymph nodes comes from multiple animal studies, but also from a phase 1 clinical study comparing the biological response to a CpG-ODN very similar in activity to 1018. In this study, rapid, dose-dependent IFN and cytokine production was measured when the ODN was given subcutaneously, but no response was observed after intravenous doses over 100-fold greater than the lowest active subcutaneous dose. [70] Based on a large body of work with ODN similar in size and structure to 1018, it is likely that 1018 is removed from circulation rapidly and degraded in the liver and kidney by the nucleases responsible for metabolizing genomic DNA. We have shown ODN structurally similar to 1018 to have a tissue half-life of approximately 3 days.

Figure 3-1: Mechanism of Action for 1018

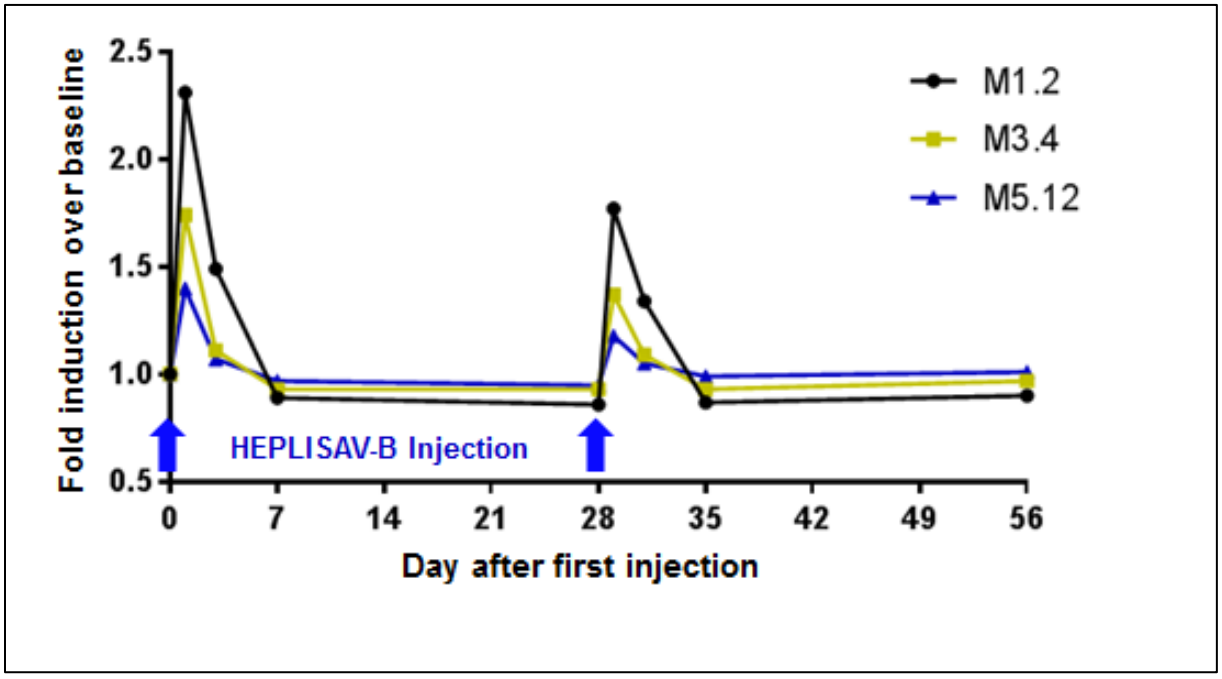


While essentially all of the direct pDC stimulation occurs at sites proximal to the injection, IFNs and cytokines produced in response to 1018 stimulation can distribute systemically and lead to responses in blood cells.[25] Figure 3-2 shows the mean changes in 3 sets of IFN-regulated genes in serial blood samples taken after HEPLISAV-B injection (Study HBV-22). Increases in these IFN-regulated genes reflect changes in IFN production induced by 1018. These IFN-dependent gene expression changes are transient, peaking at day 1 after injection and returning to pre-injection levels by day 7. This response reflects transient local IFN induction by 1018 and the kinetics are consistent with human clinical studies we have performed with 3 other CpG-ODN sequences given by subcutaneous or intrapulmonary routes.

The most comprehensive assessment of potential systemic effects of 1018 comes from a GLP monkey toxicity study using 8 weekly doses 1018 injected subcutaneously at up to 270-fold the HEPLISAV-B dose. The major systemic findings at the highest doses were lymphoid aggregates and signs of inflammation consistent with immune stimulation in the spleen and liver. There were no systemic findings with 8 weekly doses at of 1018 at 0.5 mg/kg, 10-fold greater than used in HEPLISAV-B. Importantly, all of the findings in the highest dose groups were partially or fully resolved after a 3 week recovery period.

In summary, HEPLISAV-B utilizes a highly-specific adjuvant that activates TLR9 in a defined subset of dendritic cells, whereas Engerix-B utilizes alum which induces a broad, less targeted inflammatory response. The response to 1018 mimics a component of the naturally occurring immune response to many viral and bacterial pathogens as well as to some live attenuated vaccines.

Figure 3-2: Kinetics of Response Of Interferon-Regulated Genes Sets in Whole Blood Following HEPLISAV-B Injection (HBV-22 Study Population)



3.3 Nonclinical Toxicology

The safety of the 1018 adjuvant and of HEPLISAV-B has been evaluated at doses well above the proposed recommended human dose. 1018 was tested in rodents at 43- to 200-fold greater than clinical dosage, and HBsAg was tested at 67- to 220-fold greater than clinical dosage on a body weight basis, with the combination administered for up to 4 injections. The primary safety study was conducted in mice, with 3 IM injections of the complete vaccine combination (50 mcg 1018 + 0.5 mcg HBsAg [approximately 43-fold clinical multiple for 1018 and 67-fold clinical multiple for HBsAg on a body weight basis]), did not reveal any effects that would raise concerns about the clinical use of HEPLISAV-B. The results of this study indicate that the combination of 50 mcg (approximately 2 mg/kg) 1018 + HBsAg was well tolerated in mice. Organs affected by high doses of 1018 were the hematopoietic system, spleen, liver, and injection-site. Complete resolution of treatment-related effects was observed at the end of the 3-week recovery period at lower doses (< 2 mg/kg) of 1018. All of the effects observed in this study were consistent with the known TLR9-mediated biological activities of 1018. There were no effects attributable to ODN-class-specific or off-target effects of 1018. Studies in TLR9 deficient mice have shown no measurable activity of high doses of 1018.[12]

A more intensive evaluation of toxicity of the 1018 adjuvant was conducted in cynomolgus monkeys with the 1018 adjuvant alone at doses up to 270-fold greater than clinical dosage administered weekly for 8 weeks. Monkeys are the most relevant species for toxicity evaluation due to the strong similarities with humans in TLR9 cellular distribution and biological responses to CpG-ODN, including 1018. Mice and rats, in contrast, express TLR9 in a broader spectrum of cell types and have mechanistically different and more severe inflammatory responses to CpG-ODN that are not representative of human or monkey responses. [12] In this study, evidence of immune activation in the liver and spleen, both major target organs for ODN uptake, were observed at the 2.5 mg/kg/week and 12.5 mg/kg/wk doses (54 and 270-fold greater than the HEPLISAV-B dose), given subcutaneously for 8 weeks. At the 12.5 mg/kg/week dose evidence of ODN class-specific effects were noted, specifically transient complement activation and impaired coagulation. There were no significant findings at the 0.5 mg/kg/wk dose (10-fold greater than the HEPLISAV-B dose). Importantly, all of the findings in this study were completely or substantially resolved after 4 weeks of non-dosing recovery.

3.3.1 Cardiac Toxicology

Data demonstrate that the heart is not a target organ for oligonucleotide accumulation. The absorption of phosphorothioate oligonucleotides (PS-ODN) into heart muscle is essentially absent following systemic administration of ODN and the heart is not considered a potential target organ for PS-ODN toxicity findings.[50] This is consistent with the observations from repeat-dose studies with 1018 in mice, rats and monkeys, showing no treatment-related findings of heart pathology with dosing regimens of 1018 up to 8-weeks duration at high multiples (> 200-fold) of the clinical dose for HEPLISAV-B. Furthermore, repeat-dose toxicity studies of 3 other CpG-ODN sequences conducted by Dynavax, using subcutaneous or intrapulmonary delivery have failed to show effects on the heart in both rodents and monkeys. Direct uptake of 1018 in the heart has not been measured, but studies with 2 non-CpG ODNs of similar structure demonstrated that levels in the heart are not detectable at doses of 50-100 mg/kg.

4.0 HEPLISAV-B CLINICAL DEVELOPMENT BACKGROUND

Summary of Clinical Development

Key Concepts for Hepatitis B Vaccines

- Seroprotection: antibody response to the HBsAg (anti-HBs) with a level ≥ 10 mIU/mL: recognized as the surrogate of protection, accepted by regulators, and basis of approval of previous hepatitis B vaccines.
- Seroprotection Rate (SPR): proportion of persons who achieve seroprotection
- Peak SPR: highest proportion of persons who have achieved seroprotection.
- Geometric Mean Concentration (GMC): infers durability of antibody protection; with recognized surrogate at 10mIU/ml, GMC is relevant in immunocompromised persons

Overview of Clinical Development Program

- 11 completed clinical trials including 8 supportive and 3 pivotal
- Enrolled 14,238 adults 18 years of age or older (HEPLISAV-B: N = 10,038 subjects; Engerix-B: N = 4200)
- Immunogenicity results are from the pivotal trials HBV-10, HBV-16, and HBV-23.
- Safety results are reported primarily for the 3 pivotal trials; autoantibody data are also presented for supportive clinical trials with different formulations, doses, or regimens

Pivotal Clinical Studies (3) – randomized, active-controlled, observer-blinded multi center

- HBV-10
  - 2415 subjects (HEPLISAV-B: N = 1809; Engerix-B: N = 606) 18 to 55 years of age in Canada and Germany
  - Primary Objective: Noninferiority of HEPLISAV-B SPR at Week 12 to Engerix-B SPR at Week 28
- HBV-16
  - 2452 subjects (HEPLISAV-B: N = 1969; Engerix-B: N = 483) 40 to 70 years of age in United States and Canada
  - Primary Objective: Noninferiority of HEPLISAV-B SPR at Week 12 to Engerix-B SPR at Week 32
  - Prospective surveillance and adjudication for immune-mediated disorders and autoantibody testing.
- HBV-23
  - 8374 subjects (HEPLISAV-B: N = 5592; Engerix-B: N = 2782) 18 to 70 years of age in United States
  - Primary Immunogenicity Objective: Noninferiority of HEPLISAV-B SPR to Engerix-B SPR at Week 28 in subjects with type 2 diabetes mellitus
  - Primary Safety Objective: To evaluate the overall safety of HEPLISAV-B with respect to clinically significant adverse events
  - Prospective surveillance and adjudication for any suspected immune-mediated events and laboratory substudy for antiphospholipid antibodies

4.1 Key Concepts for Hepatitis B Vaccines

The following terms are described to facilitate understanding of the data presented in this Briefing Document:

- **Seroprotection:** seroprotection is defined as an antibody response to the HBsAg (anti-HBs) in the vaccine with a level ≥ 10 mIU/ml. This level of antibody is a validated surrogate of protective efficacy as shown in early efficacy trials, in which serologic evidence of HBV infection was the primary endpoint.[40, 115] This level of antibody is well recognized as the surrogate of protection; is accepted by regulatory authorities; and has been used as the efficacy basis of approval of previous hepatitis B vaccines. If a healthy individual has an anti-HBs ≥ 10 mIU/mL, current data suggest they will be protected from hepatitis B infection through an anamnestic response (immune memory) for decades even if their antibody level drops below 10 mIU/mL.[9, 82] However, for persons with immunosuppression, antibody levels must be maintained at ≥ 10 mIU/mL for protection.[82]

- **Seroprotection Rate (SPR):** SPR is defined as the proportion of persons with seroprotection at a specified time point and is expressed in percent.

- **Peak SPR:** The peak SPR is the time point at which the highest proportion of persons has attained seroprotection. The higher the peak SPR, the greater the number of vaccinated persons who are seroprotected.

- **Geometric Mean Concentration (GMC):** The magnitude of the GMC infers durability of protection. However, GMC for hepatitis B antibody is only meaningful for seroprotection in persons who are immunosuppressed, such as patients with chronic kidney disease because they become susceptible to infection if their antibody levels decrease below 10 mIU/ mL.

4.2 HEPLISAV-B Clinical Development Program

The HEPLISAV-B clinical development program comprises 11 completed clinical trials including 8 supportive trials and 3 pivotal trials (Appendix 2 for trial details). These trials enrolled 14,238 adult subjects 18 years of age or older, including 10,038 subjects who received HEPLISAV-B and 4200 subjects who received the comparator vaccine, Engerix-B (Table 4-1). HBV-10 enrolled 13 subjects 11 to 17 years of age who are not included in this analysis.

Of 10,038 adult subjects who received HEPLISAV-B during the clinical development program, 9365 (93.3%) were in the 3 pivotal trials.

Table 4-1: Number of Adult Subjects Receiving HEPLISAV-B and Engerix-B in the Clinical Development Program

Trials	HEPLISAV-B % (N)	Engerix-B % (N)	Total % (N)
Pivotal[a]	93.3 (9365)	92.1 (3867)	92.9 (13,232)
Supportive[b]	6.7 (673)	7.9 (333)	7.1 (1006)
Total	100 (10,038)	100 (4200)	100 (14,238)

[a] Pivotal trials: HBV-10, HBV-16, and HBV-23.
[b] Supportive trials: HBV0001, HBV-02, HBV-03, HBV-04, HBV-05, HBV-08, HBV-14, and HBV-22.

The dose, schedule, and number of injections of HEPLISAV-B in the pivotal trials were based on the results of the phase 1 and 2 supportive trials. The dose of HEPLISAV-B was first established in HBV0001, a randomized phase 1 dose escalation study of the 1018 adjuvant in healthy subjects in Canada evaluating 0.3, 0.65, 1, or 3 mg of 1018 alone or in combination with 20 mcg of HBsAg on a schedule of 0 and 2 months. This trial demonstrated 3 mg 1018 as the most effective dose to enhance antibodies to HBsAg. Trials HBV-03, HBV-05, and HBV-14 provided confirmatory data that this dose of 1018 induced protective levels of anti-HBs. The number of doses was assessed in HBV-04 which evaluated doses given at 0, 2, and 6 months compared to Engerix-B given at 0, 1, and 6 months in adults 40 to 70 years of age in Asia. This trial demonstrated that 2 doses of HEPLISAV-B in older adults induced high levels of seroprotection. The timing of injections was evaluated in HBV-08, a randomized phase 2 trial in adults 18 to 39 years of age in Canada comparing a 0, 1 month schedule with a 0, 2 month schedule. This study demonstrated that the 0, 1 month schedule induced earlier seroprotection than the 0, 2 month schedule. Because the 0, 1 month schedule was also thought to promote better adherence, this schedule was used for all subsequent trials.

In these supportive trials, HEPLISAV-B consistently demonstrated a safety and tolerability profile similar to Engerix-B, with a post-injection reaction profile of mostly mild to moderate injection site pain within 1 to 2 days after injection, with no clinically significant effects on chemistry, hematology, complement, coagulation, or autoantibodies.

Supportive trials established the dose and schedule of HEPLISAV-B with an acceptable safety profile. The first pivotal trial, HBV-10, was a randomized, active-controlled, observer-blinded, multicenter trial conducted in Canada and Germany in 2415 subjects 18 to 55 years of age (1809 subjects randomized to HEPLISAV-B and 606 to Engerix-B). In HBV-10, a rare autoimmune event of granulomatosis with polyangiitis (also known as Wegener's Granulomatosis) was reported as an SAE considered by the investigator as possibly related to study medication. As a result of this event, the FDA placed a clinical hold on the HEPLISAV-B development program. Dynavax conducted a complete reassessment of HEPLISAV-B safety including autoantibody evaluation, clinical lab evaluation, and evaluation of other AEs that might have been autoimmune. The clinical hold was lifted by the FDA after the assessment showed no additional rare immune-mediated events or evidence that HEPLISAV-B was inducing

autoantibodies. Additional surveillance and evaluation of safety was proposed for the next pivotal trial, HBV-16.

In HBV-16, 2452 subjects (HEPLISAV-B: N = 1969; Engerix-B: N = 483) 40 to 70 years of age in the United States and Canada were randomized. In this trial, additional prospective surveillance for immune-mediated disorders was implemented to include administration of a questionnaire inquiring about recent onset of signs and symptoms of immune-mediated disease to every subject at each clinic visit and testing for autoantibodies. Each potential immune-mediated event was assessed by a local independent physician appropriate for evaluation of the event (eg, rheumatologist, endocrinologist, dermatologist) and then adjudicated by an independent, blinded SEAC. The SEAC was composed of an expert in infectious diseases and vaccines, an immunologist, and a rheumatologist. In addition, an independent DSMB was established to evaluate the overall safety and conduct of the trial. The DSMB reviewed the blinded adjudications of the SEAC and had the ability to unblind safety data by individual or treatment group. The DSMB was composed of an infectious disease expert, a rheumatologist, and a statistician.

In HBV-23, 8374 subjects (HEPLISAV-B: N = 5592; Engerix-B: N = 2782) 18 to 70 years of age in the US were randomized. In this trial, any suspected immune-mediated event was evaluated by a local independent physician appropriate for evaluation of the event (eg, rheumatologist, endocrinologist, dermatologist); an independent SEAC adjudicated each potential immune-mediated event; and an independent DSMB evaluated overall safety. The SEAC and DSMB used in HBV-23 were composed of the same members as the SEAC and DSMB used in HBV-16.

The immunogenicity results presented in this Briefing Document are from the pivotal trials HBV-10, HBV-16, and HBV-23. The safety results are reported primarily for the 3 pivotal trials. Autoantibody data are also presented for supportive clinical trials in which different formulations, doses, or regimens were used.

5.0 IMMUNOGENICITY

Summary of Immunogenicity

Compared with subjects vaccinated with 3 doses of Engerix-B over 6 months, subjects vaccinated with 2 doses of HEPLISAV-B administered over 1 month achieved:

- Noninferior and statistically significantly higher SPRs at the primary endpoints in all 3 pivotal trials. In HBV-23, the point estimate for persons with diabetes in HEPLISAV-B was 90% vs. 65.1% for Engerix-B;
- Statistically significantly higher peak SPRs in all pre-specified populations including subpopulations with reduced seroprotection from currently licensed HBV vaccines (older adults, men, persons with diabetes, obese persons, and smokers);
- Consistent peak SPRs in HEPLISAV-B ranging from 90% to 100% and more variable in Engerix-B ranging from 65% to 94% in all pre-specified populations; and
- Seroprotection 5 months earlier for most subjects.

5.1 Study Designs and Baseline Information for the Pivotal Trials

The demonstration of seroprotection in the 3 pivotal trials relies on head-to-head comparisons between HEPLISAV-B and Engerix-B.

5.1.1 Features Common to the Three Pivotal Trials

The 3 pivotal trials (HBV-10, HBV-16, and HBV-23) were randomized, observer-blinded, active-controlled, parallel-group, multicenter trials to compare immune responses following injection with 2 doses of HEPLISAV-B to 3 doses of Engerix-B. In these trials, HEPLISAV-B was administered at 0 and 4 weeks and a dose of placebo was administered at 24 weeks to maintain the blind. Engerix-B was administered at 0, 4, and 24 weeks. Engerix-B was chosen as the licensed comparator vaccine for these trials because, in adults, it results in the highest immune response,[3] has an acceptable safety profile, and is the most commonly used hepatitis B vaccine in the US. Levels of anti-HBs were determined using a commercially available assay (Ortho® Vitros ECi assay, Ortho Clinical Diagnostics) in a blinded manner in a central laboratory. This assay had been agreed upon by the regulatory agencies for use in the HEPLISAV-B trials.

Eligible subjects in the pivotal trials were adults who were serum negative for HBsAg, anti-HBs, and anti-HBc; had no history of HBV infection; had no prior immunization with any hepatitis B vaccine; had no autoimmune disease; and were not pregnant.

The subjects and the study personnel conducting clinical safety evaluations were blinded to treatment assignment. Study drug was not packaged in a blinded manner. Therefore, designated study site personnel with no other study responsibilities were not blinded so they could prepare and/or administer the study injections. Since the 2 study drugs differed in appearance and volume (Engerix-B: cloudy suspension, 1.0 mL; HEPLISAV-B: clear, 0.5 mL), the subject was instructed to turn their head (or a barrier put in place) at the time of injection so they could not tell which vaccine was administered. Persons preparing or administering vaccine were not involved in any safety assessments.

5.1.1.1 Statistical Methods

All 3 pivotal studies were adequately powered to allow valid comparisons of the immunogenicity of HEPLISAV-B to that of Engerix-B. The primary immunogenicity endpoint was the SPR at a specified study time point. The primary immunogenicity comparison in each study was based on a noninferiority design. A noninferiority margin was based on statistical and clinical considerations of reported SPRs with Engerix-B, potential advantages of HEPLISAV-B, and precedence from prior hepatitis B vaccine trials. This design was accepted by the regulatory agencies. If the lower bound of the 95% confidence interval of the difference in the SPR between HEPLISAV-B and Engerix-B was above -10%, then HEPLISAV-B was considered noninferior to Engerix-B. If the lower bound of the 95% confidence interval of the difference in the SPR between HEPLISAV-B and Engerix-B was above 0, then HEPLISAV-B was considered statistically significantly higher than Engerix-B.

- Study HBV-10

  Approximately 2400 eligible subjects were planned to be randomized in a 3:1 ratio to receive HEPLISAV-B or Engerix-B. The randomization was stratified by age group (11-39 versus 40-55 years). The primary immunogenicity endpoint was the SPR at Week 12 for HEPLISAV-B and the SPR at Week 28 for Engerix-B. Week 12 was chosen as the primary endpoint for HEPLISAV-B to measure early and high seroprotection. Week 28 was chosen for Engerix-B because it is the typical time-point for measuring the full effect of Engerix-B in adults. The planned sample size would ensure the study to have > 90% power to demonstrate noninferiority if the underlying SPR was 90% for HEPLISAV-B and 95% for Engerix-B.

- Study HBV-16

  Approximately 2000 eligible subjects were planned to be randomized in a 4:1 ratio to receive HEPLISAV-B or Engerix-B. The randomization was stratified by age group (40 to 49, 50 to 59, 60 to 70 years). The primary immunogenicity endpoint was the SPR at Week 12 for HEPLISAV-B and the SPR at Week 32 for Engerix-B. The time-points of Week 12 for HEPLISAV-B and Week 32 for Engerix-B were requested by FDA to measure immunogenicity at 8 weeks after the last active dose of vaccine. The planned sample size would ensure the study to have > 90% power to demonstrate noninferiority if the underlying SPR is the same for HEPLISAV-B and Engerix-B ranging from 70% to 90%.

- Study HBV-23

  Approximately 8250 eligible subjects were planned to be randomized in a 2:1 ratio to receive HEPLISAV-B or Engerix-B. The randomization was stratified by site, age group (18 to 39 and 40 to 70 years) and type 2 diabetes mellitus status. A subject with type 2 diabetes mellitus was defined as a subject with a clinical diagnosis of type 2 diabetes mellitus and taking at least an oral or non-insulin injectable antihyperglycemic agents and/or insulin. The primary immunogenicity endpoint was to compare the SPRs at Week 28 between HEPLISAV-B and Engerix-B in subjects with protocol defined type 2 diabetes mellitus. Week 28 was chosen as the time-point because the peak SPR in subjects with diabetes in previous HEPLISAV-B trials was Week 28. At least 413 subjects with type 2 diabetes mellitus were planned to be enrolled for the immunogenicity analysis, which would provide the study > 90% power to demonstrate noninferiority if the underlying SPR is 84% for HEPLISAV-B and 79% for Engerix-B. The total sample size was driven by the safety analysis objective to study infrequent immune-mediated adverse events. For subjects randomized to HEPLISAV-B, it was estimated that approximately 5000 subjects would allow ruling out an incidence of 0.49% or higher with a type 1 error rate of 5% if a particular event of interest was observed in less than 15 (0.3%) subjects. For a very rare event with an incidence of 45 per 100,000, it would be expected to have 90% chance to observe at least 1 such event.

5.1.2 HBV-10

Eligible subjects were 11 through 55 years of age in Germany and Canada. Subjects were followed for 28 weeks after the first injection and returned to the study site at Weeks 0, 4, 8, 12, 24, and 28 to undergo clinical safety evaluations and to have blood drawn for safety laboratory studies and anti-HBs serum concentrations.

A total of 2415 adult subjects were randomized (1809 to HEPLISAV-B and 606 to Engerix-B), and 2334 (96.6%) subjects completed all study visits. Data from 13 subjects younger than 18 years of age are not included as they are not part of the proposed indication.

5.1.3 HBV-16

Eligible subjects were adults 40 through 70 years of age in the US and Canada. Subjects were followed for 52 weeks after the first injection and returned to the study site at Weeks 4, 8, 12, 18, 24, 28, 32, 36, 44, and 52 to undergo clinical safety evaluations and to have blood drawn for safety laboratory studies and anti-HBs serum concentrations.

A total of 2452 subjects were randomized (1969 to HEPLISAV-B and 483 to Engerix-B), and 2269 subjects (92.5%) completed all study visits. One lot of HEPLISAV-B vaccine (lot TDG006) in HBV-16 was manufactured prior to minor changes that were incorporated into the manufacturing process for the intended commercial vaccine. These changes did not affect the specifications of the vaccine. Lot TDG006 was used in a bridging study to compare the

immunogenicity of HEPLISAV-B from the previous manufacturing process to the 3 new consistency lots using processes intended for commercialization. This lot is not included in the immunogenicity analyses but is included in safety analyses, as it contained 1018 adjuvant.

5.1.4 HBV-23

The primary immunogenicity objective for HBV-23 was to demonstrate the noninferiority of the SPR induced by HEPLISAV-B compared with the SPR induced by Engerix-B at Week 28 in subjects with type 2 diabetes mellitus. A secondary immunogenicity objective was to demonstrate the noninferiority of the peak immune response to HEPLISAV-B as measured by the SPR at Week 24 compared to the SPR for Engerix-B at Week 28 in the total population and in the following subgroups: by age, sex, BMI, and smoking status. If noninferiority was established, a further secondary objective was to demonstrate the SPRs in the HEPLISAV-B group were statistically significantly higher than in the Engerix-B group in the pre-specified populations.

Eligible subjects were adults 18 through 70 years of age in the US. Subjects were followed for 56 weeks after the first injection and returned to the study site at Weeks 4, 24, 28, and 56 to undergo clinical safety evaluations. Blood for anti-HBs concentrations was collected at baseline and at Weeks 24 and 28. Subjects also answered questions via the internet about health care encounters at Weeks 8, 40, and 52; those who had conditions that met protocol-defined criteria for a MAE were contacted by telephone to provide the relevant medical information. Subjects from 2 sites (N = 309) had laboratory assessments for hematology, chemistry, renal function, clotting risk factors, and antiphospholipid antibodies.

A total of 8374 subjects were randomized (5592 to HEPLISAV-B and 2782 to Engerix-B), and 7659 subjects (91.5%) completed all study visits. Of the 8374 subjects randomized, 1144 (13.7%) satisfied the protocol-specified definition of type 2 diabetes mellitus and were randomized to either HEPLISAV-B (n = 763; 13.6%) or Engerix-B (n = 381; 13.7%).

5.1.5 Immunogenicity Analysis Populations in the Pivotal Trials

In the comparison of the 2-dose regimen of HEPLISAV-B with the 3-dose regimen of Engerix-B, the Per-Protocol (PP) Population was chosen for the primary endpoint analyses in the individual trials to minimize bias towards HEPLISAV-B. The PP Population was defined prior to unblinding to comprise those subjects who received study treatments within the protocol-defined windows, received all study injections as randomized, had no major protocol deviations that would affect immunogenicity, and had anti-HBs levels obtained within the protocol-defined study visit windows at baseline and at the visits for the primary endpoints. Reasons for exclusion from the PP Population varied somewhat across the trials but were similar between the treatment groups in each trial (Table 5-1).

The mITT Population was used in immunogenicity analyses in support of the PP Population analyses. It comprised all randomized subjects who received at least 1 study injection and had at least 1 post-injection immunogenicity evaluation.

5.1.6 Subject Disposition

Table 5-1 presents subject disposition for all randomized subjects in each pivotal trial.

In HBV-10, HBV-16, and HBV-23, discontinuation rates were low and were comparable for subjects randomized to receive HEPLISAV-B or Engerix-B. The most frequent reasons for discontinuation from the trials were lost to follow-up and consent withdrawn. Across the trials, 92.4% of HEPLISAV-B and 93.2% of Engerix-B subjects completed all study visits (Table 5-1).

Table 5-1: Subject Disposition in HBV-10, HBV-16, and HBV-23 (Randomized Population)

Disposition	HBV-10		HBV-16		HBV-23		Total HEPLISAV-B % (N)[a]	Total Engerix-B % (N)
	HEPLISAV-B % (N)	Engerix-B % (N)	HEPLISAV-B % (N)[a]	Engerix-B % (N)	HEPLISAV-B % (N)	Engerix-B % (N)		
Randomized (N)	1809	606	1441	483	5592	2782	9370	3871
Completed	96.5 (1746)	97.0 (588)	92.6 (1335)	93.4 (451)	91.1 (5092)	92.3 (2567)	92.4 (8656)	93.2 (3606)
Discontinued	3.5 (63)	3.0 (18)	7.4 (106)	6.6 (32)	8.9 (500)	7.7 (215)	7.6 (714)	6.8 (265)
Adverse Event	0.1 (2)	0.3 (2)	0.1 (1)	0	0.1 (4)	0	<0.1 (7)	<0.1 (2)
Subject noncompliance	0.2 (3)	0.3 (2)	0.3 (5)	0.6 (3)	0.1 (7)	<0.1 (1)	0.2 (16)	0.2 (6)
Consent withdrawn	1.0 (18)	0.3 (2)	2.1 (30)	2.5 (12)	1.8 (100)	1.4 (39)	1.7 (163)	1.4 (53)
Lost to follow-up	1.7 (30)	1.7 (10)	3.7 (53)	2.7 (13)	5.7 (319)	5.5 (153)	4.6 (430)	4.5 (176)
Death	0	0	0	0.2 (1)	0.4 (25)	0.3 (7)	0.3 (26)	0.2 (8)
Protocol deviation	0.1 (2)	0	0.2 (3)	0.2 (1)	<0.1 (1)	0	<0.1 (6)	<0.1 (1)
Other	0.4 (8)	0.3 (2)	1.0 (14)	0.4 (2)	0.8 (44)	0.5 (15)	0.7 (66)	0.5 (19)
mITT Population	98.9 (1789)	99.5 (603)	99.0 (1426)	98.6 (476)	94.4 (5278)	94.7 (2635)	96.2 (9014)	95.9 (3714)
PP Population	83.5 (1511)	86.0 (521)	77.8 (1121)	73.1 (353)	81.1 (4537)	82.3 (2289)	NA	NA
Subjects excluded from PP[b]	16.5 (298)	14.0 (85)	22.2 (320)	26.7 (129)	18.9 (1055)	17.7 (493)	-	-
No anti-HBs result at primary endpoint	4.4 (79)	3.1 (19)	2.7 (39)	4.3 (21)	7.7 (431)	6.8 (188)	-	-
Did not receive all study injections	3.0 (54)	2.6 (16)	5.7 (82)	5.4 (26)	6.6 (371)	6.3 (176)	-	-
Taken prohibited medication	0.9 (15)	1.0 (6)	3.7 (53)	4.3 (21)	3.9 (217)	4.1 (113)	-	-
Serum sample collection was outside windows outside 4 weeks (± 7 days) following the third study injection	9.3 (168)	7.9 (48)	5.7 (82)	5.6 (27)	3.4 (190)	3.1 (86)	-	-

Table 5-1: Subject Disposition in HBV-10, HBV-16, and HBV-23 (Randomized Population) (Contd)

Disposition	HBV-10		HBV-16		HBV-23		Total HEPLISAV-B % (N)[a]	Total Engerix-B % (N)
	HEPLISAV-B % (N)	Engerix-B % (N)	HEPLISAV-B % (N)[a]	Engerix-B % (N)	HEPLISAV-B % (N)	Engerix-B % (N)		
Vaccination was given outside window at Week 4	7.0 (126)	5.9 (36)	7.2 (104)	8.3 (40)	2.9 (164)	2.7 (76)	-	-
Did not meet 1 or more enrollment criteria	3.8 (68)	2.6 (16)	1.5 (21)	1.7 (8)	1.2 (67)	1.3 (36)	-	-

mITT = modified Intent to Treat; N = number of subjects in the population; n = number of subjects in the group; PP = Per-Protocol.

[a] Lot TDG006 was a bridging lot to a previous manufacturing process and was therefore not included in immunogenicity analyses. However, it is included in the total population, thus adding the individual study populations will not equal the total populations.

[b] Subjects may be included in more than 1 category; however, not all reasons are listed for every subject.

5.1.7 Demographic and Baseline Characteristics

The demographic and baseline characteristics in the Randomized Populations, including those most likely to affect seroprotection (age, male sex, BMI ≥ 30 kg/m^2, diabetes, and smoking history), were balanced between the HEPLISAV-B and Engerix-B groups in the pivotal trials and were not expected to bias the immunogenicity results (Table 5-2).

Table 5-2: Demographic and Baseline Characteristics in HBV-10, HBV-16, and HBV-23 (Randomized Population)

Trial Subgroup	HBV-10 18 to 55 Years		HBV-16 40 to 70 Years		HBV-23 18 to 70 Years	
	HEPLISAV-B % (N)	Engerix-B % (N)	HEPLISAV-B[a] % (N)	Engerix-B % (N)	HEPLISAV-B % (N)	Engerix-B % (N)
Randomized (N)	1809	606	1441	483	5592	2782
Age (years), % (n)						
18-39	45.2 (818)	45.4 (275)	0	0	20.3 (1135)	20.2 (561)
40-70	54.8 (991)	54.6 (331)	100.0 (1441)	100.0 (483)	79.7 (4457)	79.8 (2221)
Mean (SD)	9.36 (39.9)	9.01 (39.8)	7.79 (54.0)	7.84 (53.8)	11.74 (50.4)	11.68 (50.4)
Range (years)	18.0, 55.0	18.0, 55.0	40.0, 70.0	40.0, 70.0	18.0, 71.0	18.0, 70.0
Sex, % (n)						
Women	52.9 (957)	56.8 (344)	52.3 (753)	50.9 (246)	49.1 (2747)	50.0 (1391)
Men	47.1 (852)	43.2 (262)	47.7 (688)	49.1 (237)	50.9 (2845)	50.0 (1391)
Race, % (n)						
White	93.4 (1690)	91.7 (556)	82.7 (1192)	83.2 (402)	71.0 (3972)	72.1 (2007)
Black	2.2 (39)	3.3 (20)	15.1 (217)	14.1 (68)	26.1 (1462)	25.1 (697)
Asian	2.4 (43)	3.6 (22)	1.0 (14)	0.8 (4)	1.0 (57)	1.4 (38)
Other[b]	2.0 (37)	1.3 (8)	1.2 (18)	1.9 (9)	1.8 (99)	1.4 (40)
Unknown	0	0	0	0	<0.1 (2)	0
Ethnicity, % (n)						
Hispanic/ Latino	2.5 (46)	4.0 (24)	6.1 (88)	6.8 (33)	9.3 (521)	8.6 (239)
Non-Hispanic /Non-Latino	97.5 (1763)	96.0 (582)	93.8 (1351)	93.2 (450)	90.6 (5067)	91.4 (2542)
Unknown	0	0	0.1 (2)	0	<0.1 (4)	<0.1 (1)

Table 5-2: Demographic and Baseline Characteristics in HBV-10, HBV-16, and HBV-23 (Randomized Population) (Contd)

Trial Subgroup	HBV-10 18 to 55 Years		HBV-16 40 to 70 Years		HBV-23 18 to 70 Years	
	HEPLISAV-B % (N)	Engerix-B % (N)	HEPLISAV-B[a] % (N)	Engerix-B % (N)	HEPLISAV-B % (N)	Engerix-B % (N)
Type 2 Diabetes Status, % (n)[c]						
With Type 2 Diabetes	2.3 (41)	1.8 (11)	8.0 (115)	7.0 (34)	13.6 (763)	13.7 (381)
Without Type 2 Diabetes	97.7 (1768)	98.2 (595)	92.0 (1326)	93.0 (449)	86.4 (4829)	86.3 (2401)
BMI (kg/m^2)						
N	1806	605	1438	482	5589	2780
Mean (SD)	5.81 (27.4)	6.18 (27.6)	6.43 (30.0)	6.43 (29.9)	7.54 (31.0)	7.62 (30.7)
Range	15.0, 58.2	16.4, 63.2	14.2, 59.2	18.1, 61.3	12.9, 71.9	14.9, 76.0
BMI Stratum, % (n)						
< 30 kg/m2	74.2 (1343)	72.3 (438)	56.0 (807)	57.3 (277)	51.2 (2861)	53.7 (1494)
≥ 30 kg/m2	25.6 (463)	27.6 (167)	43.8 (631)	42.4 (205)	48.8 (2728)	46.2 (1286)
Unknown	0.2 (3)	0.2 (1)	0.2 (3)	0.2 (1)	<0.1 (3)	<0.1 (2)
Smoker, % (n)[d]						
Yes	36.2 (654)	37.0 (224)	21.7 (312)	24.4 (118)	33.0 (1844)	32.7 (909)
No	63.8 (1155)	63.0 (382)	78.3 (1129)	75.6 (365)	67.0 (3748)	67.3 (1873)

BMI = body mass index; n = number of subjects with characteristic; N = number of subjects in the treatment group; PP = Per-Protocol; SD = standard deviation.

[a] Lot TDG006 not included.

[b] Includes American Indian/Alaska Native, Native Hawaiian or other Pacific Islander, and Other race.

[c] Type 2 diabetes is defined as medical history of type 2 diabetes mellitus and taking at least an oral or non-insulin injectable antihyperglycemic agent and/or insulin.

[d] Implies regular smoking within 1 year before enrollment in the study.

5.2 Immunogenicity Results

5.2.1 Overview of Immunogenicity in the Per-Protocol Population

In the pivotal trials, HEPLISAV-B met the primary immunogenicity objective in each trial, induced statistically significantly higher peak SPRs and statistically significantly higher SPRs at each study visit, and provided earlier seroprotection than Engerix-B.

5.2.2 Primary Endpoint Result

In the 3 pivotal trials, HEPLISAV-B met the primary endpoint of noninferiority and induced a statistically significantly higher SPR compared to that induced by Engerix-B.

Table 5-3 presents the primary immunogenicity analyses for HBV-10 and HBV-16. In both trials, the difference in SPRs (HEPLISAV-B minus Engerix-B) met the prospectively-defined criterion for the primary endpoint of noninferiority (lower limit of the 95% CI greater than -10%). In addition, the SPR in the HEPLISAV-B group was statistically significantly higher than in the Engerix-B group (lower limit of the 95% CI greater than 0%). Results of the mITT analysis were similar to the PP analysis.

Table 5-3: Seroprotection Rates at the Primary Immunogenicity Endpoint in HBV-10 and HBV-16 (Per-Protocol Population)

Trial	HBV-10[a] 18 to 55 Years			HBV-16 40 to 70 Years		
Visit	HEPLISAV-B[b] SPR (%) (95% CI) (N = 1511)	Engerix-B[c] SPR (%) (95% CI) (N = 521)	Difference in SPRs (%) (HEPLISAV-B - Engerix-B) (95% CI)	HEPLISAV-B [b] SPR (%) (95% CI) (N = 1121)	Engerix-B[c] SPR (%) (95% CI) (N = 353)	Difference in SPRs (%) (HEPLISAV-B - Engerix-B) (95% CI)
Week 12[d]/32[e]	NA	NA	NA	90.1 (88.2, 91.8)	70.5 (65.5, 75.2)	19.6[f] (14.7, 24.8)
Week 12[d]/28[e]	95.0 (93.9, 96.1)	81.3 (77.8, 84.6)	13.7[f] (10.4, 17.5)	NA	NA	NA

CI = confidence interval; N = number of subjects in the analysis population in the group; NA = not applicable because Week 28 was not the primary endpoint in HBV-16 and HBV-10 concluded at Week 28; PP = Per-Protocol; SPR = seroprotection rate.
The PP Population for the HEPLISAV-B group in HBV-16 is the Noninferiority PP Population excluding subjects who received Lot TDG006.

[a] Test for statistical significance was not pre-specified in the HBV-10 Statistical Analysis Plan.
[b] Study injections were given at Weeks 0, 4, and 24 (placebo).
[c] Study injections were given at Weeks 0, 4, and 24.
[d] HEPLISAV-B.
[e] Engerix-B.
[f] $p < 0.0000001$.

Table 5-4 presents the primary immunogenicity analysis for subjects with type 2 diabetes in HBV-23. In subjects with type 2 diabetes mellitus, the difference between SPRs (HEPLISAV-B minus Engerix-B) also met the prospectively-defined criterion for the primary endpoint of noninferiority (lower limit of the 95% CI greater than -10%) as well as the secondary objective of a statistically significantly higher SPR (lower limit of the 95% CI greater than 0%).

Table 5-4: SPR in Subjects With Type 2 Diabetes Mellitus at the Primary Immunogenicity Endpoint (Week 28) in HBV-23 (Per-Protocol Population)

HEPLISAV-B [a]			Engerix-B[b]			Difference
N	n	SPR (%) (95% CI)	N	n	SPR (%) (95% CI)	(HEPLISAV-B - Engerix-B) (95% CI)
640	576	90.0 (87.4 - 92.2)	321	209	65.1 (59.6 – 70.3)	24.9 (19.3 - 30.7)[c]

CI = confidence interval; N = number of subjects in the analysis population in the group; n = number of subjects with post-injection anti-HBs ≥ 10 mIU/mL; PP = Per-Protocol; SPR = seroprotection rate.
Note: A subject with type 2 diabetes mellitus was defined as a subject with a clinical diagnosis of type 2 diabetes mellitus and taking at least an oral or non-insulin injectable antihyperglycemic agent and/or insulin.
[a] Study injections were given at Weeks 0, 4, and 24 (placebo).
[b] Study injections were given at Weeks 0, 4, and 24.
[c] $p < 0.0000001$.

A sensitivity analysis for the primary endpoint examined duration of diabetes (< 5 years vs ≥ 5 years), baseline hemoglobin A1c category (< 6.5%, 6.5% - 9.0%, and > 9.0%), number of diabetes complications, metformin use, immunosuppressive medication use, as well as treatment group, age, sex, race, BMI, and smoking history. A stepwise logistic regression found that treatment group, age, BMI, and duration of diabetes significantly affected the level of SPR. The odds ratio for seroprotection between HEPLISAV-B and Engerix-B was 4.946 (95% CI: 3.462, 7.065). Older subjects were less likely than younger subjects to be seroprotected following hepatitis B vaccination, and obese subjects were less likely to be seroprotected than the non-obese subjects. These observations confirm the results from the univariate analysis shown in Table 5-4. Results for the mITT population were similar to the PP population.

5.2.3 Secondary and Exploratory Endpoint Results (Subpopulations in HBV-23)

In HBV-23, HEPLISAV-B met the secondary endpoint of noninferiority and induced a statistically significantly higher peak SPR compared to that induced by Engerix-B in the total HBV-23 population and subpopulations known to have reduced SPRs observed with currently licensed hepatitis B vaccines (older adults, men, obese persons, and smokers). [3, 6, 34, 39, 104, 106, 118, 122, 124, 125, 127-129] HEPLISAV-B also induced higher peak SPRs than Engerix-B in subpopulations known to have higher SPRs with licensed vaccines (young adults, women, non-obese subjects, nonsmokers, and subjects without diabetes mellitus) (Figure 1-2 in the Executive Summary).

In HBV-23, immunogenicity by race was an exploratory endpoint. Table 5-5 compares SPRs by race for HEPLISAV-B at Week 24 and Engerix-B at Week 28. The peak SPR in the HEPLISAV-B group was noninferior and statistically significantly higher than in the Engerix-B group in racial groups except those with small numbers of subjects.

Table 5-5: Comparison of SPR Between HEPLISAV-B at Week 24 and Engerix-B at Week 28 by Race (Per Protocol Population)

Race	HEPLISAV-B[a]		Engerix-B[b]		Difference
	N	SPR (%) (95% CI)	N	SPR (%) (95% CI)	(HEPLISAV-B - Engerix-B) (95% CI)
White	3084	94.4 (93.5, 95.1)	1675	80.6 (78.6, 82.5)	13.8 (11.7, 15.9)
Black or African American	1169	98.1 (97.2, 98.8)	554	82.3 (78.9, 85.4)	15.8 (12.7, 19.3)
Asian	45	95.6 (84.9, 99.5)	29	93.1 (77.2, 99.2)	2.5 (-9.3, 18.2)
Native American	46	95.7 (85.2, 99.5)	20	85.0 (62.1, 96.8)	10.7 (-3.2, -32.4)
Native Hawaiian or Other Pacific Islander	12	100 (73.5, 100)	3	100 (29.2, 100)	0
Other	18	100.0(81.5, 100)	8	87.5 (47.3, 99.7)	12.5 (-7.3, - 47.8)

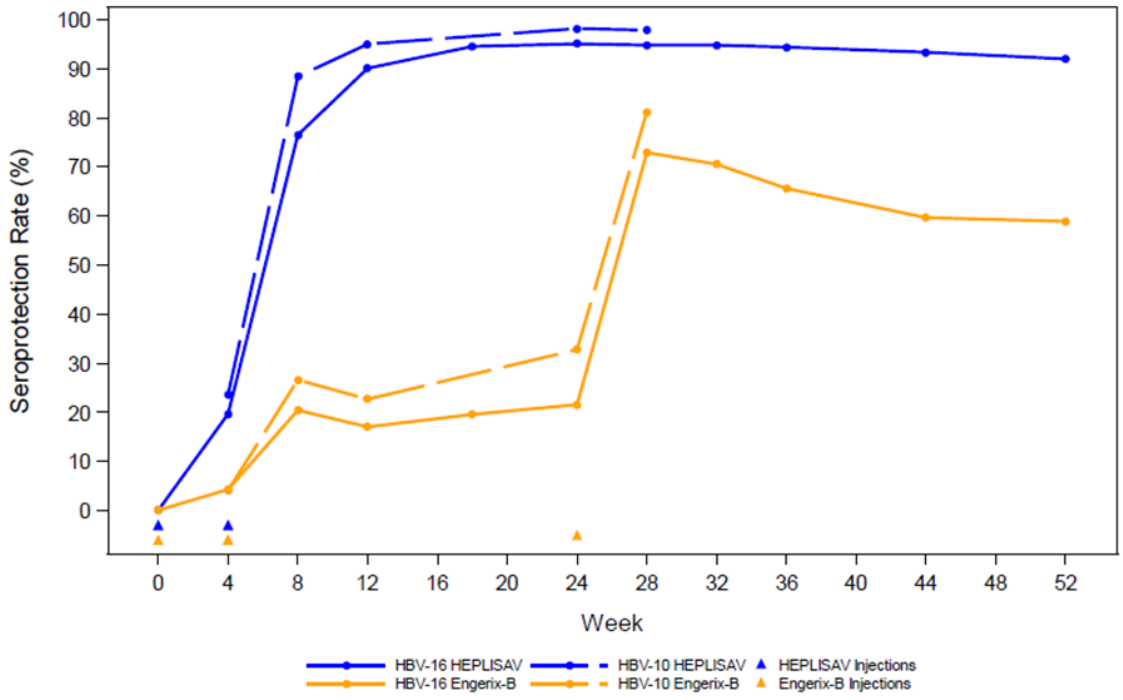
CI = confidence interval; N = number of evaluable subjects; SPR = seroprotection rate.
[a] Study injections were given at Weeks 0, 4, and 24 (placebo).
[b] Study injections were given at Weeks 0, 4, and 24.
Race was unknown for 2 HEPLISAV-B subjects.

5.2.4 Exploratory Endpoint Results (Seroprotection by Visit in HBV-10 and HBV-16)

Figure 5-1 and Table 5-6 present SPRs by visit for HBV-10 and HBV-16. In each pivotal trial, the peak SPR in the HEPLISAV-B group occurred at Week 24, 20 weeks after the last dose of HEPLISAV-B, and was statistically significantly higher than the peak SPR in the Engerix-B group that occurred at Week 28, 4 weeks after the last dose of Engerix-B. In addition, at each trial visit, the SPR in the HEPLISAV-B group was statistically significantly higher than in the Engerix-B group (Table 5-6).

In the 2 pivotal trials (HBV-10 and HBV-16) in which anti-HBs was measured at early time points, HEPLISAV-B also provided earlier seroprotection than Engerix-B. In both trials, HEPLISAV-B provided statistically significantly higher SPRs at 4 weeks after first dose and 4 weeks after second dose compared with Engerix-B. At Week 8, the SPR in the HEPLISAV-B group was not only statistically significantly higher than the SPR in the Engerix-B group at Week 8, but was also higher than the peak SPR in the Engerix-B group at Week 28.

Figure 5-1: SPR by Visit in the Pivotal Trials (HBV-10 and HBV-16) (Per-Protocol Population)



Note: The primary endpoint for HEPLISAV-B in HBV-10 and HBV-16 was Week 12. The primary endpoint for Engerix-B was Week 28 in HBV-10 and Week 32 in HBV-16. In HBV-10, immunogenicity was assessed for 28 weeks after the first injection, and in HBV-16 for 52 weeks.

Table 5-6: SPR by Visit in HBV-10 and HBV-16 (Per-Protocol Population)

Trial Subgroup	HBV-10 18 to 55 Years					HBV-16 40 to 70 Years				
	HEPLISAV-B [a]		Engerix-B[b]		Difference in SPRs (%) (HEPLISAV-B - Engerix-B) (95% CI)	HEPLISAV-B [a]		Engerix-B[b]		Difference in SPRs (%) (HEPLISAV-B -Engerix-B) (95% CI)
Visit	n/N	SPR (%) (95% CI)	n/N	SPR (%) (95% CI)		n/N	SPR (%) (95% CI)	n/N	SPR (%) (95% CI)	
Week 24/28[c]	1476/ 1503	98.2 (97.4, 98.8)	423/ 521	81.2 (77.6, 84.5)	17.0 (13.8, 20.6)	1066/ 1121	95.1 (93.7, 96.3)	256/ 351	72.9 (68.0, 77.5)	22.2 (17.6, 27.2)
Week 4	354/ 1502	23.6 (21.4, 25.7)	21/ 519	4.1 (2.4, 5.7)	19.5 (16.6, 22.2)	220/ 1121	19.6 (17.3, 22.1)	15/ 353	4.2 (2.4, 6.9)	15.4 (11.9, 18.3)
Week 8	1330/ 1504	88.4 (86.8, 90.1)	138/ 519	26.7 (22.8, 30.4)	61.7 (57.5, 65.7)	857/ 1120	76.5 (73.9, 79.0)	72/ 353	20.4 (16.3, 25.0)	56.1 (50.9, 60.7)
Week 12[d]	1436/ 1511	95.0 (93.9, 96.1)	118/ 521	22.7 (19.1, 26.2)	72.3 (68.4, 75.8)	1010/ 1121	90.1 (88.2, 91.8)	60/ 353	17.0 (13.2, 21.3)	73.1 (68.4, 77.0)
Week 24	1476/ 1503	98.2 (97.5, 98.9)	170/ 519	32.7 (28.7, 36.8)	65.3 (61.1, 69.3)	1066/ 1121	95.1 (93.7, 96.3)	76/ 353	21.5 (17.4, 26.2)	73.6 (68.8, 77.7)
Week 28[e]	1479/ 1511	97.9 (97.2, 98.6)	423/ 521	81.2 (77.8, 84.6)	16.6 (13.4, 20.2)	1062/ 1120	94.8 (93.4, 96.0)	256/ 351	72.9 (68.0, 77.5)	21.9 (17.3, 26.9)
Week 32[f]	—	—	—	—	—	1063/ 1121	94.8 (93.4, 96.0)	249/ 353	70.5 (65.5, 75.2)	24.3 (19.6, 29.4)
Week 36	—	—	—	—	—	1048/ 1110	94.4 (92.9, 95.7)	229/ 349	65.6 (60.4, 70.6)	28.8 (23.8, 34.1)
Week 52	—	—	—	—	—	1013/ 1101	92.0 (90.2, 93.5)	205/ 348	58.9 (53.5, 64.1)	33.1 (27.8, 38.5)

Anti-HBsAg = antibody against hepatitis B surface antigen; CI = confidence interval; N = number of subjects in the analysis population in the group; n = number of subjects with post-injection anti-HBsAg greater than or equal to 10 mIU/mL; PP = Per-Protocol; SPR = seroprotection rate.

[a] HEPLISAV-B study injections were given at Weeks 0, 4, and 24 (placebo).

[b] Engerix-B study injections were given at Weeks 0, 4, and 24.

[c] In subjects who received HEPLISAV-B , the peak SPR was at Week 24. In subjects who received Engerix-B, the peak SPR was at Week 28.

[d] Primary endpoint for HEPLISAV-B in HBV-16 and HBV-10.

[e] Primary endpoint for Engerix-B in HBV-10.

[f] Primary endpoint for Engerix-B in HBV-16.

5.2.5 Exploratory Endpoint Results (Geometric Mean Concentration of anti-HBs by Visit) in the Pivotal Trials

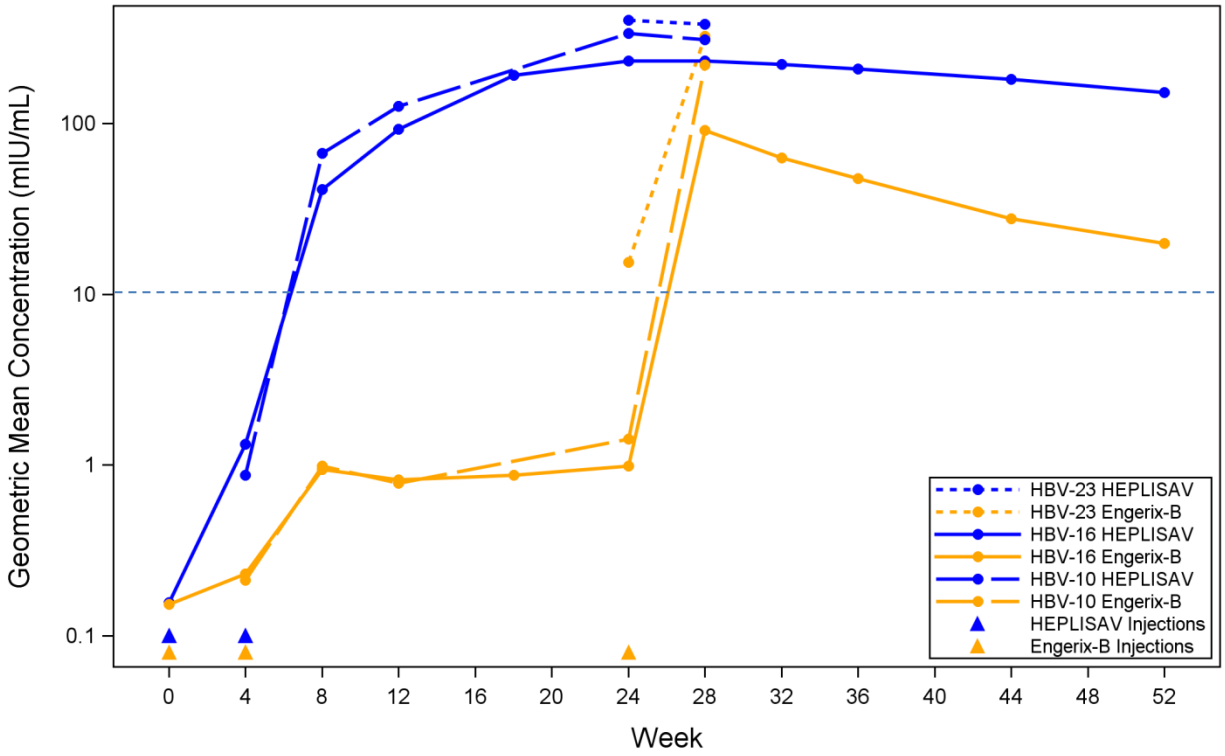
Figure 5-2 presents adjusted GMCs by visit in HBV-23, HBV-16, and HBV-10 (PP Population).

In HBV-10, the GMC was significantly higher in the HEPLISAV-B group than in the Engerix-B group at each visit from Week 4 through Week 24. However, at Week 24, the GMC in the HEPLISAV-B group (341.6 mIU/mL) was similar to the GMC in the Engerix-B group at Week 28 (352.1 mIU/mL).

In HBV-16, the GMC was significantly higher in the HEPLISAV-B group at Week 24 (231.2 mIU/mL) than in the Engerix-B group at Week 28 (90.9 mIU/mL) because the lower limit of the 95% CI of the ratio of the GMCs was greater than 1.0 (ratio of GMCs = 2.5; 95% CI: 1.9, 3.4). The GMC in the HEPLISAV-B group was also significantly higher than in the Engerix-B group at each visit from Week 4 through Week 52.

In HBV-23 at Week 24, the GMC in the HEPLISAV-B group (401.0 mIU/mL) was significantly higher than the GMC at Week 28 in the Engerix-B group (324.0 mIU/mL) (ratio of GMCs = 1.2; 95% CI: 1.1, 1.4).

Figure 5-2: Adjusted GMC of Anti-HBs by Visit in the Pivotal Trials (HBV-23, HBV-16, and HBV-10) (Per Protocol Population)

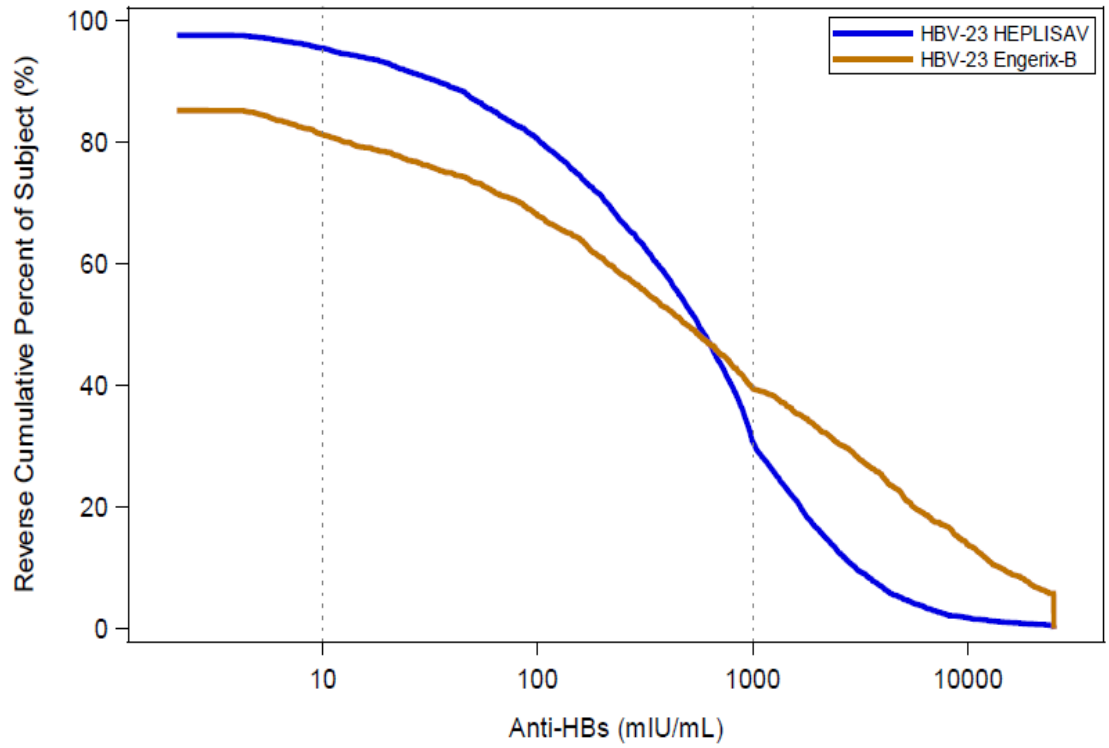


Anti-HBs = antibody against hepatitis B surface antigen.
Note: In analyses of GMCs in HBV-23, HBV-16, and HBV-10, different antibody concentrations were assigned to samples with an antibody concentration less than the limit of reporting by the laboratory. In HBV-23, 2.115 was assigned to values less than 4.23 mIU/mL; in HBV-16, 0.15 mIU/mL was assigned to values less than 0.3 mIU/mL; in HBV-10, 2.5 mIU/mL was assigned to values less than 5.0 mIU/mL. For this analysis, sample values less than the lower limit of reporting in each trial were assigned a value of 0.15 mIU/mL.
Anti-HBs levels were measured at Weeks 24 and 28 in HBV-23.
The horizontal line at 10 mIU/mL denotes the cutoff for seroprotection.

5.2.6 Distribution of Anti-HBs Responses by Treatment Group in HBV-23

The greater efficacy of HEPLISAV-B is not due to the induction of higher overall antibody levels across the vaccinated population, rather it is the result of a much more uniform and efficient induction of protective antibody levels across a broad spectrum of recipient populations. Figure 5-3 presents the reverse cumulative frequency of anti-HBs concentrations at Week 24 for HEPLISAV-B and Week 28 for Engerix-B in HBV-23. The HEPLISAV-B curve has a fairly steep slope indicating a relative narrow distribution of antibody levels. The Engerix-B curve has a relatively shallow slope indicating a greater variability in the antibody response than the response to HEPLISAV-B. While a higher proportion of subjects who received Engerix-B compared with HEPLISAV-B had anti-HBs levels ≥ 1000 mIU/mL, a significantly higher proportion of Engerix-B subjects did not develop seroprotective antibody levels.

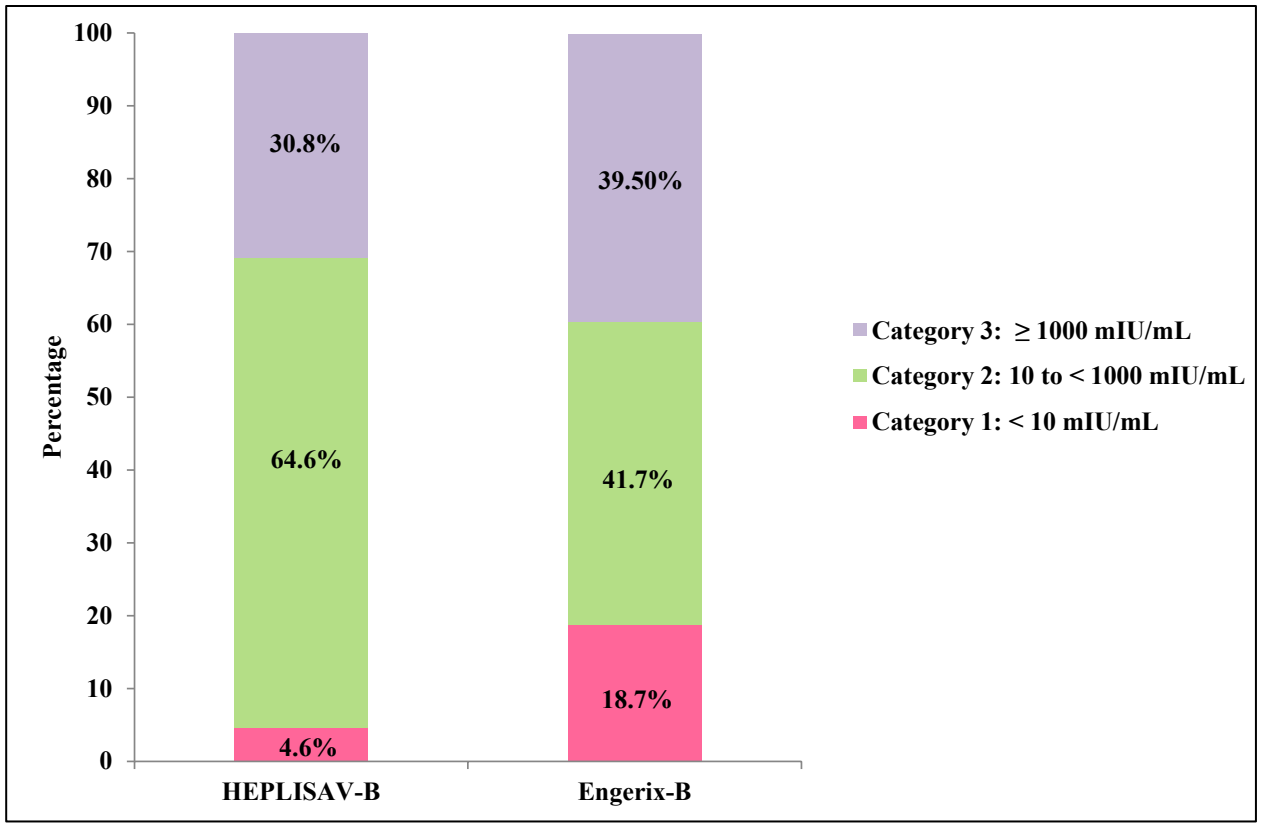
Figure 5-3: Reverse Cumulative Frequency Plot of Anti-HBs Level by Group at Peak Weeks (Week 24 for HEPLISAV-B and Week 28 for Engerix-B) in HBV-23 (PP Population)



Anti-HBs = antibody against hepatitis B surface antigen; PP =Per-protocol.
The dotted vertical line represents an anti-HBs level of 10 mIU/mL, a level above which an individual is considered to have developed seroprotection.

In HBV-23, the distribution of anti-HBs levels in subjects at Week 24 for HEPLISAV-B and Week 28 for Engerix-B is provided by treatment group in Figure 5-4. A higher proportion of HEPLISAV-B subjects had antibody levels between 10 mIU/mL and 1000 mIU/mL than Engerix-B subjects. Although the underlying mechanisms are responsible for the differences in immunogenicity between 1018 and alum, it appears that the distinct pathways activated by 1018 are more robust and less influenced by factors such as age, diabetes, and obesity.

Figure 5-4: Distribution of Anti-HBs Levels at Peak Weeks (Week 24 for HEPLISAV-B and Week 28 for Engerix-B) in HBV-23



Anti-HBs = antibody against hepatitis B surface antigen.

5.3 Immunogenicity Conclusions

The 3 pivotal trials met their primary endpoints, demonstrating noninferiority and statistically significantly higher seroprotection by HEPLISAV-B compared with Engerix-B. In addition, vaccination with 2 doses of HEPLISAV-B over 1 month achieved statistically significantly higher peak SPRs and earlier seroprotection than vaccination with 3 doses of Engerix-B administered over 6 months. These results were consistent at all clinic visits and across all pre-specified subpopulations including populations typically with reduced seroprotection to licensed HBV vaccines.

6.0 SAFETY

Summary of Safety

The overall safety profile of HEPLISAV-B was similar to that of Engerix-B:

- HEPLISAV-B had a lower frequency of systemic post-injection reactions (including fever) and a similar frequency of local post-injection reactions compared with Engerix-B.
- AEs and MAEs were balanced in type and frequency between the HEPLISAV-B and Engerix-B treatment groups.
- Risk of immune-mediated disease in recipients of HEPLISAV-B was balanced with that of Engerix-B:
  - AESIs were balanced between vaccine groups.
  - Rates of Bell's palsy were balanced between vaccine groups.
  - Rates of rare serious, new-onset AESIs were balanced between vaccine groups.
  - No differences between HEPLISAV-B and Engerix-B regarding exacerbations of pre-existing AESIs.
  - Changes in antinuclear antibody (ANA), antibody to double-stranded deoxyribonucleic acid (anti-dsDNA), and anti-neutrophil cytoplasmic antibody (ANCA) occurred at similar rates in recipients of HEPLISAV-B and recipients of Engerix-B.
- In the HBV-23 Laboratory Substudy (N = 309), a transient increase in the nonspecific beta 2 glycoprotein 1 IgM antiphospholipid antibody occurred in a higher proportion of HEPLISAV-B subjects than Engerix-B subjects but was not associated with thrombotic events and was not diagnostic of antiphospholipid syndrome.
- Rates of SAEs were balanced between the HEPLISAV-B and Engerix-B groups with the exception of 2 preferred terms that were more frequent in the Engerix-B group in the PSP: *prostate cancer* and *dehydration*. In a single study, HBV-23, the preferred term of *acute myocardial infarction* was reported in a higher proportion of HEPLISAV-B than Engerix-B recipients. A comprehensive evaluation found:
  - myocardial infarctions and MACE outcomes occurred in subjects in whom they would be expected at rates similar to or below background;
  - no evidence for theoretically plausible vaccine-induced immune etiologies;
  - the most reasonable conclusion is the numerical imbalance is likely due to random variation in small numbers of events; and
  - a large, observational, post-marketing surveillance study is proposed as the most feasible and appropriate design to confirm the safety of HEPLISAV-B.

- Rates of deaths were generally balanced between vaccine groups:
  - Causes of deaths were balanced across treatment groups except for death due to illicit or therapeutic drug overdose that was higher in the HEPLISAV-B group; and
  - No death was considered to be related to vaccine by investigators.
- No events of anaphylaxis were attributed to study vaccine by the investigator or Sponsor.
- Pregnancy outcomes were balanced between the treatment groups.

In conclusion, the safety data demonstrate that HEPLISAV-B was generally well tolerated, with an overall safety profile like that of Engerix-B. These data support the safety of HEPLISAV-B for immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older.

6.1 Safety of 1018 in Cancer, Asthma, and Allergy Studies

The HEPLISAV-B adjuvant, 1018, has been evaluated in several other clinical settings in doses up to 100 mg per dose: as a cancer immunotherapeutic by the subcutaneous route, as an asthma immunotherapeutic by the aerosol route, and as an allergy immunotherapeutic conjugated to ragweed by the subcutaneous route. In these programs, 1263 subjects received 1018, including 149 in the cancer and asthma programs who received higher doses (35 mg to 100 mg) and more doses (ranging from 4 to 8 total, given weekly) of 1018. Notably, no cardiovascular SAEs occurred in these development programs.

In the non-Hodgkin's lymphoma program, which used 1018 alone at doses approximately 12 times the dose of 1018 in HEPLISAV-B, a rapid and transient induction of the downstream effects of TLR9 was observed. Production of IFN-inducible genes rose within 24 hours and returned to baseline within 14 days. There were no cardiovascular SAEs.[41]

6.2 Safety Evaluation Plan

6.2.1 Safety Assessments

The safety assessments in the clinical program included the following:

- Post-Injection Reactions (PIR)

  PIRs solicited within 7 days of study injection were collected in HBV-10 and HBV-16. PIRs were not collected in HBV-23.

- Adverse Events (AEs)

  AEs were collected in HBV-10 and HBV-16 through the Week 28 study visit. AEs were not collected in HBV-23.

- Medically-attended Adverse Events (MAEs)

  MAEs were collected for the duration of HBV-23. MAEs were events in which the subject sought medical attention from a doctor's office, clinic, study site, emergency room or the subject was hospitalized.

- Serious Adverse Events (SAEs) and Deaths

  SAEs and deaths were collected for the duration of HBV-10, HBV-16, and HBV-23.

- Immune-mediated adverse events
  - Potential immune-mediated adverse events were collected for the duration of HBV-10, HBV-16, and HBV-23.
  - Safety data related to immune-mediated events are presented for the PSP and include:
  - New-onset AESIs identified retrospectively from the clinical database in HBV-10
  - Immune-mediated AEs adjudicated by an independent, blinded SEAC in HBV-16 and HBV-23
  - Laboratory assessments of autoantibodies (includes data from supportive trials)

6.2.2 Evaluation of Immune-mediated Adverse Events

In HBV-16 and HBV-23, Dynavax implemented active surveillance as well as independent review and adjudication of potential AESIs.

In HBV-16, investigators used an autoimmune questionnaire to solicit signs and symptoms of potential immune-mediated events for each subject at each visit. This questionnaire was not used as a screening instrument in HBV-23 due to its high sensitivity and low specificity in detecting immune-mediated events.

For AEs representing potential immune-mediated events, investigators were instructed to notify Dynavax of their awareness of such an event and to refer the subject for expert evaluation. In HBV-16, if the expert evaluation confirmed the diagnosis, the event was categorized as a potential autoimmune event and was submitted to an independent SEAC. In HBV-23, all events considered to be potentially immune-mediated were submitted to the SEAC regardless of the outcome of the expert evaluation.

The SEAC was established to review potential immune-mediated diseases. It was comprised of 2 experts in autoimmune disease and 1 expert in infectious disease external to Dynavax who were not otherwise involved in the conduct of the trials. The same SEAC members participated in HBV-16 and HBV-23. The SEAC was blinded to treatment group and adjudicated all potential immune-mediated events for autoimmune etiology, timing of onset, and relatedness to study treatment. The SEAC confirmed events as autoimmune if the preponderance of evidence was

consistent with an autoimmune etiology in their expert judgment. The SEAC also based its adjudication of timing of onset and relatedness on the preponderance of evidence.

6.3 Safety Analysis Populations

Table 6-1 presents a summary of the safety analysis populations.

Solicited adverse events and unsolicited AEs are integrated for HBV-10 and HBV-16. MAEs are presented for HBV-23. Immune-mediated adverse events, deaths, and SAEs are integrated for HBV-10, HBV-16, and HBV-23 in the PSP (Table 1-1). The PSP has a subject allocation ratio of 2.4:1 (HEPLISAV-B: Engerix-B).

Table 6-1: Safety Populations

Safety Population	HEPLISAV-B	Engerix-B	Total
HBV-10 and HBV-16	3778	1086	4864
HBV-23	5587	2781	8368
Primary Safety Population[a]	9365	3867	13,232
Supporting Trials[b]	673	333	1006
Total	**10,038**	**4200**	**14,238**

[a] Primary Safety Population: HBV-10, HBV-16, and HBV-23.
[b] Supporting Trials: HBV0001, HBV-02, HBV-03, HBV-04, HBV-05, HBV-08, HBV-14, and HBV-22

6.4 Extent of Exposure

Table 6-2 presents the extent of exposure to HEPLISAV-B and Engerix-B by treatment group in the PSP.

In the PSP, 9365 HEPLISAV-B subjects and 3867 Engerix-B subjects ≥ 18 years of age received at least 1 dose of vaccine; 98.0% of subjects completed the 2-dose regimen of HEPLISAV-B , and 94.4% of subjects completed the 3-dose regimen of Engerix-B. In the PSP, 9365 HEPLISAV-B recipients contributed 8528 person years of follow-up and 3867 Engerix-B recipients contributed 3621 person years of follow-up.

Table 6-2: Extent of Exposure by Treatment Group (PSP)

Subjects Who Received Dose(s)	HEPLISAV-B (N = 9365) % (n)	Engerix-B (N = 3867) % (n)
1 Dose	2.0 (190)	1.9 (72)
2 Doses	98.0 (9175)	3.7 (143)
3 Doses	NA	94.4 (3652)

PSP = Primary Safety Population; NA = not applicable.

6.5 Demographic and Baseline Characteristics

Demographics and baseline characteristics for the Randomized Population are presented and discussed in Section 5.1.7, Table 5-2. Demographics and baseline characteristics for the PSP are similar to the Randomized Population.

6.6 Medical History

HBV-10 and HBV-16 were conducted in generally healthy adults, whereas many HBV-23 subjects had multiple comorbidities requiring multiple chronic concomitant medications. Thus, HBV-23 includes a more diverse range of subjects with clinical conditions. Table 6-3 shows selected examples of medical history preferred terms by pivotal trial. These preferred terms represent acute and chronic conditions that may lead to subsequent adverse events including SAEs and deaths during the trial. The most common preferred terms include hypertension, hyperlipidemia, type 2 diabetes mellitus, chronic obstructive pulmonary disease, and coronary artery disease. Conditions present at baseline were generally balanced between treatment groups in each trial although there were imbalances in some individual preferred terms. For example, while *coronary artery disease* was balanced in HBV-23, 19 (0.3%) subjects who received HEPLISAV-B and 4 (0.1%) of subjects who received Engerix-B had a history of *coronary artery arteriosclerosis*.

Table 6-3: Medical History by Selected Comorbidities in the Phase 3 Trials (PSP)

Condition	HBV-10 N = 2415 % (n)	HBV-16 N = 2449 % (n)	HBV-23 N = 8368 % (n)
Hypertension	10.4 (250)	29.5 (722)	35.1 (2937)
Hyperlipidemia	4.2 (101)	4.7 (115)	15.0 (1258)
Type 2 Diabetes Mellitus	1.5 (37)	8.9 (219)	13.7 (1143)[a]
Chronic Obstructive Pulmonary Disease	0.79 (19)	1.2 (29)	2.5 (206)
Coronary Artery Disease	0.17 (4)	0.94 (23)	2.4 (205)
Chronic Renal Failure	0	0.04 (1)	1.1 (95)
Hepatic Steatosis	0.25 (6)	0.24 (6)	1.1 (90)
Atrial Fibrillation	0	0.45 (11)	1.0 (84)
Coronary Arterial Stent Insertion	0.12 (3)	0.20 (5)	0.99 (83)
Cerebrovascular Accident	0.04 (1)	0.33 (8)	0.85 (71)
Coronary Artery Bypass	0.04 (1)	0.61 (15)	0.75 (63)
Heart Failure	0.04 (1)	0.08 (2)	0.69 (58)
Transient Ischemic Attack	0.04 (1)	0.20 (5)	0.48 (40)
Arteriosclerosis	0.08 (2)	0.20 (5)	0.47 (39)
Peripheral Vascular Disorder	0	0.08 (2)	0.44 (37)
Cardiomyopathy	0	0.04 (1)	0.25 (21)

[a] n for HBV-23 is based on the trial definition for type 2 diabetes mellitus that required drug treatment for diabetes.

6.7 Safety Results

6.7.1 Overview of Solicited and Unsolicited Adverse Events and MAEs

An overview of solicited post-injection reactions and unsolicited AEs and MAEs is presented in Table 6-4. Solicited post-injection local reactions, AEs and treatment discontinuations due to AEs were balanced between the treatment groups in HBV-10 and HBV-16 while solicited post-injection systemic reactions were lower in the HEPLISAV-B group. MAEs and treatment discontinuations due to MAEs in HBV-23 were also similar between the treatment groups.

Table 6-4: Overview of Solicited PIRs After All Active Injections and Unsolicited AEs and MAEs (HBV-10 and HBV-16 Safety Population)

Type of Event (Study)	HEPLISAV-B	Engerix-B
Post-injection Reactions (HBV-10 and HBV-16), N	3762	1084
Any PIR, % (n)	55.1 (2071)	57.1 (619)
Local PIRs, % (n)	42.8 (1612)	41.1 (445)
Systemic PIRs, % (n)	32.3 (1215)	37.4 (405)
AEs (HBV-10 and HBV-16), N	3778	1086
Any AE, % (n)	55.3 (2089)	58.1 (631)
Discontinuation of treatment due to AE, % (n)	0.5 (19)	0.4 (4)
MAEs (HBV-23), N	5587	2781
Any MAE, % (n)	46.0 (2569)	46.2 (1286)
Discontinuation of treatment due to MAE, % (n)	0.6 (32)	0.5 (15)

AE = adverse event; MAE = medically-attended adverse event; N = number of subjects in the safety analysis population in the treatment group; n = number of subjects with a reaction; PIR = post-injection reaction.

[a] Post-injection reaction rates are presented only as percentages because the denominator was different and was based on the percentage of subjects returning a diary card.

6.7.2 Post-Injection Reactions

Table 6-5 presents an overview of solicited post-injection reactions after all active injections.

HEPLISAV-B and Engerix-B had similar rates of overall PIRs in the pooled analyses of HBV-10 and HBV-16.

Table 6-5: Overview of Solicited PIRs (Reactogenicity) Within 7 Days Post-Injection After All Active Injections (HBV-10 and HBV-16 Safety Population)

Solicited Post-Injection Reactions	HEPLISAV-B (N = 3777) % (n)	Engerix-B (N = 1087) % (n)
Subjects Who Returned a Diary Card, N	3762	1084
Any Reaction	55.1 (2071)	57.1 (619)
Severe Reactions	3.2 (119)	5.1 (55)
Local Reaction		
Any Reaction	42.8 (1612)	41.1 (445)
Severe Reactions	0.6 (21)	0.4 (4)
Systemic Reaction		
Any Reaction	32.2 (1215)	37.4 (405)
Severe Reactions	2.8 (106)	4.9 (53)

N = number of subjects in the safety population with nonmissing results in the treatment group.
If a subject had the same type of reaction (local, systemic) more than once across the study period, only the most severe 1 within that type was counted.

6.7.2.1 Local Post-Injection Reactions

Local post-injection reactions are presented in Table 6-6 as frequencies of redness, swelling, and pain after all active injections by treatment group and severity.

The frequency of local PIRs was balanced in HEPLISAV-B subjects and Engerix-B subjects. Injection site pain was the most frequent local reaction in both groups. Severe pain was infrequent and balanced between treatment groups. Local PIRs tended to peak in frequency between 1 and 3 days after injection in both groups.

Table 6-6: Percent of Subjects With Local PIRs After All Active Injections by Treatment Group (HBV-10 and HBV-16 Safety Population)

Local Post-Injection Reactions	HEPLISAV-B % (n)	Engerix-B % (n)
Subjects With Any Post-Injection Reaction, N	3762	1084
Local reactions	42.8 (1612)	41.1 (445)
Injection-Site Redness[a]		
Any Redness	3.7 (141)	1.1 (12)
Severe	0 (1)	0
Injection-Site Swelling[a]		
Any Swelling	2.4 (90)	1.3 (14)
Severe	0 (1)	0
Injection-Site Pain		
Any Pain	41.7 (1567)	40.5 (439)
Severe	0.5 (20)	0.4 (4)

[a] Redness/Swelling: Severe = greater than 100 mm.

6.7.2.2 Systemic Post-injection Reactions

Table 6-7 presents an analysis of solicited systemic post-injection reactions after all active injections by treatment group and severity.

The frequency of systemic PIRs was lower in HEPLISAV-B subjects than in Engerix-B subjects. The most frequent systemic post-injection reactions in both treatment groups were headache and fatigue. Systemic PIRs tended to peak between 1 and 2 days after injection in both groups.

Table 6-7: Percent of Subjects With Solicited Systemic PIRs After All Active Injections by Treatment Group (HBV-10 and HBV-16 Safety Population)

Systemic Post-Injection Reactions	HEPLISAV-B (N = 3777) % (n)	Engerix-B (N = 1087) % (n)
Subjects with systemic reactions %	32.3	37.4
Fatigue, n	3762	1084
Any Fatigue, % (n)	21.4 (805)	25.1 (272)
Severe, % (n)	1.6 (59)	2.4 (26)
Headache, n	3762	1084
Any Headache, % (n)	20.1 (755)	25.3 (274)
Severe, % (n)	1.5 (55)	2.0 (22)
Malaise, n	3762	1084
Any Malaise, % (n)	13.8 (520)	16.0 (173)
Severe, % (n)	1.1 (40)	2.1 (23)
Fever, n	3733	1076
Any fever (≥ 38°C) , % (n)	1.7 (64)	3.4 (37)
Severe (39°C to 40°C) , % (n)	0.2 (9)	0.9 (10)

6.7.3 Adverse Events

6.7.3.1 Treatment-Emergent Adverse Events in HBV-10 and HBV-16

Table 6-8 presents an analysis of AEs by frequency of preferred term in HBV-10 and HBV-16.

AEs were balanced in frequency between treatment groups. The 3 most common AEs in both treatment groups were nasopharyngitis, headache, and back pain.

Table 6-8: Treatment-Emergent AEs by Preferred Term Occurring in ≥ 2.0% of Subjects in Either Treatment Group by Preferred Term (HBV-10 and HBV-16 Safety Population)

Preferred Term	HEPLISAV-B (N = 3777) % (n)	Engerix-B (N = 1087) % (n)
Subjects with any AE	55.3 (2089)	58.0 (631)
Nasopharyngitis	10.1 (383)	11.5 (125)
Headache	6.9 (260)	7.0 (76)
Back Pain	3.4 (130)	3.5 (38)
Sinusitis	2.9 (109)	2.4 (26)
Upper Respiratory Tract Infection	2.8 (105)	3.5 (38)
Oropharyngeal Pain	2.7 (102)	3.2 (35)
Arthralgia	2.5 (93)	2.9 (32)
Cough	2.4 (89)	2.3 (25)
Diarrhea	2.0 (75)	2.0 (22)
Hypertension	1.6 (62)	2.9 (31)
Nausea	1.5 (55)	2.2 (24)

AE = adverse event.

6.7.3.2 Adverse Events Leading to Treatment Discontinuation in HBV-10 and HBV-16

In HBV-10 and HBV-16 with a subject allocation ratio of 3.5:1 (HEPLISAV-B:Engerix-B), 0.5% (n = 19) of subjects in the HEPLISAV-B group and 0.4% (n = 4) of subjects in the Engerix-B group had treatment withdrawn due to an AE.

In the HEPLISAV-B group, subjects had study treatment withdrawn for the following reasons: Guillain-Barré syndrome (n = 1), pulmonary embolism (n = 1), pain in the injection arm (n = 2), hyperglycemia (n = 1), upper respiratory tract infection (n = 1), thermal burn (n = 1), gunshot wound (n = 1), worsening of hypertension (n = 1), rash (n = 1), breast cancer (n = 1), small bowel obstruction (n = 1), vesicular rash (n = 1), neutropenia (n = 1), hypothyroidism (n = 1),

erythema nodosum (n = 1), and microscopic colitis (n = 1). One subject had treatment withdrawn due to AEs of hyponatremia, nausea, vomiting, weight loss, and headache. One subject had treatment withdrawn for 8 AEs (peripheral edema, allergy to vaccine, rhinitis, upper respiratory tract infection, back pain, sneezing, macular rash, and skin exfoliation).

In the Engerix-B group, subjects had study treatment withdrawn for the following reasons: prostate cancer (n = 1), coronary artery disease (n =1), glaucoma and vision blurred (n = 1), and arthritis/flare up of arthritis to hands (n = 1).

6.7.4 Medically-Attended Adverse Events in HBV-23

Table 6-9 presents a summary of MAEs in HBV-23 occurring in ≥ 1.0 % of subjects in either treatment group by preferred term. The most frequently occurring MAEs by preferred term (occurring in ≥ 2.0% in either treatment group) were upper respiratory tract infections, bronchitis, sinusitis, hypertension, urinary tract infection, and back pain. MAEs by preferred term were generally evenly distributed between vaccine groups.

Table 6-9: Treatment-Emergent MAEs by Preferred Term Occurring in ≥ 1.0% of Subjects in Either Treatment Group by Preferred Term (HBV-23 Safety Population)

Preferred Term	HEPLISAV-B (N=5587) % (n)	Engerix-B (N=2781) % (n)
Subjects with at least 1 qualifying MAE	46.0 (2569)	46.2 (1286)
Upper Respiratory Tract Infection	3.4 (192)	3.3 (92)
Bronchitis	3.2 (176)	3.7 (102)
Sinusitis	2.7 (149)	3.0 (84)
Hypertension	2.4 (133)	2.1 (59)
Urinary Tract Infection	2.4 (132)	2.3 (64)
Back Pain	2.1 (116)	1.9 (54)
Arthralgia	1.8 (98)	1.9 (54)
Osteoarthritis	1.4 (77)	1.2 (32)
Pain in Extremity	1.3 (72)	1.0 (28)
Type 2 Diabetes Mellitus	1.2 (67)	1.3 (37)
Cough	1.1 (62)	1.3 (37)
Acute Sinusitis	1.1 (59)	1.3 (37)
Laceration	1.0 (54)	0.7 (19)
Musculoskeletal Pain	0.8 (45)	1.1 (30)

MAE = medically attended event.

6.7.4.1 Numerical Imbalances in Medically Attended Adverse Events in HBV-23

Assessing whether small numerical differences between treatment arms represent true and clinically meaningful treatment effects or random variation is a consistent challenge in clinical development. MAEs with relative risks (RRs) with 95% CIs that exclude 1 merit further investigation. Of the 1405 MAEs, 10 had an RR with a 95% CI excluding 1 (Table 1-2). In addition, the relative risk of other MAEs that occur in a small number of subjects may be fairly large and have wide 95% CIs that include 1. These also merit further evaluation.

To assess the extent to which any such numerical imbalance discovered post-hoc represents a meaningful clinical effect, observed imbalances in MAEs were comprehensively assessed. As part of the assessment, RRs and 95% CIs were calculated for HEPLISAV-B compared with Engerix-B.

Of the 1405 MAEs reported, 19 had relatively large RRs with 95% CIs that include 1 (Table 6-10). Five MAEs with a variety of etiologies occurred at a higher frequency in the HEPLISAV-B group: *wound, excoriation, lipoma, acute myocardial infarction,* and *bipolar I disorder*. Because of the clinical importance of the term, *acute myocardial infarction*, it was extensively investigated (See Section 6.7.11). Fourteen other MAEs with a variety of etiologies occurred with a higher frequency in the Engerix-B group including: *coronary artery arteriosclerosis, irritable bowel syndrome, acute cholecystitis,* and *oral herpes*. None of these 14 MAEs have been previously known to be associated with Engerix-B and none have a known biologically plausible explanation.

From a statistical perspective, given the large number of events observed in this study, it is to be expected that a small number of events will reach relatively high RRs even though there is no true treatment effect. This situation may be expected to arise when very few events are reported for the vast majority of AE terms.

Table 6-10: MAE Preferred Terms With Relative Risks > 6.0 or < 0.17 and With 95% Confidence Intervals That Include 1 (HBV-23 Safety Population)

Preferred Term	HEPLISAV-B (N=5587) % (n)	Engerix-B (N=2781) % (n)	Relative Risk (HEPLISAV-B / Engerix-B) 95% CI [a]
Excoriation	0.18 (10)	0	10.45 (0.61 -178.33)
Wound	0.16 (9)	0	9.46 (0.55 -162.45)
Lipoma	0.14 (8)	0	8.46 (0.49 -146.57)
Acute Myocardial Infarction	0.15 (14)	0.04 (1)	6.97 (0.92 - 52.97) [b]
Bipolar I Disorder	0.11 (6)	0	6.47 (0.36 -114.83)
Coronary Artery Arteriosclerosis	0.02 (1)	0.11 (3)	0.17 (0.02 - 1.59)
Back Injury	0.02 (1)	0.11 (3)	0.17 (0.02 - 1.59)
Injection Site Pain	0.02 (1)	0.11 (3)	0.17 (0.02 - 1.59)
Musculoskeletal Stiffness	0.02 (1)	0.11 (3)	0.17 (0.02 - 1.59)
Nasal Septum Deviation	0.02 (1)	0.11 (3)	0.17 (0.02 - 1.59)
Presbyopia	0.02 (1)	0.11 (3)	0.17 (0.02 - 1.59)
Respiratory Tract Infection	0.02 (1)	0.11 (3)	0.17 (0.02 - 1.59)
Rhinitis	0.02 (1)	0.11 (3)	0.17 (0.02 - 1.59)
Irritable Bowel Syndrome	0.02 (1)	0.14 (4)	0.12 (0.01 - 1.11)
Oral Candidiasis	0.02 (1)	0.14 (4)	0.12 (0.01 - 1.11)
Adenomyosis	0	0.11 (3)	0.07 (0.004 - 1.38)
Cholecystitis Acute	0	0.11 (3)	0.07 (0.004 - 1.38)
Muscle Rupture	0	0.11 (3)	0.07 (0.004 - 1.38)
Oral Herpes	0	0.11 (3)	0.07 (0.004 - 1.38)

CI = confidence interval.

Note: Events with rates > 1/1000 are included.

[a] Relative risks and asymptotic 95% CIs were calculated using the Wald method if both treatment groups had one or more AEs. Otherwise the Wald Modified method was used to calculate continuity corrected RRs and asymptotic 95% CIs.

[b] In addition to the asymptotic 95% CI shown in the table, the exact 95% confidence interval for acute myocardial infarction (95% CI: 1.00, 184.90) was estimated with StatXact 11.1 (Cytel, 2016) using the method of inverting 2, 1-sided tests based on the standardized statistic proposed by Miettinen and Nurminen.

6.7.4.2 Medically-Attended Adverse Events Leading to Treatment Discontinuation

Table 6-11 presents a summary of MAEs leading to treatment discontinuation by SOC. No notable differences between groups were identified for any SOC.

Table 6-11: Treatment-Emergent MAEs That Were Primary Reason for Early Study Treatment Discontinuation by System Organ Class (HBV-23 Safety Population)

System Organ Class	HEPLISAV-B (N=5587) % (n)	Engerix-B (N=2781) % (n)
Subjects with at least 1 qualifying adverse event	0.6 (32)	0.5 (15)
Blood and Lymphatic System Disorders	0	<0.1 (1)
Cardiac Disorders	<0.1 (3)	<0.1 (2)
Endocrine Disorders	<0.1 (2)	0
Eye Disorders	<0.1 (1)	0
Gastrointestinal Disorders	<0.1 (4)	0.1 (4)
General Disorders and Administration Site Disorders	<0.1 (2)	0
Hepatobiliary Disorders	<0.1 (2)	<0.1 (1)
Immune system Disorders	<0.1 (1)	0
Infections and Infestations	<0.1 (2)	0
Injury, poisoning and procedural complications	<0.1 (2)	0
Metabolism and nutrition disorders	0	<0.1 (1)
Musculoskeletal and Connective Tissue Disorders	0	<0.1 (1)
Neoplasms benign, malignant and unspecified (include cysts and polyps)	0.1 (7)	<0.1 (2)
Nervous System Disorders	0.2 (12)	0.1 (3)
Pregnancy, puerperium and perinatal conditions	<0.1 (1)	<0.1 (2)
Psychiatric disorders	<0.1 (1)	0
Renal and urinary disorders	0	<0.1 (2)
Reproductive system and breast disorders	0	<0.1 (2)
Respiratory, Thoracic and Mediastinal Disorders	<0.1 (4)	<0.1 (1)
Skin and subcutaneous tissue disorders	<0.1 (3)	<0.1 (2)
Vascular disorders	<0.1 (2)	<0.1 (1)

6.7.5 Overview of Immune-mediated AEs, Deaths, and SAEs in the PSP

Table 1-1 presents a summary of the immune-mediated AEs, deaths, and SAEs in the PSP.

Immune-mediated AEs, deaths, and SAEs were balanced between the HEPLISAV-B and Engerix-B groups with the exception of differences in a few preferred terms. A higher proportion of subjects in the HEPLISAV-B group died due to illicit or therapeutic drug overdose and a higher proportion of subjects in the HEPLISAV-B group reported the SAE preferred term of *acute myocardial infarction*. A higher proportion of subjects in the Engerix-B group reported the SAE preferred terms of *prostate cancer* or *dehydration*.

6.7.6 Assessments of Immune-mediated Conditions

To assess the risk of immune-mediated adverse events in recipients of HEPLISAV-B compared with recipients of Engerix-B, multiple analyses were performed:

- Immune-mediated AEs in the PSP
  - New-onset AESIs
    - Bell's palsy
    - AESIs excluding Bell's palsy
  - Immune-mediated AEs not on list of AESIs, adjudicated as autoimmune by SEAC
  - Thyroid Disorders
- Exacerbations of pre-existing AESIs
- Laboratory assessments of autoantibodies

6.7.7 Immune-mediated Adverse Events

Table 6-12 presents an overall summary of subjects with immune-mediated AEs.

Immune-mediated AEs occurred in a higher proportion of Engerix-B recipients in HBV-10 and a higher proportion of HEPLISAV-B recipients in HBV-16 and HBV-23. The most frequent event was Bell's palsy that was balanced between treatment groups in the PSP. The 3 autoimmune AEs not on the AESI list were cases of hypothyroidism that occurred in women at an incidence that was lower than background.

Table 6-12: Overall Summary of Subjects With Immune-mediated Adverse Events (Primary Safety Population)

Study	HBV-10		HBV-16		HBV-23		PSP	
Treatment Arm	HEPLISAV-B (N = 1810) % (n)	Engerix-B (N = 605) % (n)	HEPLISAV-B (N = 1968) % (n)	Engerix-B (N = 481) % (n)	HEPLISAV-B (N = 5587) % (n)	Engerix-B (N = 2781) % (n)	HEPLISAV-B (N = 9365) % (n)	Engerix-B (N = 3867) % (n)
Potential New-Onset Immune-mediated AE	0.22 (4)	0.66 (4)	0.41 (8)	0	0.36 (20)	0.36 (10)	0.34 (32)	0.39 (15)
SEAC adjudicated as preexisting	NA	NA	0.10 (2)	0	0.11 (6)	0.36 (10)	0.09 (8)	0.26 (10)
SEAC Adjudicated as not AESI or secondary to other Condition	NA	NA	0	0	0.09 (5)	0	0.05 (5)	0
New-Onset Immune-mediated AE	0.22 (4)	0.66 (4)	0.30 (6)	0	0.16 (9)	0.04 (1)	0.20 (19)	0.13 (5)
Bell's Palsy	0	0.17 (1)	0.05 (1)	0	0.09 (5)	0.04 (1)	0.06 (6)	0.05 (2)
AESI Excluding Bell's Palsy	0.22 (4)	0.50 (3)	0.15 (3)	0	0.05 (3)	0	0.11 (10)	0.08 (3)
Autoimmune AE not on AESI list	NA	NA	0.10 (2)	0	0.02 (1)	0	0.03 (3)	0

AE = adverse event; AESI = adverse event of special interest; NA = not applicable because there was no SEAC in HBV-10; SEAC = Safety Evaluation and Adjudication Committee.
One subject in HBV-10 was randomized to receive Engerix-B but received HEPLISAV-B. This subject was analyzed in the HEPLISAV-B group for safety analyses

6.7.7.1 Analysis of Adverse Events of Special Interest

In all clinical trials, AEs or MAEs (HBV-23 only) were reported based on standard clinical practice, including use of an interim medical history to elicit symptoms that were then evaluated further as deemed appropriate by the investigator. Dynavax incorporated multiple approaches for the identification of immune-mediated AEs including published literature, other sponsors' protocols, and a list of AESIs provided by FDA (Appendix 3). The majority of conditions on the AESI list represent autoimmune disorders with the addition of conditions of inflammatory reactions (eg, sarcoidosis) and hypersensitivity reactions (eg, erythema nodosum, Stevens-Johnson Syndrome).

The first analysis is of all subjects in HBV-23 and HBV-16 with treatment-emergent AESIs that are *potentially* new-onset that were submitted to the SEAC for adjudication of the diagnosis and timing of onset of the event. In addition, for HBV-10 that did not use a SEAC, all subjects with treatment-emergent AESIs that were not reported in medical history or did not have an exacerbation of a disease such as *rheumatoid arthritis aggravated* are included.

The second analysis is of subjects in HBV-23 and HBV-16 with a SEAC *adjudicated* new-onset AESIs in whom the SEAC confirmed the AESI diagnosis and assessed the event as new onset. In HBV-10, subjects with treatment-emergent AESIs not also in medical history or an exacerbation of an existing disease are considered to be new onset and are included in the analysis. In HBV-23, the SEAC did not adjudicate the onset for Bell's palsy events; in this analysis treatment-emergent Bell's palsy events are assumed to be new onset. Because Bell's palsy is the only AESI that occurred in more than 1 HEPLISAV-B subject, subjects with these events are also analyzed separately from the other AESIs (Section 6.7.7.1.1.1.1).

6.7.7.1.1 Potential New-Onset Adverse Events of Special Interest in the Primary Safety Population

Table 6-13 presents potential new-onset AESIs in the PSP. In the PSP, 45 subjects reported at least 1 potential new-onset AESI. In each treatment group, 1 subject reported 2 events. One subject in the HEPLISAV-B group in HBV-23 reported 2 potential AESIs: Sjogren's syndrome and Raynaud's phenomenon. One subject in the Engerix-B group in HBV-10 reported 2 potential AESIs: ANCA positive vasculitis and scleroderma.

In the PSP, the most frequent SOC was nervous system disorders (n =11) with 8 cases of VIIth nerve paralysis (Bell's palsy). The next most frequent was endocrine disorders (n = 10) including autoimmune thyroiditis and Basedow's (Grave's) disease. Overall, a slightly higher proportion of AESIs were reported in the Engerix-B group compared with the HEPLISAV-B group due to higher frequency of events in the endocrine and gastrointestinal SOCs. A higher proportion of events in the nervous disorders SOC were reported in the HEPLISAV-B group due to subjects with Bell's palsy.

Table 6-13: Subjects With Potential New-Onset AESI by System Organ Class and Preferred Term (Primary Safety Populations)

System Organ Class/Preferred Term n (%)	HEPLISAV-B (N = 9365) % (n)	Engerix-B (N = 3867) % (n
Subjects with at least 1 potential adverse event of special interest	0.3 (30)	0.4 (15)
Nervous System Disorders	<0.1 (9)	<0.1 (2)
Guillain-Barré Syndrome	<0.1 (1)	0
VIth Nerve Paralysis	<0.1 (2)	0
VIIth Nerve Paralysis (Bell's palsy)	<0.1 (6)	<0.1 (2)
Endocrine Disorders	<0.1 (5)	0.1 (5)
Autoimmune Thyroiditis	<0.1 (2)	<0.1 (2)
Basedow's Disease	<0.1 (3)	<0.1 (3)
Skin and Subcutaneous Tissue Disorders	<0.1 (5)	<0.1 (3)
Alopecia Areata	<0.1 (1)	0
Cutaneous lupus erythematosus	0	<0.1 (1)
Dermatitis Herpetiformis[a]	<0.1 (1)	0
Erythema Nodosum	<0.1 (1)	0
Lichen Planus	<0.1 (1)	<0.1 (2)
Vitiligo	<0.1 (1)	0
Musculoskeletal and Connective Tissue Disorders	<0.1 (4)	<0.1 (2)
Mixed Connective Tissue Disease	0	<0.1 (1)
Polymyalgia Rheumatica	<0.1 (1)	0
Rheumatoid Arthritis	<0.1 (1)	0
Scleroderma	0	<0.1 (1)
Sjogren's Syndrome	<0.1 (1)	0
Systemic Lupus Erythematosus	<0.1 (1)	0
Vascular Disorders	<0.1 (3)	<0.1 (1)
Granulomatosis With Polyangiitis	<0.1 (1)	0
Raynaud's Phenomenon	<0.1 (1)	<0.1 (1)
Takayasu's arteritis[b]	<0.1 (1)	0
Gastrointestinal Disorders	<0.1 (2)	<0.1 (2)
Coeliac Disease	0	<0.1 (2)
Colitis Ulcerative	<0.1 (2)	0
Hepatobiliary Disorders	<0.1 (1)	0
Biliary Cirrhosis Primary	<0.1 (1)	0
Infections and Infestations	<0.1 (1)	0
Cavernous Sinus Syndrome[c]	<0.1 (1)	0
Metabolism and Nutrition Disorders	<0.1 (1)	0
Type 1 Diabetes Mellitus	<0.1 (1)	0
Immune System Disorders	0	<0.1 (1)
Anti-Neutrophil Cytoplasmic Antibody Positive Vasculitis	0	<0.1 (1)

[a] Unconfirmed diagnosis in HBV-16.
[b] Alternative diagnosis of intramural hematoma of the aorta.
[c] Unconfirmed diagnosis of Tolosa Hunt syndrome.

6.7.7.1.1.1 New-Onset Adverse Events of Special Interest

In HBV-23 and HBV-16, 36 subjects reported 37 potential new-onset AESIs. The SEAC adjudicated 18 events in 18 subjects as pre-existing based on results of tests on baseline blood samples or pretrial medical records (HEPLISAV-B: n = 8; Engerix-B: n = 10). In addition, in HBV-23, the SEAC could not confirm the diagnosis of 5 events in 4 subjects (Sjogren's syndrome and Raynaud's phenomenon, rheumatoid arthritis, VIth cranial nerve palsy, and Takayasu's arteritis) and considered 1 additional event (VIth cranial nerve palsy) to be secondary to diabetes mellitus. The remaining 13 events in 13 subjects were new onset either by SEAC adjudication as new onset (n = 5), or assumed to be new onset: Bell's palsy (n = 7) and cavernous sinus syndrome (n = 1). In HBV-10, 8 subjects reported 9 AESIs. Thus, in the PSP, 21 subjects had 22 AESIs that were considered to be new-onset.

In addition to the prospectively identified and SEAC adjudicated AESIs, Dynavax has included 1 AESI considered to be new onset from HBV-16, a case of cavernous sinus syndrome (preferred term of *cavernous sinus thrombosis*) with the unconfirmed diagnosis of Tolosa Hunt syndrome. Dynavax excluded a report of *dermatitis herpetiformis* that occurred during HBV-16 that was later determined to be incorrect as the subject and her physician denied that she had ever had the disease. These events were not considered to be AESIs during the trial and were not adjudicated by the SEAC.

6.7.7.1.1.1.1 Bell's Palsy

Table 6-14 presents subjects with Bell's palsy in the PSP listed by days since last active dose. Of events occurring within 90 days of the last vaccination, 3 were in the HEPLISAV-B group and 1 in the Engerix-B group. The remaining 4 events in the HEPLISAV-B group and the 1 in the Engerix-B group occurred 91 or more days after the last active dose of vaccine.

In a case-control study of an intranasal influenza vaccine that used *Escherichia coli* heat-labile toxin as adjuvant that had a very strong association with Bell's palsy (adjusted odds ratio = 84.0; 95% CI 20.1, 351.9),[94] 93.8% of Bell's palsy cases occurred within 90 days of intranasal vaccination. In contrast, in the comparator group of persons who received parenteral influenza vaccine that had no association with Bell's palsy (odds ratio = 1.1; 95% CI 0.6, 2.0), 38.5% of cases occurred within 90 days of vaccination.

In the HEPLISAV-B group in the PSP, 33% (2 of 6 subjects) had events that occurred within 90 days of vaccination. This frequency is similar to the temporal pattern noted after administration of the parenteral influenza vaccine.

Table 6-14: Listing of Subjects with Bell's Palsy by Days Since Last Active Dose (Primary Safety Population)

Trial	Treatment Assignment	Age (y)	Sex	Last Active Dose	Days Since Last Active Dose	Severity	Outcome
HBV-23	HEPLISAV-B	49	F	2	0a (55)	2	Resolved
HBV-10	Engerix-B	34	M	2	122	2	Resolved
HBV-23	HEPLISAV-B	31	F	2	170	3	Resolved
HBV-23	HEPLISAV-B	49	M	2	172	3	Ongoing
HBV-23	HEPLISAV-B	52	M	2	256	3	Resolved
HBV-16	HEPLISAV-B	59	M	2	271	1	Resolved

F = female; M = male; y = years.
[a] Event occurred approximately 12-18 hours after the subject received the second dose of study vaccine and 55 days after the first dose.
Note: Severity: 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Life-threatening or disabling; 5 = Death.

6.7.7.1.1.1.2 New-Onset Adverse Events of Special Interest Excluding Bell's Palsy

Table 6-15 presents the new-onset AESIs excluding Bell's palsy listed by days since last active dose in treatment group in the PSP.

Bell's palsy was the most frequent event in both treatment groups and Basedow's (Grave's) disease was the only other event to occur in both treatment groups. The remaining AESIs occurred in 1 subject each, with variable time to onset, and involved a variety of organ systems and immune mechanisms.

In the PSP, AESIs assessed by the investigator as severe in intensity occurred in 5 HEPLISAV-B subjects (0.05%) and 1 Engerix-B subject (0.02%). Three rare, serious AESIs were reported in the HEPLISAV-B group: granulomatosis with polyangiitis, Guillain-Barré syndrome, and cavernous sinus syndrome (unconfirmed Tolosa Hunt syndrome). Narratives for these events are in Appendix 7. The event of Guillain-Barré syndrome occurred more than 3.5 months after the last HEPLISAV-B dose and 5 days after an influenza vaccination. One rare, serious AESI was reported in the Engerix-B group: ANCA positive vasculitis.

Thus, there is no evidence that suggests that HEPLISAV-B triggers any common autoimmune mechanism.

Table 6-15: Subjects With New-Onset AESI Excluding Bell's Palsy by Days Since Last Active Dose (PSP)

Trial	Age	Sex	Preferred Term	Last Active Dose	Days Since Last Active Dose	Immune Classification[a]
HEPLISAV-B						
HBV-16	69	M	Vitiligo	2	2	Classical autoimmune
HBV-16	62	M	Erythema Nodosum	2	20	Innate immune mediated
HBV-10	48	F	Lichen Planus	2	26	Innate immune mediated
HBV-10	41	F	Basedow's (Grave's) Disease	2	44	Classical autoimmune
HBV-10	54	F	Granulomatosis with Polyangiitis	2	73	Classical autoimmune
HBV-10	35	F	Guillain-Barré Syndrome	2	111	Molecular mimicry
HBV-23	46	F	Colitis Ulcerative	2	221	Intermediate disease MHC-class I
HBV-23	52	F	Alopecia Areata	2	229	Innate immune mediated
HBV-23	68	M	Polymyalgia Rheumatica	2	292	Innate immune mediated
HBV-16	68	M	Cavernous Sinus Syndrome[b]	2	292	Unknown
Engerix-B						
HBV-10	46	M	Raynaud's Phenomenon	3	33	Vasospasm
HBV-10	30	F	Basedow's (Grave's) Disease	2	78	Classical autoimmune
HBV-10	44	F	ANCA Positive Vasculitis	2	127	Classical autoimmune
			Scleroderma	2	127	Innate immune mediated

F = female; M = male.
a 65

b Diagnosis of Tolosa Hunt syndrome unconfirmed by radiology or pathology.

6.7.7.2 Immune-mediated Adverse Events Not on the List of AESI

SEAC adjudicated autoimmune events not on the AESI list comprised 3 events of hypothyroidism in women in the HEPLISAV-B group: 2 in HBV-16 and 1 in HBV-23 (See below). Four events of hypothyroidism in HBV-10 (HEPLISAV-B: n = 3; Engerix-B: n = 1) are not included because they were not adjudicated by a SEAC. The incidence of hypothyroidism in women in the HEPLISAV-B group in (0.8 per 1000 person years) was lower than an estimate from a systematic literature review that included population-based studies (3.5 per 1000 person years).[85]

- In HBV-16, a 58 year old white woman with a history of depression, hypoglycemia, fatigue, and anemia had onset of low blood pressure, dizziness, fatigue, and weakness 27 days after her first HEPLISAV-B dose. She had an elevated TSH and low T4. Forty-three days after her initial complaints she had a thyroid peroxidase antibody level of 167 IU/mL (0-34 IU/mL) and an antithyroid antibody level of 881 IU/mL (0-40 IU/mL). Baseline TSH was normal but antibodies were not evaluated.

- In HBV-16, a 52-year-old woman had a medical history that included obesity, anxiety, vasomotor symptoms of menopause, and alopecia. Over the year prior to enrollment, the subject had noted cold intolerance, fatigue, weight gain, and brittle fingernails. She was diagnosed with hypothyroidism 29 days after her second dose of HEPLISAV-B based on a low T4 and elevated TSH but negative antithyroid antibodies. The SEAC adjudicated the case as autoimmune even though she did not have antibodies because most primary hypothyroidism is autoimmune. They also thought her disease onset was prior to the study but because of the normal baseline thyroid test results, they considered her disease to be new onset.

- In HBV-23, a 61-year-old woman with an unremarkable medical history was diagnosed with nonclinical hypothyroidism 246 days after her second HEPLISAV-B dose based on an elevated TSH and normal free T4. On retrospective testing, she was found to have antithyroglobulin antibodies 3 months before her diagnosis of hypothyroidism. Six months after her diagnosis, she was diagnosed with thyroid papillary carcinoma associated with Hashimoto's thyroiditis. Her baseline sample had a normal thyroid panel but was not tested for antithyroglobulin antibodies. The SEAC adjudicated the event as a new-onset autoimmune event related to her papillary cancer.

6.7.7.3 Thyroid Adverse Events

Table 6-16 presents thyroid events by treatment group in the PSP.

To assess the frequency of thyroid adverse events, all events of hypothyroidism and hyperthyroidism using the narrow subsets of the 2 MedDRA SMQs designed to detect these events were analyzed. In the PSP, the frequency of thyroid events was balanced between the treatment groups.

Table 6-16: Thyroid AEs and MAEs by Preferred Term (PSP)

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

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

6.7.7.4 Exacerbation of Pre-existing Immune-mediated Adverse Events

There is a theoretical concern that adjuvants may exacerbate pre-existing immune-mediated conditions. Thus, the safety of HEPLISAV-B was also assessed in subjects who had pre-existing AESI. In the PSP, 140 subjects (HEPLISAV-B: n = 106; Engerix-B: n = 34) had a pre-existing AESI prior to enrollment. Four subjects (3.8%) in the HEPLISAV-B group (systemic lupus erythematosus, 2 with rheumatoid arthritis, and ulcerative colitis) and 1 subject (2.9%) in the Engerix-B group (mixed connective tissue disease) experienced an exacerbation of a pre-existing AESI.

6.7.7.5 Immune-mediated Adverse Event Conclusion

Evaluation of immune-mediated AEs focused on the frequency of events as well as the nature of individual events. In the PSP, the only disorders that occurred in more than 1 subject were the common disorders of Bell's palsy, Grave's disease, and hypothyroidism. No rare, serious AESI occurred in more than 1 subject. These results suggest that HEPLISAV-B does not increase the risk of immune-mediated AEs compared with Engerix-B.

6.7.8 Laboratory Assessments of Autoimmunity and Inflammation

Laboratory assays for autoantibodies were performed in certain trials as safety biomarkers related to autoimmunity. These assessments were performed independently of processes for clinical evaluation of AESIs or adjudicated immune-mediated events. ANA testing was performed as a protocol-specified assessment in all trials except HBV-04, HBV-22, and HBV-23. Anti-dsDNA testing was performed as a protocol-specified assessment in all trials except HBV-04, HBV-08, HBV-22, and HBV-23. ANCA testing was performed retrospectively on available banked specimens from study HBV-10 and HBV-14 based on the occurrence of an ANCA-associated vasculitis in HBV-10. Antiphospholipid antibodies were assessed in a subset of subjects in HBV-23.

6.7.8.1 Antinuclear Antibodies

The frequency of development of ANAs or increase in titers of pre-existing ANAs was similar between treatment groups. For analysis purposes, an ANA titer of 1:160 or higher was considered positive. As shown in Table 6-17, the percentage of subjects with positive post-vaccination ANA results was similar in the HEPLISAV-B and Engerix-B groups. The percentage of subjects seroconverting from a negative to a positive ANA result and with a post-treatment rise in a positive titer was also similar between groups.

Table 6-17: ANA Results by Treatment Group (HBV-10, HBV-16, HBV-02, HBV-03, HBV-05, HBV-08, and HBV-14 Safety Populations)

Antinuclear Antibodies[a]	HEPLISAV-B	Engerix-B
Pre-Vaccination, N	4164	1209
Positive (1:160 and above), % (n)	7.4 (310)	8.9 (108)
Post-Vaccination, N	3960	1156
Positive (1:160 and above), % (n)	8.5 (337)	9.2 (106)
Negative Pre-Vaccination, N[b]	3684	1057
Positive Post-Vaccination, % (n)	5.5 (201)	5.1 (54)

[a] Includes only trials in which ANA was analyzed (HBV-10, HBV-16, HBV-02, HBV-03, HBV-05, HBV-08 and HBV-14.
[b] Includes only subjects with evaluable (non-missing) pre-treatment and post-treatment results.

6.7.8.2 Anti-double-stranded Deoxyribonucleic Acid Antibodies

Table 6-18 presents anti-dsDNA results in HEPLISAV-B trials.

The rate of development of anti-dsDNA antibodies in recipients of HEPLISAV-B was similar to that in recipients of Engerix-B. As shown in Table 6-18, the percentage of subjects converting from a negative to a positive titer was 1.2% in the HEPLISAV-B group and 1.0% in the Engerix-B group.

Table 6-18: Anti-ds DNA Results by Treatment Group (HBV-10, HBV-16, HBV0001, HBV-05, and HBV-14 Safety Populations)

Anti-dsDNA[a]	HEPLISAV-B	Engerix-B
Pre-Vaccination, N	4117	1177
Positive, % (n)	1.0 (43)	1.4 (17)
Post-Vaccination, N	3922	1133
Positive, % (n)	1.6 (61)	1.8 (20)
Negative Pre-Vaccination, N[b]	3876	1111
Positive Post-Vaccination, % (n)	1.2 (46)	1.0 (11)

Anti-dsDNA = antibody to double-stranded DNA.
[a] Includes only trials in which anti-dsDNA was analyzed (HBV-10, HBV-16, HBV0001, HBV-05, and HBV-14).
[b] Includes only subjects with evaluable (non-missing) pre-treatment and post-treatment results.

6.7.8.3 Anti-neutrophil Cytoplasmic Antibodies

Table 6-19 presents ANCA results in HEPLISAV-B trials.

ANCA testing involved a screening enzyme-linked immunosorbent assay (ELISA) for anti-MPO or anti-PR3, followed by confirmatory immunofluorescence assay (IFA) for any positive ELISA result. Specimens that were negative by both screening ELISAs were not tested further. Denominators in Table 6-19 are based on the number of subjects with evaluable pre- and post-vaccination results. Specimens were not available for testing from the subjects who had ANCA-positive vasculitis in HBV-10.

In summary, retrospective pre- and post-vaccination testing for ANCA in HBV-10 and HBV-14 did not reveal any additional development of ANCA in either vaccination group. Positive screening ELISA results were infrequent and none were confirmed as cytoplasmic staining anti-neutrophil cytoplasmic antibody (c-ANCA) or perinuclear-staining anti-neutrophil cytoplasmic antibody (p-ANCA) positive by IFA.

Table 6-19: ANCA Testing Results in HBV-10 and HBV-14 by Treatment Group

Study	HBV-10 11 to 55[a]		HBV-14[b] 18 to 55
Treatment Arm	**HEPLISAV-B (N = 1780)**	**Engerix-B (N = 596)**	**HEPLISAV-B (N = 192)**
Pre-Treatment, % (n)			
Anti-PR3 positive	0.1 (2)	0.3 (2)	0
c-ANCA positive	0	0	Not done
Anti-MPO positive	0.1 (1)	0	0
p-ANCA positive	0	Not done[b]	Not done[c]
Post-Treatment, % (n)			
Anti-PR3 positive	0.1 (2)	0.3 (2)	0
c-ANCA positive	0	0	Not done[b]
Anti-MPO positive	0	0	1
p-ANCA positive	Not done[b]	Not done[b]	0

anti-MPO = antibody to myeloperoxidase; anti-PR3 = antibody to proteinase 3; c-ANCA = cytoplasmic staining anti-neutrophil cytoplasmic antibody; p-ANCA = perinuclear staining anti-neutrophil cytoplasmic antibody.
[a] Includes 13 subjects 11-17 years of age in HBV-10 (HEPLISAV-B: 11; Engerix-B: 2)
[b] HBV-14 did not have a comparator.
[c] Includes only subjects who had evaluable pre- and post-treatment time points.
If no screening test was positive, then no confirmatory test was done.

6.7.8.4 Antiphospholipid Antibodies

In the Laboratory Substudy in HBV-23, 309 subjects (HEPLISAV-B: n = 207; Engerix-B: n = 102) were tested at baseline only (Week 0) for genetic risk factors (Protein C, Protein S, antithrombin III, Factor V Leiden) and at Weeks 0, 4, 8, 24, and 56 for antiphospholipid antibodies (anticardiolipin IgG/IgM, anti-beta 2 glycoprotein 1 IgG/IgM, and lupus anticoagulant screen/confirmatory) which may be a risk factor for thrombotic or thromboembolic disease.

New-onset antiphospholipid antibodies were similar in both groups for anticardiolipin IgG and IgM, beta 2 glycoprotein 1 IgG, and lupus anticoagulant confirmatory. A higher proportion of HEPLISAV-B subjects (7.7%) had transient elevations of anti-beta 2 glycoprotein 1 IgM than Engerix-B subjects (1.0%) at Week 8 that returned essentially to normal levels by the next visit at Week 24.

No subject with an elevated anti-beta 2 glycoprotein 1 IgM had a co-incident thrombotic or thromboembolic event or developed antiphospholipid syndrome. Such antibodies have been described transiently following vaccination with Engerix-B and other vaccines [32, 80, 89] and in isolation have not been shown to increase the risk of thrombotic/thromboembolic events.[31]

6.7.9 Deaths

Table 6-20 presents causes of deaths occurring in the PSP and a listing of deaths is presented in Appendix 4. No death occurred in HBV-10.

There were 34 deaths in the PSP: 26 in recipients of HEPLISAV-B and 8 in recipients of Engerix-B. Most deaths occurred in subjects with significant pre-existing diseases, comorbidities, or contributory social circumstances; none of the deaths were considered by the investigator or Sponsor to be related to study treatment. Causes of deaths were balanced across treatment groups except for 6 deaths due to illicit or therapeutic drug overdose documented at autopsy in the HEPLISAV-B group compared with 1 in the Engerix-B group in HBV-23. Excluding drug overdoses, the proportion of subjects who died in the HEPLISAV-B group was 0.21% and in the Engerix-B was 0.18%.

Table 6-20: Deaths (Primary Safety Population)

Causes of death	HEPLISAV-B (N=9365) % (n)	Engerix-B (N=3867) % (n)
Total deaths	**0.28 (26)**	**0.21 (8)**
Drug overdose	0.06 (6)	0.03 (1)
Trauma	0.03 (3)	0.05 (2)
Hypertensive heart disease	0.03 (3)	0.03 (1)
Myocardial infarction	0.03 (3)	0.03 (1)
Cardiac arrest and cardiorespiratory arrest	0.02 (2)	0.03 (1)
Cancer	0.02 (2)	0.03 (1)
Unknown	0.02 (2)	0
Hepatic cirrhosis	0.01 (1)	0
Hepatitis C	0.01 (1)	0
Acute Respiratory Distress Syndrome	0.01 (1)	0
Acute Respiratory Failure	0.01 (1)	0
Pulmonary Embolism	0.01 (1)	0
Cardiac failure	0	0.03 (1)

6.7.10 Serious Adverse Events

Table 6-21 presents SAEs by preferred term for HEPLISAV-B events occurring in more than 0.1% of subjects in either vaccine group in the PSP.

SAEs were generally similar between treatment groups in type and frequency in the PSP and were commensurate with common morbidities in the general adult population. In the PSP, differences between treatment groups with a higher proportion in Engerix-B in 2 PTs (*prostate cancer and dehydration*) had 95% CIs that excluded 1.

In the PSP, a numerical imbalance toward HEPLISAV-B was observed in the single preferred term of a*cute myocardial infarction* only in HBV-23 and is discussed in Section 6.7.11. A complete summary of SAEs by preferred term is provided in Appendix 5.

Table 6-21: Summary of SAEs ≥ 0.1% by Preferred Term (Primary Safety Population)

System Organ Class Preferred Term	HEPLISAV-B (N=9365) % (n)	Engerix-B (N=3867) % (n)
Subjects with at least 1 event	4.8 (449)	4.8 (184)
Pneumonia	0.17 (16)	0.21 (8)
Osteoarthritis	0.17 (16)	0.13 (5)
Acute Myocardial Infarction	0.17 (16)	0.05 (2)
Non-cardiac Chest Pain	0.13 (12)	0.21 (8)
Chronic Obstructive Pulmonary Disease	0.11 (10)	0.10 (4)
Atrial Fibrillation	0.07 (7)	0.10 (4)
Cellulitis	0.07 (7)	0.10 (4)
Prostate cancer	0.04 (4)	0.18 (7)
Deep Vein Thrombosis	0.06 (6)	0.10 (4)
Cholelithiasis	0.04 (4)	0.10 (4)
Syncope	0.02 (2)	0.10 (4)
Dehydration	0.01 (1)	0.10 (4)

6.7.11 Strategy to Assess the Numerical Imbalance in *Acute Myocardial Infarctions*

The numerical imbalance in *acute myocardial infarctions* in HBV-23 was an unexpected finding. It was not observed in nonclinical studies or in previous clinical trials and there is no known plausible association between 1018, other CpG ODNs, or other hepatitis B vaccines and cardiovascular disease. Cardiovascular endpoints were not prospectively evaluated in any HEPLISAV-B trial including HBV-23. Thus, the evaluation of the numerical imbalance was post-hoc with no formal hypothesis testing.

A comprehensive strategy to assess whether the numerical imbalance in *acute myocardial infarctions* in HBV-23 could be associated with treatment was developed in collaboration and consultation with Darren McGuire, MD, MHSc (University of Texas Southwestern Medical Center) (Table 1-3). Dr. McGuire is a cardiologist with extensive clinical trial and regulatory experience in the cardiovascular area. This systematic strategy included:

1. Performing blinded review of clinical annotations and cardiac catheterization data by Dr. McGuire for all reported acute myocardial infarction events;

2. Broadly searching for other possibly missed acute myocardial infarctions or strokes using the MedDRA SMQs — a strategy that augments capture of all potential myocardial infarction and stroke events;

3. Engaging the Cleveland Clinic C5 Research Center to perform post-hoc, blinded, central adjudication of all deaths and all potential myocardial infarctions and strokes identified by preferred term/SMQs using standardized processes and case definitions for events commonly used in clinical development of cardiovascular therapeutics;[51]

4. Conducting analyses of the reported acute myocardial infarction events and analyses of the composite outcome of adjudication-confirmed major adverse cardiovascular events (MACE) comprising cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, and analysis of each independent component of the composite. Analysis of this 3-point MACE composite outcome is the gold standard for cardiovascular outcomes assessment of atherosclerotic vascular diseases that share a common underlying pathophysiology and represent a continuum of the natural history of atherosclerotic vascular disease and its acute complications;[110]

5. Using confirmed MACE outcomes to examine:

    a. Baseline characteristics of subjects who experienced events,

    b. Timing of events relative to vaccination, and

    c. Observed rates of events with expected background rates modeled using population-based databases and risk prediction methods commonly used in clinical practice;

6. Evaluating possible vaccine-induced immunological etiologies of myocardial infarction and MACE outcome:

    a. Mimicking an acute systemic infection (that increases the risk of myocardial infarction and stroke shortly after diagnosis);

    b. Vasculitis;

    c. Myocarditis; or

    d. Hypercoagulable state.

Based on this systematic evaluation, we found that myocardial infarctions and MACE outcomes occurred:

- In persons in whom they would be expected, who had a high burden of cardiovascular risk factors with advanced and often multi-vessel obstructive coronary artery disease;
- With no evidence by clinical annotations and cardiac catheterization data for inflammatory/immune-mediated vasculitides or myocarditis;
- With no evidence of a hypercoagulable state as other venous or arterial thrombotic/thromboembolic events were balanced;
- Without close temporal relationship to vaccination administration;
- At rates in the HEPLISAV-B group that were similar to or lower than predicted background.

The observed numerical difference between treatment groups in the occurrence of events coded to the MedDRA preferred term *acute myocardial infarction* in HBV-23 is an isolated finding in the HEPLISAV-B database that appears most likely explained by random variation resulting in an unexpectedly low number of events observed in the Engerix-B group in HBV-23.

6.7.11.1 *Acute Myocardial Infarction*

In HBV-23, there was a numerical imbalance in safety events coded to the single MedDRA preferred term of *acute myocardial infarction* (Table 6-22). In HBV-23, a higher proportion of HEPLISAV-B than Engerix-B recipients were reported to have an *acute myocardial infarction*. In HBV-16, albeit small numbers, a lower proportion of HEPLISAV-B than Engerix-B recipients were reported to experience such an event. No *acute myocardial infarctions* were reported in HBV-10. Of note, in HBV-23, *acute myocardial infarctions* occurred in 0.26% (n = 2) of 762 subjects with diabetes who received HEPLISAV-B and in 0.26% (n = 1) of 381 subjects with diabetes who received Engerix-B. Death due to *acute myocardial infarction* was reported in 1 HEPLISAV-B recipient and 0 Engerix-B recipients.

Table 6-22: Treatment-Emergent SAEs Reported Coded to the MedDRA Preferred Term *Acute Myocardial Infarction* in HEPLISAV-B Phase 3 Clinical Trials

Study	HEPLISAV-B		Engerix-B		Relative Risk	95% CI
	n/N	%	n/N	%		
HBV-23	14/5587	0.25	1/2781	0.04	6.97	0.92, 52.97
HBV-16	2/1968	0.10	1/481	0.21	0.49	0.04, 5.38
HBV-10	0/1810	0	0/605	0	NA	NA

CI = confidence interval; NA = not applicable
Note: an *acute myocardial infarction* occurred in a 54-year-old obese woman during the screening period and 2 weeks prior to receiving an injection of HEPLISAV-B. This event is not included in these analyses. She received both doses of HEPLISAV-B and did not report a treatment-emergent cardiovascular event.

6.7.11.1.1 Cardiac Catheterization Results

Cardiac catheterization reports were available for most subjects reported with *acute myocardial infarction* (16/18). Of the 2 without a catheterization report, 1 had catheterization results summarized well in the discharge summary and the other subject died prior to having cardiac catheterization. These reports and the case summaries were reviewed by Dr. McGuire blinded to investigational product assignment. In each case, Dr. McGuire determined that the clinical presentation was determined to be most consistent with a typical acute coronary syndrome event, and for the majority with catheterization data, there were consistent descriptions of typical acute "culprit" lesions in the setting of advanced, most often multi-vessel obstructive coronary artery disease.

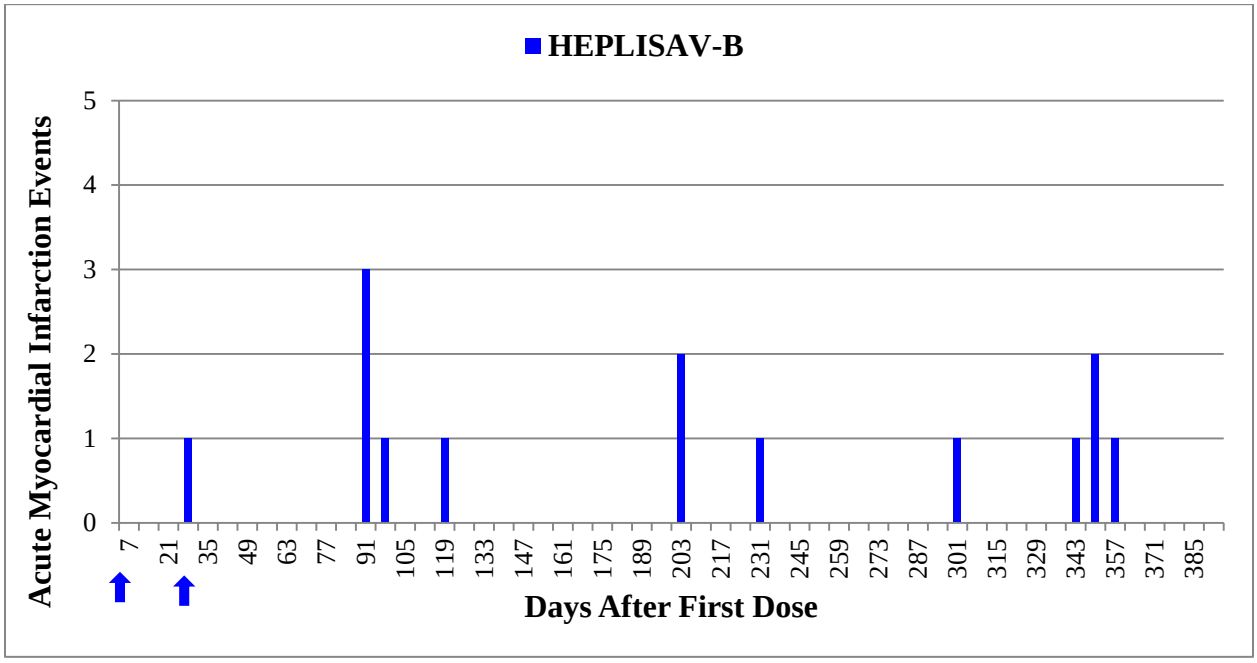
Importantly, the catheterization reports rule out atypical causes for acute myocardial infarction that could be mediated by inflammation or immune mechanisms, such as coronary vasculitis, aneurysmal disease, coronary dissection, vasospasm, embolism/*in situ* thrombosis, or myocarditis masquerading as an acute myocardial infarction. These clinical annotations and catheterization reports also exclude "type 2 myocardial infarctions"-that is, myocardial infarction due to myocardial supply demand mismatch often driven by acute stressors such as sepsis, shock, anemia, hypertensive crisis, heart failure decompensation, hypoxia, acute kidney failure, etc.

6.7.11.2 Temporal Distribution of *Acute Myocardial Infarctions* in the HEPLISAV-B Group in HBV-23

Figure 6-1 presents the day of occurrence of *acute myocardial infarctions* in subjects who received HEPLISAV-B in HBV-23.

In HBV-23, *acute myocardial infarctions* in subjects who received HEPLISAV-B were sparse and occurred throughout the study.

Figure 6-1: Distribution of *Acute Myocardial Infarctions* Over Time (HBV-23 Safety Population)



The arrows represent HEPLISAV-B injections.

6.7.11.3 Myocardial Infarction by Standardized MedDRA Query

The MedDRA preferred term *acute myocardial infarction* represents only one of several preferred terms that potentially describes an acute coronary syndrome event. Because the preferred terms *acute coronary syndrome* and *myocardial infarction* as well as others might also represent myocardial infarctions, a broader search of the HEPLISAV-B safety database was conducted using the myocardial infarction SMQ. SMQs are validated tools developed to facilitate retrieval of MedDRA-coded data as a first step in investigating drug safety issues in pharmacovigilance and clinical development.

Table 6-23 presents data from subjects who had events identified using the MedDRA myocardial infarction SMQ in the PSP.

Using the myocardial infarction SMQ, 0.22% of HEPLISAV-B subjects and 0.10% of Engerix-B subjects had at least 1 such event in the PSP (RR = 2.17; 95% CI: 0.75, 6.31). The only imbalance was in the preferred term *acute myocardial infarction*; the small number of subjects with events in other terms indicative of myocardial infarction were balanced between the 2 vaccine groups.

Table 6-23: Treatment-Emergent SAEs in the Myocardial Infarction SMQ by Preferred Term (Primary Safety Population)

Preferred Term	HEPLISAV-B (N=9365) % (n)	Engerix-B (N=3867) % (n)
Subjects with at least 1 qualifying adverse event	0.22 (21)	0.10 (4)
Acute Coronary Syndrome	0.01 (1)	0
Acute Myocardial Infarction	0.17 (16)	0.05 (2)
Angina Unstable	0.01 (1)	0.03 (1)
Coronary Artery Occlusion	0.01 (1)	0.03 (1)
Myocardial Infarction	0.02 (2)	0.03 (1)

SMQ = Standardised MedDRA queries.

6.7.11.4 Major Adverse Cardiovascular Events

To fully assess the potential relationship of HEPLISAV-B and myocardial infarctions, an analysis of major adverse cardiovascular events (MACE) was conducted. MACE is the gold standard for cardiovascular outcomes assessment to capture the spectrum of events associated with unstable atherosclerosis such as myocardial infarction and stroke.[110] A 3-point MACE analysis comprises the composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, and analysis of each of the 3 individual components. These MACE outcomes share a common underlying pathophysiology so that a difference in the incidence in myocardial infarction would be expected to be similarly observed in cardiovascular death and stroke.

MACE outcomes were ascertained by identifying all treatment-emergent deaths and preferred terms representing non-fatal myocardial infarction and non-fatal stroke. A myocardial infarction that occurred in a HEPLISAV-B recipient in the screening period before receiving any vaccine injection is not included.

Dynavax engaged the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) to perform independent and blinded post-hoc adjudication of all potential MACE outcomes.[11] Preferred terms selected to identify potential MACE outcomes were chosen by Dr. Darren McGuire, based on established SMQ terms for each outcome, blinded to study assignment and reported preferred terms. C5Research adjudicated events using standard case definitions for cardiovascular event adjudication in registration research[51] and standard to their routine adjudication practice and processes. Events were adjudicated as: 1) a MACE outcome, 2) not a MACE outcome, or 3) insufficient information to make a determination. Adjudicated events confirmed to be MACE outcomes were used in the analyses of the composite MACE endpoint and each of the 3 component outcomes. One subject who received HEPLISAV-B and 1 subject who received Engerix-B each had 2 stroke events; otherwise, only 1 event occurred in each subject with a confirmed MACE outcome. The subjects are counted only once except in the graphical distribution of MACE outcomes over time in which each of the 2 recurrent stroke events are included.

6.7.11.4.1 Potential Major Adverse Cardiovascular Events

Table 6-24 presents the summary of events that were submitted to C5Research for adjudication. No MACE outcomes occurred in HBV-10.

In the small number of potential MACE outcomes in HBV-16, composite 3-point MACE outcomes, deaths, and myocardial infarctions, were reported more frequently in the Engerix-B group than in the HEPLISAV-B group. No strokes were observed in HBV-16.

In HBV-23, the composite 3-point MACE, deaths, and myocardial infarctions were reported more frequently in the HEPLISAV-B group than in the Engerix-B group but strokes were similar between the groups.

In the PSP, the primary difference was in myocardial infarction.

Table 6-24: Potential Treatment-Emergent, Serious MACE by Treatment Group Sent for Blinded Event Adjudication (PSP)

Study	HBV-16		HBV-23		Primary Safety Population	
Treatment	HEPLISAV-B (N = 1968) % (n)	Engerix-B (N = 481) % (n)	HEPLISAV-B (N = 5587) % (n)	Engerix-B (N = 2781) % (n)	HEPLISAV-B (N = 9365) % (n)	Engerix-B (N = 3867) % (n)
Composite MACE	0.15 (3)	0.42 (2)	0.93 (52)	0.47 (13)	0.59 (55)	0.39 (15)
Death from Cardiovascular cause[a]	0.05 (1)	0.21 (1)	0.45 (25)	0.25 (7)	0.28 (26)	0.21 (8)
Myocardial infarction[b]	0.10 (2)	0.21 (1)	0.34 (19)	0.11 (3)	0.22 (21)	0.10 (4)
Stroke[c]	0	0	0.20 (11)	0.18 (5)	0.12 (11)	0.13 (5)

MACE = Major Adverse Cardiovascular Events.

[a] Includes all deaths including death from cardiovascular cause: Acute Coronary Syndrome, Acute Myocardial Infarction, Acute Respiratory Failure, Cardiac Arrest, Cardiac Failure, Cardio-respiratory Arrest, Death, Hypertensive Heart Disease, Myocardial Infarction, or Pulmonary Embolism.

[b] Myocardial infarction comprises the following preferred terms: Acute Coronary Syndrome, Acute Myocardial Infarction, Coronary Artery Embolism, Coronary Artery Occlusion, Coronary Artery Thrombosis, Coronary Bypass Thrombosis, Myocardial infarction, Post Procedural Myocardial Infarction, Silent Myocardial Infarction, or Unstable Angina.

[c] Stroke comprises the following preferred terms: Basal Ganglia Stroke, Brain Stem Stroke, Cerebrovascular Accident, Hemorrhagic Stroke, Hemorrhagic Transformation Stroke, Stroke in Evolution, Basal Ganglia Infarction, Basal Ganglia Stroke, Brain Stem Embolism, Brain Stem Infarction, Brain Stem Stroke, Cerebellar Embolism, Cerebellar Infarction, Cerebral Artery Embolism, Cerebral infarction, Cerebrovascular Accident, Embolic Cerebral Stroke, Embolic Stroke, Ischemic Cerebral infarction, Ischemic Stroke, Lacunar Infarction, Lacunar Stroke, Thalamic Infarction, Thrombotic Cerebral Infarction, or Thrombotic Stroke.

6.7.11.4.1.1 Data Available for Adjudication of Myocardial Infarctions

Although clinical cardiovascular information was not collected prospectively, data to support the adjudication process was reasonably complete for most subjects reported to have myocardial infarctions, with cardiac enzyme data for 15 of the 21 non-fatal events and cardiac catheterization data available for all non-fatal events (Table 6-25).

Table 6-25 presents a summary of the data available for adjudication of myocardial infarctions included in the myocardial infarction SMQ. Brief narratives that include information from cardiac catheterization reports for each event are presented in Appendix 6.

Table 6-25: Data Available for Adjudication of Potential Myocardial Infarctions (Primary Safety Population)

Subject ID	Symptoms	ECG Interpretation	Cardiac Enzymes	Cardiac Catheterization		
				Data Available	# of Diseased Vessels	Culprit Lesion Described
HBV-16						
-335	✓		✓	✓	2	
-610	✓		✓	✓	1	
-614	✓		✓	✓	2	
HBV-23						
-291[a]	✓	✓	✓	✓	3	✓
-011	✓	✓	✓	✓	1	✓
-076	✓	✓	✓	✓	2	✓
-045	✓		✓	✓	2	
-118	✓	✓	✓	✓	1	✓
-154	✓	✓	✓	✓	0	✓
-189	✓	✓	✓	✓	1	✓
-312	✓			✓	2	
-090	✓	✓	✓	✓	2	✓
-1050	✓	✓	✓	✓	3	✓
-174	✓	✓	✓	✓	Not reported	
-992	✓	✓	✓	✓	2	✓
-206	✓			✓	3	✓
-373	✓	✓	✓	✓	1	✓
-037	✓	✓	✓	✓	2	
-099	✓	✓	✓	✓	1	✓
-110	✓	✓	✓	✓	1	✓
-102[a]	✓			✓	3	
-613				NA[b]		
-084				NA[b]		
-091				NA[b]		
-070				NA[b]		

ECG = electrocardiogram; NA = not applicable.
[a] Subject had coronary artery bypass surgery
[b] Subject died without catheterization

6.7.11.4.1.2 Outcome of C5 Research Adjudication Process

Table 6-26 presents a summary of the outcome of the adjudication process.

Of the 34 potential MACE outcomes of death due to cardiovascular cause (HEPLISAV-B: n = 26; Engerix-B: n = 8), 6 (HEPLISAV-B: n = 4; Engerix-B: n = 2) were confirmed as a cardiovascular death. Deaths that were not confirmed as MACE outcomes included other causes of death such as *gunshot wound*, *acute respiratory failure*, and *metastatic pancreatic carcinoma*.

Of the 25 potential MACE outcomes of myocardial infarction (HEPLISAV-B: n = 21; Engerix-B: n = 4), 18 (HEPLISAV-B: n = 16; Engerix-B: n = 2) were confirmed as MACE outcomes. Four events adjudicated as not myocardial infarctions were fatal events, 2 of which were adjudicated as cardiovascular deaths and 2 as deaths of undetermined cause.

Of the 16 subjects with potential MACE outcomes of stroke (HEPLISAV-B: n = 11; Engerix-B: n = 5), 15 (HEPLISAV-B: n = 11; Engerix-B: n = 4) were confirmed as MACE outcomes. One stroke was excluded because the patient had a normal brain MRI.

Table 6-26: Summary of Outcome of Adjudication Process

Outcome	Cardiovascular Death	Myocardial Infarction	Stroke
Total Subjects with Potential Events Reviewed			
HEPLISAV-B	26	21	11
Engerix-B	8	4	5
Outcome of Adjudication			
Confirmed as MACE Outcome			
HEPLISAV-B	4	16	11
Engerix-B	2	2	4
Confirmed as Not a MACE Outcome			
HEPLISAV-B	15	4	0
Engerix-B	6	2	1
Undetermined MACE Outcome			
HEPLISAV-B	7	1	0
Engerix-B	0	0	0

Note: Some subjects had more than 1 event that was adjudicated. One subject who received HEPLISAV-B and 1 subject who received Engerix-B each had 2 stroke events.

6.7.11.4.2 Confirmed 3-Point MACE Outcomes

Figure 1-3 in the Executive Summary presents the analysis of confirmed 3-point MACE outcomes by trial and in the PSP.

In HBV-16, composite MACE outcomes and the individual component outcomes of deaths due to cardiovascular cause and myocardial infarctions occurred in a higher proportion of subjects in the Engerix-B group than in the HEPLISAV-B group. No strokes were observed in HBV-16.

In HBV-23, composite MACE outcomes and myocardial infarctions occurred in a higher proportion of subjects in the HEPLISAV-B group than in the Engerix-B group; however, the frequencies of cardiovascular deaths and strokes were similar between treatment groups.

In the PSP, a numerical imbalance was observed only in myocardial infarction attributable to the imbalance observed in the single trial, HBV-23; death due to cardiovascular cause and stroke were balanced between groups. Removing adjudication-confirmed myocardial infarction events observed in HBV-23 from the PSP, 0.18% (n = 17) of subjects in the HEPLISAV-B group and 0.18% (n = 7) of subjects in the Engerix-B group experienced a MACE outcome. The difference between treatment groups is thus driven entirely by the imbalance in myocardial infarctions in HBV-23.

6.7.11.4.2.1 Multivariable Logistic Regression Analysis

In a multivariable logistic regression model using the PSP and analyzing confirmed MACE outcomes, candidate variables tested were age, sex, race, hypertension, BMI, diabetes mellitus, smoking, history of myocardial infarction or stroke, and treatment group. In the model, hypertension (Odds Ratio [OR] = 4.22; 95% CI: 1.92, 9.29), sex (OR = 2.02 for male vs female; 95% CI: 1.01, 4.02) and age (OR = 1.07 for 1 year increase; 95% CI: 1.03, 1.12) were statistically significant independent predictors of myocardial infarction. HEPLISAV-B compared with Engerix-B was not a significant independent predictor of the risk of MACE event (OR = 1.63; 95% CI: 0.75, 3.55).

6.7.11.4.3 Baseline Cardiovascular Risk Factors in Subjects with a MACE

Table 6-27 presents cardiovascular risk factors and medications among subjects who had a MACE outcome compared with the PSP. These baseline characteristics and medication use were similar between treatment groups, but with a clustering of cardiovascular risk factors and medication use in those subjects experiencing MACE outcomes.

The subjects who had MACE outcomes were older and had more than a 2-fold higher prevalence of hypertension, diabetes, and hyperlipidemia and were more commonly on antihypertensive, antithrombotic or lipid lowering medication at enrollment. Every subject who had a MACE outcome in the HEPLISAV-B trials had one or more of these cardiovascular risk factors and/or prior cardiovascular disease.

In addition, for the adjudication-confirmed myocardial infarctions, the clinical presentation was determined to be most consistent with a typical acute coronary syndrome event, and for the majority, there were consistent descriptions of typical acute "culprit" lesions in the setting of advanced, most often multi-vessel obstructive coronary artery disease.

Table 6-27: Baseline Cardiovascular Risk Factors in Subjects Who Had a MACE Outcome Compared With the Primary Safety Population

Risk Factors	MACE (N = 39)	HEPLISAV-B (N = 9365)	Engerix-B (N = 3867)
Age: median in years (range)	60 (39 – 70)	49.1 (18 – 70)	49.2 (18 – 70)
Medical Condition	**% (n)**	**% (n)**	**% (n)**
Hypertension	74.4 (29)	29.8 (2792)	30.5 (1178)
Hyperlipidemia	25.6 (10)	10.9 (1019)	11.8 (455)
Obesity	46.2 (18)	43.2 (4050)	42.8 (1657)
Diabetes mellitus	20.5 (8)	10.3 (961)	11.0 (425)
Smoking	28.2 (11)	31.3 (2928)	32.4 (1251)
Anatomical Therapeutic Chemical Classification System Level 2 Drug Class			
Agents acting on the renin angiotensin system	43.6 (17)	20.1 (1883)	20.7 (799)
Antithrombotic agents	28.2 (11)	13.2 (1233)	13.6 (527)
Beta blocking drugs	28.2 (11)	8.3 (781)	8.3 (321)
Lipid modifying agents	38.5 (15)	19.9 (1865)	20.4 (790)

MACE = Major Adverse Cardiovascular Events.

6.7.11.4.3.1 Baseline Number of Cardiovascular Risk Factors in Subjects With MACE Outcomes

Table 6-28 presents subjects with MACE outcomes by number of baseline cardiovascular risk factors in the HEPLISAV-B group compared with the Engerix-B group in the PSP.

In both treatment groups, the proportion of subjects with MACE outcomes increased with increasing numbers of risk factors.

Among subjects who had MACE outcomes, the estimated 10-year risk for heart disease or stroke at baseline using the Pooled Cohort Equations hard atherosclerotic cardiovascular disease (ASCVD) risk calculator in common clinical use was similar for subjects who received HEPLISAV-B (12.6%) and subjects who received Engerix-B (12.4%).[45]

Table 6-28: Number of Baseline Cardiovascular Risk Factors in Subjects Who Had a MACE Outcome by Treatment Group (Primary Safety Population)

Risk Factor	HEPLISAV-B N=9365		Engerix-B N=3867	
	n/N	%	n/N	%
0	1/1531[a]	0.07	0/590	0
1	5/3160	0.16	0/1305	0
2	9/2534	0.36	2/1081	0.19
3+	16/2140	0.75	6/891	0.67

Risk Factors = Male ≥ 45/Female ≥ 55; diabetes; hypertension; obesity; current smoker

[a] One 46-year old woman who had a stroke in HBV-23 had a history of a previous stroke in the same vascular distribution but did not have 1 of the risk factors analyzed in this table.

6.7.11.4.4 Temporal Distribution of MACE

Figure 1-4 in the Executive Summary presents the time of occurrence of MACE outcomes per 1000 subjects in the PSP.

MACE outcomes occurred over the entire duration of the trials without clear evidence of a cluster of events at any time.

6.7.11.4.4.1 Time to Onset of MACE

Acute respiratory tract infections and urinary tract infections have been associated with an increased risk of both myocardial infarction and stroke shortly after diagnosis and for 28 days afterward. For example, a large study by Smeeth and colleagues provided evidence of an increased incidence of myocardial infarction and stroke after lower respiratory tract infection such as influenza or pneumonia or urinary tract infection.[113] The increased incidence rate of myocardial infarction was greatest in the first 1 to 3 days after infection was diagnosed (up to 4.95-fold higher), declined substantially by 28 days, and approached baseline values between 28 and 91 days. Importantly, no increased risk was observed following influenza, tetanus, or pneumococcal vaccination.[26, 27, 107, 112, 113, 123] Other studies demonstrated a similar transiently increased risk of myocardial infarction at the time of or following infection including upper respiratory infection with the highest risk in the first week and risk returning to baseline by 28 days. Figure 1-5 in the Executive Summary presents a Kaplan-Meier curve of time to first MACE outcome occurring in the PSP over the entire follow-up period. Through 28 days after the second injection (Study Day 56), the proportion of subjects reporting events is balanced between the 2 treatment groups (HEPLISAV-B: 0.05% [n = 5]; Engerix-B: 0.05% [n = 2]). The imbalance in MACE outcomes occurred late in the studies beginning after Study Day 100. Of note, the incidence in the HEPLISAV-B group in the first 100 days (4.3/1000 person years) was similar to the last 100 days (4.6/1000 person years).

6.7.11.4.5 Comparison of Observed With Expected Rates of MACE Outcomes

To estimate the expected frequency of MACE outcomes in the trial populations, 2 different approaches were used:

1. Dynavax chose population-based data published from studies in the US that were most comparable to the HEPLISAV-B study populations and to data collection methods. These databases were used to estimate the expected rate and number of events in HBV-16 and HBV-23. The HEPLISAV-B age-, sex-, and race-adjusted results were likely conservative because they did not consider cardiovascular risk factors that were higher in HBV-16 and HBV-23 than in the general population.

2. Estimates for expected coronary heart disease and atherosclerotic cardiovascular disease event rates based on baseline cardiovascular risk factors were derived from well-validated risk prediction models for the US, the Pooled Cohort Equations ASCVD risk calculator and the Framingham Risk Score.

6.7.11.4.5.1 Estimates of Myocardial Infarction and Stroke Based on Population-Based Data

Population-based estimated rates of myocardial infarction and stroke for the US are available for whites and blacks 35 years of age and older.[92] Dynavax used these sources to estimate the rate and number of MACE outcomes that would be expected to occur in 35- to 70-year-old white and black subjects in the Dynavax trials in North America (HBV-16 and HBV-23). HBV-10 is not included in this analysis as this trial enrolled subjects in Germany who may have different cardiac risk factors than a US population.

Table 6-29 presents a comparison of the observed and expected rates and numbers of MACE outcomes in HBV-16 and HBV-23.

In HBV-16, in the HEPLISAV-B group, the rate of observed composite and individual component MACE outcomes were lower than expected. In the Engerix-B group, rates were similar to or lower than expected.

In HBV-23, in the HEPLISAV-B group, observed composite MACE outcomes and cardiovascular deaths were lower than expected, and myocardial infarction and strokes were similar to expected. In HBV-23, in the Engerix-B group, observed composite MACE outcomes, deaths, myocardial infarctions, and strokes were each lower than expected. Notably, in HBV-23, the observed rate of myocardial infarction in the Engerix-B group was 6.8-fold lower than expected.

In the PSP, rates and numbers of MACE outcomes adjusted by age, sex, and race, but not for other cardiovascular risk factors in the HEPLISAV-B group, were similar to or lower than expected. In the Engerix-B group, rates were lower than expected.

Table 6-29: Comparison of Observed With Expected Rates and Numbers of MACE in 35 to 70 Year-old Whites and Blacks in HBV-16 and HBV-23 (HBV-16 and HBV-23 Safety Populations)

HBV-16 and HBV-23 Safety Populations		HBV-16		HBV-23		Pooled HBV-16 and HBV-23	
		HEPLISAV-B (N = 1830 person years)	Engerix-B (N = 451 person years)	HEPLISAV-B (N = 4893 person years)	Engerix-B (N = 2453 person years)	HEPLISAV-B (N = 6724 person years)	Engerix-B (N = 2903 person years)
MACE	Expected rate	6.1/1000 p-y		6.7/1000 p-y		6.5/1000 p-y	
	Expected -- n	11	3	33	16	44	19
	Observed /1000 p-y (n)	1.6 (3)	4.4 (2)	5.7 (28)	2.4 (6)	4.6 (31)	2.8 (8)
Cardio-vascular Deaths	Expected rate	1.5/1000 p-y		1.6/1000 p-y		1.6/1000 p-y	
	Expected -- n	3	1	8	4	11	5
	Observed /1000 p-y (n)	0.5 (1)	2.2 (1)	0.6 (3)	0.4 (1)	0.6 (4)	0.7 (2)
MI	Expected rate	2.5/1000 p-y		2.7/1000 p-y		2.6/1000 p-y	
	Expected -- n	5	1	13	6	18	8
	Observed/1000 p-y (n)	1.1 (2)	2.2 (1)	2.9 (14)	0.4 (1)	2.4 (16)	0.7 (2)
Stroke	Expected rate	2.1/1000 p-y		2.4/1000 p-y		2.3/1000 p-y	
	Expected -- n	4	1	12	6	15	7
	Observed/1000 p-y (n)	0	0	2.2 (11)	1.6 (4)	1.6 (11)	1.4 (4)

MACE = Major Adverse Cardiovascular Events; MI = myocardial infarction; p-y = person-year.
NOTE: All MACE outcomes occurred in white and black subjects. There were no MACE outcomes in HBV-10. Population-based estimates were based on incidence of events in whites and blacks in the US: 1) Vital Statistics surveillance for deaths [23, 64]; 2) the Atherosclerosis Risk in Communities Surveillance for myocardial infarction; and 3) the Greater Cincinnati/Northern Kentucky Stroke Study for strokes.[92]

6.7.11.4.5.2 Estimates Using Risk Prediction Models

Table 6-30 presents the proportion of subjects with cardiovascular risk factors in HBV-16 and HBV-23. The proportion of subjects with hypertension in HBV-16 and HBV-23 was similar to background but a higher proportion of subjects had diabetes or were obese or smokers than in the background population.

Table 6-30: Risk Factors for Cardiovascular Disease in the United States and in HBV-16 and HBV-23

Risk Factors	United States %	HBV-16 and HBV-23 (Safety Population) %
Hypertension	32.6	34.4
Diabetes mellitus	8.5	12.3[a]
Obese	35.2	46.9
Smoker	17.9	30.5

[a] Defined as diagnosis of diabetes and taking medication for diabetes.

Table 6-31 presents the expected number of MACE outcomes and myocardial infarctions in subjects using risk prediction models that take into consideration the cardiovascular risk factors in the study populations.

In the absence of lipid profile data in the HEPLISAV-B trials, conservative parameter estimates were used for cholesterol values in the Pooled Cohort Equations ASCVD risk model and in the Framingham Risk Score model for coronary heart disease event prediction. Accounting for risk factors in the population-based risk estimation models increased the expected number of events over the age-, sex-, and race-adjusted estimates. The number of observed events was similar to or lower than predicted in each trial and in HBV-16 and HBV-23 combined.

Table 6-31: Comparison of Observed and Expected Number of MACE and Myocardial Infarctions in White and Black Subjects Using Risk Prediction Models (HBV-16 and HBV-23 Safety Populations)

	HEPLISAV-B		Engerix-B	
	Observed n / N	Expected n (95% CI)	Observed n / N	Expected n (95% CI)
Pooled Cohort Equations—ASCVD (MACE)				
HBV-16	3/1916	10.9 (9.9, 11.9)	2/468	2.8 (2.5, 3.0)
HBV-23	28/5429	38.6 (34.6, 42.6)	6/2703	18.5 (16.6, 20.5)
HBV-16 and HBV-23	31/7345	49.5 (44.5, 54.5)	8/3171	21.3 (19.1, 23.5)
Risk Equation for Hard CHD Framingham Heart Study				
HBV-16 [a]	2/1916	7.7 (6.5, 8.9)	1/468	2.0 (1.7, 2.3)
HBV-23 [a]	14/5429	24.0 (20.4, 27.7)	1/2703	11.6 (9.8, 13.4)
HBV-16 and HBV-23 [a]	16/7345	31.7 (27.0, 36.5)	2/3171	13.6 (11.5, 15.7)

ASCVD = atherosclerotic cardiovascular disease; Hard CHD = hard coronary heart disease; CI = Confidence Interval; MACE = Major Adverse Cardiovascular Events; PSP = Primary Safety Population.

[a] Observed number is for the myocardial infarction component of MACE

All observed MACE outcomes occurred in white and black subjects. There are no MACE outcomes in HBV-10.

6.7.11.4.6 Biological Plausibility

There are 3 major underlying causes of acute myocardial infarction and stroke: 1) rupture or destabilization of atherosclerotic plaque; 2) mismatch of myocardial oxygen supply and demand; and 3) acute vessel thrombosis/thromboembolism.[8]

6.7.11.4.6.1 Rupture or Destabilization of Atherosclerotic Plaque

One hypothesis for a possible causal association of HEPLISAV-B with an increased risk of myocardial infarction is based on analogy to the well-documented association between acute infections and an increased incidence of both myocardial infarction and stroke. The specific mechanisms by which acute infections may trigger plaque rupture and subsequent thrombosis are not clearly defined. They are likely to reflect, in part, the inflammatory responses to infection initiated by PRR recognition of multiple pathogen-encoded ligands.[4, 27, 108] The 1018 adjuvant is an analog of microbial DNA and acts through a signaling pathway involved in the innate immune responses to infection by bacteria and DNA viruses. Signaling through TLR9 in bacterial or viral infections could mimic infection, especially if 1018 is present in plaques at biologically active concentrations.

Several of the TLRs, especially TLRs 1, 2 and 4, are highly expressed by human atherosclerotic plaques and at higher levels than in normal vascular tissue.[36, 130] In contrast, expression of TLR9

mRNA is very low in plaques, likely reflecting its very limited cellular distribution (primarily pDC). During infection, common TLR ligands such as proteoglycans (TLR2), lipopolysaccharides (TLR4), and some viral proteins (TLR4) likely reach systemically active levels, as shown by their induction of sepsis and fever. A number of possible mechanisms for plaque destabilization and rupture by infection-triggered inflammatory pathways have been described,[47, 48, 74] and all predict that the highest myocardial infarction risk would occur during the period of active infection and decline as infection and inflammation subsides. This close temporal association between acute infection and both myocardial infarction and stroke has been clearly defined in multiple studies, with the highest risk occurring in the first 3-7 days after diagnosis of infection.[4, 27, 113, 123]

The conditions required for HEPLISAV-B to mimic the inflammatory events leading to plaque rupture that are associated with acute infections are unlikely to be met. TLR9 expressing pDCs have been shown to be present with greater frequency in unstable plaques. In vitro, pDCs from plaques have been shown to make modest levels of interferon-α (IFNα) when stimulated with CpG-ODN.[98, 131] Pharmacokinetic studies after HEPLISAV-B injection show that plasma levels reach 85 ng/ml 1 hour after injection but decline rapidly and are below detection after 4 hours. However, direct intravenous injection of a CpG-ODN with a structure and potency very similar to 1018 failed to produce a detectable biological response at blood levels 50 to 100 times greater.[70] Thus, pDCs residing in plaques are unlikely to be exposed to stimulatory concentrations of 1018 as a result of an IM injection of HEPLISAV-B.

IFN-γ producing T cells responding to antigens within plaques are major contributors to plaque formation and progression,[75, 77] but are not stimulated by intramuscular injection of HEPLISAV-B. Functional evidence in human studies shows induction of genes regulated by IFN-α, but not genes regulated by IFN-γ.[41] Additionally, CpG-ODNs do not act systemically to activate T cells responding to antigens at a distant anatomical site. The adjuvant activity of 1018 requires exposure to both the antigen and 1018 at the same injection site.[117]

In summary, although a plausible mechanism can be proposed by which the 1018 adjuvant could increase the risk of myocardial infarction by analogy with the increased risk associated with acute infection, the essential predictions of that mechanism are not met. The transient systemic responses to 1018 are not consistent with lack of close temporal association between HEPLISAV-B injections and myocardial infarction. Furthermore, the absence of an imbalance in stroke between the 2 vaccine groups does not fit with the equally strong association of increased stroke risk and acute infections. Finally, 1018 is present in the systemic circulation for only a few hours after injection and does not reach levels that would stimulate pDCs associated with atherosclerotic plaques. The systemic effects of pDCs activation at the injection site and draining lymph node, such as IFNs and IFN-regulated genes, are elevated above background for only a few days after a HEPLISAV-B injection.

6.7.11.4.6.2 Myocardial Oxygen Supply and Demand Mismatch

Secondly, there was no evidence of a myocardial oxygen supply/demand mismatch that can occur because of an increase in myocardial oxygen demand. This most commonly occurs through an increase in heart rate and/or blood pressure, or due to a decrease in oxygen supply such as in anemia or hypoxemia.

Heart rate (Figure 6-2) and blood pressure (Figure 6-3) were measured in the pivotal trials prior to each dose of vaccine. There was no change in either measure from baseline for either HEPLISAV-B or Engerix-B. Furthermore, none of the cases of myocardial infarction had extremes of heart rate or blood pressure at the time of presentation. In addition, anemia was reported by 0.32% (n = 30) of HEPLISAV-B subjects and 0.26% (n = 10) of Engerix-B subjects in the PSP. One HEPLISAV-B subject (HBV-23 Subject 129-032) had a lacunar infarct 13 days after being diagnosed with anemia, rectal adenocarcinoma, chronic kidney disease, and hypertension and 283 days after his second HEPLISAV-B dose. No other subject with anemia had a MACE outcome.

Figure 6-2: Mean Heart Rate Over Time (Primary Safety Population)

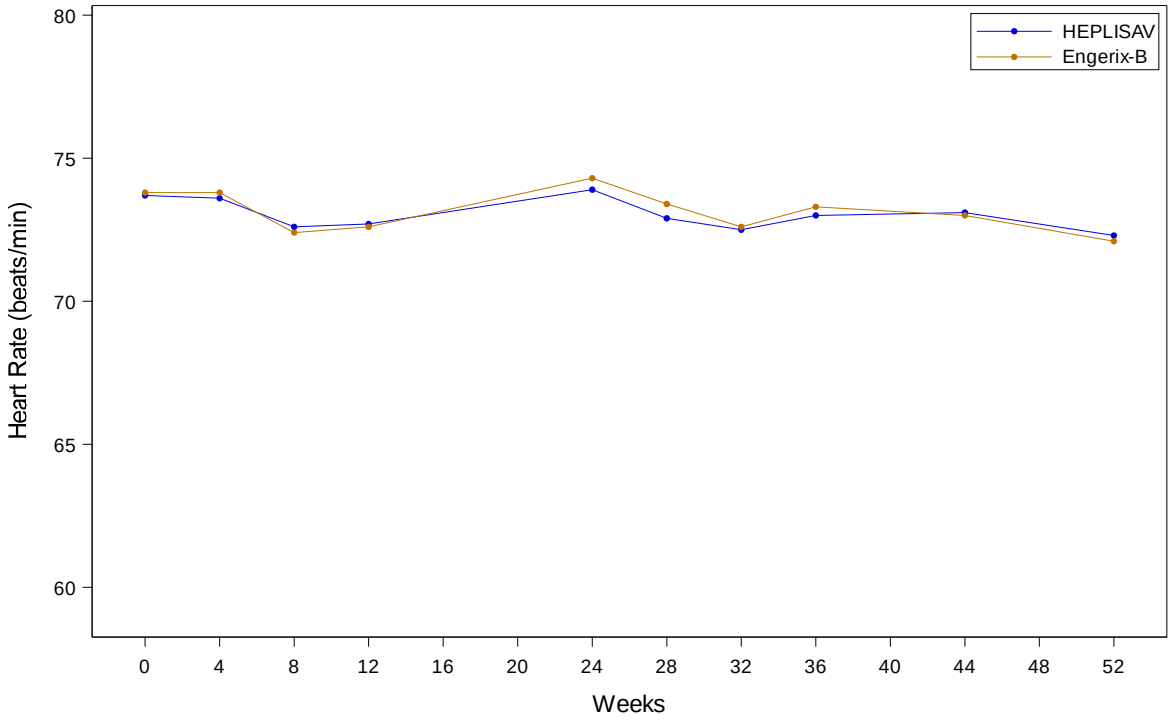
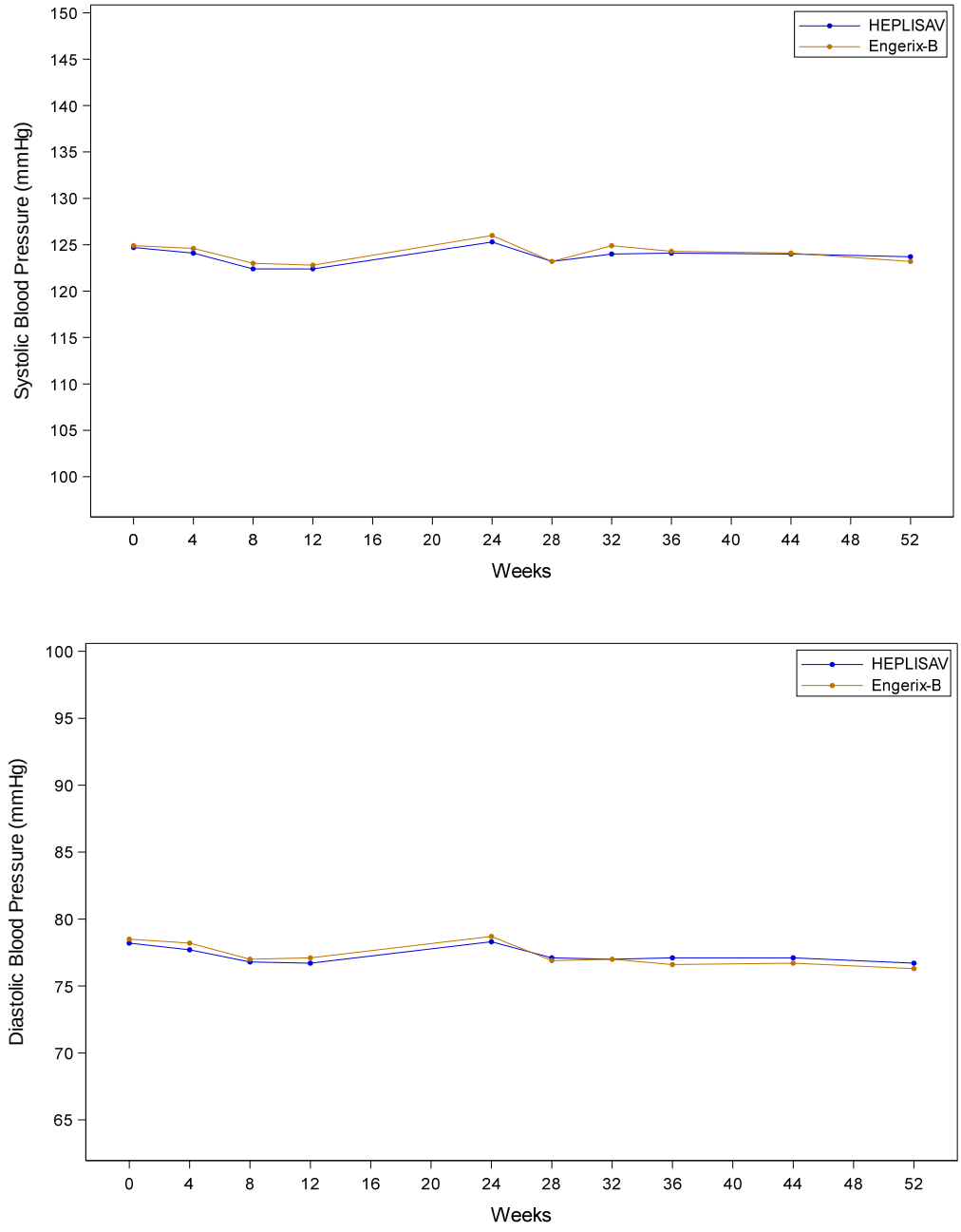


Figure 6-3: Mean Blood Pressure Over Time (Primary Safety Population)



6.7.11.4.6.3 Acute Vessel Thrombosis/Thromboembolism

A third potential cause of myocardial infarction and stroke is hypercoagulability, which was assessed by review of venous thrombotic events in the PSP in addition to myocardial infarction and stroke, and laboratory markers in the laboratory substudy of HBV-23. Venous thrombotic/thromboembolic events were reported with a similar frequency between the treatment groups in the PSP, as was stroke (Figure 1-3). In the HEPLISAV-B group, 0.22% (n = 21) of subjects had thrombotic/thromboembolic events compared with 0.26% (n = 10) of subjects in the

Engerix-B group. Pulmonary embolism was reported by 0.09% (n = 8) of HEPLISAV-B subjects and 0.05% (n = 2) of Engerix-B subjects. Deep vein thrombosis was reported by 0.10% (n = 9) of HEPLISAV-B subjects and 0.13% (n = 5) of Engerix-B subjects.

In the laboratory substudy of HBV-23, 309 subjects (HEPLISAV-B: 207; Engerix-B: 102) had prothrombin time, activated partial thromboplastin time (aPTT), and antiphospholipid antibodies assessed at 4, 8, 24, and 56 weeks after first injection. No clinically meaningful change in prothrombin time or aPTT over baseline was seen in either treatment group. Of subjects with a normal prothrombin time at baseline, 1.4% (n = 3) of subjects in the HEPLISAV-B group and 1.0% (n = 1) of subjects in the Engerix-B group had a prolonged time at Week 8. Of subjects with a normal aPTT at baseline, 1.4% (n = 3) of subjects in the HEPLISAV-B group and 1.0% (n = 1) of subjects in the Engerix-B group had a prolonged time at Week 8.

In this laboratory substudy, a higher proportion of HEPLISAV-B subjects (7.7%) had transient elevations of anti-beta 2 glycoprotein 1 IgM than Engerix-B subjects (1.0%) at Week 8. None of the subjects with elevated anti-beta2 glycoprotein 1 IgM had a thrombotic or MACE outcome and no subject developed antiphospholipid syndrome. This transient nonspecific rise in anti-beta 2 glycoprotein 1 IgM antibody has previously been observed in clinical and nonclinical models following vaccination with Engerix-B, diphtheria-tetanus vaccine, and with infections.[32, 80, 89] Antiphospholipid antibodies are found in up to 5% of healthy adults and increase with age. The presence of these antibodies alone has not been shown to increase the risk of venous thrombotic/thromboembolic events.[31]

Direct effects of 1018 leading to increased thrombosis are not expected. A well-recognized sequence-independent class effect of ODN is the opposite effect with a transiently increased aPTT. A modest increase in aPTT was observed in the 8 week repeat dose toxicity study in monkeys, however this occurred only at the highest dose tested, 12.5 mg/kg/week.

6.7.11.4.6.4 Atherosclerosis

An hypothesis for a mechanistic link between myocardial infarctions that are delayed relative to HEPLISAV-B injection is that local stimulation by 1018 leads to systemic levels of cytokines that can promote the development and progression of atherosclerotic plaques, increasing the risk of acute coronary events throughout the safety monitoring period. The importance of inflammation and immune-mediated processes to the development of atherosclerotic lesions is now well established. However, substantial evidence suggests that lesion development is a gradual process requiring chronic inflammation and occurring over decades, rather than a process triggered by a transient inflammatory insult.[48, 74, 76] The major cell types involved in plaque formation are macrophages and T cells, which do not express TLR9, however other immune cells may be involved, including dendritic cells (DC).[33, 99] Signaling through TLR4, in particular, has been strongly implicated in plaque development, through recognition of endogenous damage-associated molecules, such as oxidized low-density lipoproteins[55, 91] and, possibly, through recognition of chronic bacterial or viral infections.[33, 97]

The possibility that 2 local injections of the 1018 adjuvant stimulate chronic, systemic inflammation lacks plausibility for multiple reasons. The principal systemically measurable responses to CpG-ODN, given subcutaneously, are increased levels of a number of interferon-regulated genes. These are induced by Type I IFNs generated primarily in the draining lymph nodes (circulating levels of IFN-α itself are below detection in subjects given a B class CpG-ODN). The circulating levels of these IFN-regulated genes and gene products peak 24-48 hours after CpG-ODN injection and return to baseline levels within 7 days (Figure 3-2).[41, 70] The systemic inflammation caused by local application of the relatively low dose of 1018 in HEPLISAV-B is transient. It can be compared in magnitude to that reported in subjects immunized with influenza and yellow fever vaccines that have not been associated with myocardial infarction.[10, 42, 102]

Additional evidence that 2 injections of HEPLISAV-B do not lead to chronic inflammation comes from studies of C-reactive protein (CRP). CRP is a very sensitive indicator of systemic inflammation and the correlation between elevated CRP and increased risk of myocardial infarction is well established.[29, 100] CRP levels were measured, post hoc, in samples from study HBV-10; 3.3% of 1620 subjects who received HEPLISAV-B and 5.0% of 533 subjects who received Engerix-B had normal CRP results at baseline and elevated at 8 weeks post-second injection. These data do not indicate a pattern of increased serum CRP resulting from either HEPLISAV-B or Engerix-B treatment.

The role of TLR9 signaling and the potential for chronic treatment with a CpG-ODN to enhance plaque development have been studied in mouse models of atherosclerosis. In interpreting these studies, it is important to note that TLR9 is expressed on many more cell types in mice than in humans, including macrophages and all DC subsets.[12] A protective effect of TLR9 signaling was shown by the enhanced lesion development in double-knockout ApoE-/- TLR9-/- mice.[68] This contrasts with atherosclerotic mice with deletions of the TLR2 or TLR4 gene, which have significantly reduced disease.[90, 93] To confirm this, the same group showed that low weekly doses of a CpG-ODN reduced the severity of lesions in the ApoE-/- model.[68] The cumulative dose of CpG-ODN administered (0.08 mg/kg) was in the same range as 2 doses of HEPLISAV-B (0.09 mg/kg). However, in the same ApoE-/- mouse model , CpG-ODN given 3 times weekly for 7 weeks at a cumulative dose of 61 mg/kg (680X HEPLISAV-B dose) enhanced atherosclerotic plaque formation, whereas a more modest cumulative dose of 2.1 mg/kg (23X HEPLISAV-B dose) had no effect on plaque development.[71] In summary, in this widely studied murine model, it is possible to enhance spontaneous plaque formation with a CpG-ODN, but it requires frequent dosing of the CpG-ODN at doses far higher on a per body weight basis than present in HEPLISAV-B and may reflect activities on cell types whose human counterparts do not express the receptor for 1018.

Data from the HEPLISAV-B clinical trials do not support the concept that HEPLISAV-B induces or accelerates atherosclerosis. If it were true, one would expect to see a higher incidence of and coherence among MACE outcomes across the spectrum considered to have atherosclerosis as the underlying mechanism of disease. However, in the PSP, excluding acute

myocardial infarction, 0.72% (n = 67) of HEPLISAV-B subjects and 0.70% (n = 27) of Engerix-B subjects had such events attributable to atherosclerosis.

6.7.11.4.6.5 Immune-mediated Mechanisms

A final theoretical mechanism for late occurring myocardial infarctions is autoimmune as the long-term effect of 1018 is on the adaptive immune system. There are few autoimmune causes of myocardial infarction. Risk of myocardial infarction can be increased in patients with systemic autoimmune diseases such as lupus erythematosus but no subject with a MACE outcome had such a disease. In addition, there was no evidence of vasculitis on coronary artery catheterization and there was no evidence that HEPLISAV-B induced antiphospholipid syndrome (see Sections 6.7.11.1.1 and 6.7.11.4.6.3).

6.7.11.4.6.6 Biological Plausibility Conclusion

In order to evaluate the biological plausibility of a link between HEPLISAV-B injection and myocardial infarction, potential mechanisms for such an association were evaluated. The increased incidence of myocardial infarction and stroke associated with acute infections suggests by analogy a plausible mechanism, however there is no evidence for a role of TLR9 signaling in these infection-triggered events, or in animal models of plaque rupture or destabilization. Both the absence of a temporal association between HEPLISAV-B injection and the absence of an increased incidence of stroke, as was observed with acute infections, are not consistent with HEPLISAV-B mimicking the effects of acute infection. Nearly all of the cases of myocardial infarction in study HBV-23 appeared to result from an acute coronary syndrome event and there was no evidence for myocarditis or for a myocardial oxygen supply/demand mismatch. Furthermore, there was no clinical evidence consistent with a thrombotic mechanism, especially 1 due to autoimmune events which could explain the occurrence of myocardial infarctions long after the last dose of HEPLISAV-B and the disappearance of the 1018 adjuvant. Other possible autoimmune causes, particularly vasculitis, were not consistent with the catheterization data from the subjects with myocardial infarction in HBV-23. Lastly, delayed effects due to enhanced development of atherosclerosis by the 1018 adjuvant appear very unlikely. Atherosclerosis development is a slow, progressive process requiring chronic inflammation in the developing plaque, rather than a transient inflammatory signal localized to a distant site. In 1 mouse model of atherosclerosis, CpG-ODN can accelerate atherosclerosis development, but only when given systemically and repeatedly at doses far higher than those used in HEPLISAV-B. In summary, there is no support for a known biologically plausible mechanism for HEPLISAV-B or the 1018 adjuvant to lead to an increased incidence on acute myocardial infarctions.

6.7.11.5 Conclusions Regarding Myocardial Infarction and Major Adverse Cardiovascular Events

From these assessments we conclude that myocardial infarctions as well as MACE:

- Were unexpected based on nonclinical data;
- Occurred in subjects in whom such events would be expected based on their high prevalence of baseline cardiovascular risk factors. Myocardial infarctions occurred in patients with prevalent, often multi-vessel, obstructive coronary disease, and in most cases, with a clear culprit lesion;
- Occurred randomly throughout the duration of the trials with no temporal relationship to time of vaccine administration;
- In the HEPLISAV-B group occurred at incidence rates similar to or lower than expected and in the Engerix-B group lower than expected; and
- Were not related to a persistent inflammatory state or an autoimmune condition causing myocardial infarction including coronary vasculitis or antiphospholipid syndrome in the HEPLISAV-B group.

Therefore, the events appear to represent background incidence of acute myocardial infarctions and MACE in an at-risk adult patient population.

If the events are background and we ruled out possible vaccine-induced immune etiologies, *why was there an imbalance between the groups*? Only 1 myocardial infarction occurred in 2781 subjects who received Engerix-B in HBV-23. In contrast, 6 such events would have been expected based on estimated age-, sex-, and race-adjusted background rates (Table 6-29). This unexpectedly low number of events in the Engerix-B group was observed only in HBV-23 in which subjects in both treatment groups carried a similar and substantial level of cardiovascular risk.

Such an imbalance in a preferred term is expected in analyses of very small numbers of subjects reporting events, particularly in the context of testing 1405 MAE preferred terms in HBV-23. These very small proportions provide inherently unreliable estimates that may not be reproducible upon repeated testing.

Due to the absence of any supportive evidence or scientific rationale for the numerical imbalance to be associated with vaccine, the most reasonable conclusion is the imbalance is due to random variation. Our systematic evaluation of the myocardial infarction and extended cardiovascular event data cannot prove the imbalance in myocardial infarctions is due to random variation. Therefore, a large observational post-marketing surveillance study is proposed to rapidly confirm the lack of association of HEPLISAV-B with myocardial infarction and cardiovascular outcomes (Section 7.0).

6.7.12 Anaphylaxis

In the PSP, 5 subjects were reported with anaphylactic or anaphylactoid events (HEPLISAV-B: n = 4, < 0.1%; Engerix-B: n = 1, < 0.1%). The most frequent AE was type I hypersensitivity attributed to food allergy or insect envenomation. All events were 14 days or more post injection except for 2 events of fainting which coded to the MedDRA preferred term of "circulatory collapse" (HEPLISAV-B: day 1 after injection; Engerix-B: day 4 after injection). None of the events were attributed to study vaccine by the investigator or Sponsor.

Anaphylaxis is a known risk with all injectable therapeutics. In comparison with Engerix-B, HEPLISAV-B does not appear to cause an increased incidence of anaphylaxis or anaphylactoid events in HEPLISAV-B clinical trials.

6.7.13 Pregnancies in the Pivotal Trials

Table 6-32 presents pregnancies in the pivotal trials. Pregnancies were balanced between treatment groups.

Table 6-32: Pregnancy Outcomes by Treatment Group in the Primary Safety Population

Pregnancy Outcomes	HEPLISAV-B (N = 36)	Engerix-B (N = 18)
Healthy term delivery	21	10
Premature delivery	2	0
Congenital (Ebstein's) anomaly	1	1
Stillbirth	0	0
Elective termination	4	3
Fetal complications leading to SAEs	0	1
Spontaneous abortions	3	2
Lost to follow up	5	1

6.8 Overall Safety Summary

Safety data from the phase 3 pivotal trials HBV-10, HBV-16, and HBV-23 demonstrate that HEPLISAV-B was well tolerated with an overall safety profile comparable to Engerix-B. HEPLISAV-B and Engerix-B had balanced rates of local PIRs, AEs, SAEs, and deaths. Despite the numerical imbalance in the single preferred term of *acute myocardial infarction* in a single trial, HBV-23, a causal association between HEPLISAV-B and myocardial infarction is not supported by the data. Intensive surveillance for immune-mediated events revealed rates that were balanced between treatment groups for immune-mediated AEs, exacerbation of pre-existing events of special interest, and autoantibody development.

7.0 PROPOSED POST-MARKETING SURVEILLANCE STUDY OF HEPLISAV-B

Summary of Post Marketing Surveillance Study

Large, post-marketing surveillance study is proposed to rapidly confirm overall safety of HEPLISAV-B in medical practice

- 20,000 recipients of HEPLISAV-B compared with 20,000 recipients of another hepatitis B vaccine
- Conducted in large health maintenance organization experienced in conducting vaccine post-marketing studies
- To be finalized in consultation with FDA

Objectives:

- Compare rates of 3-point MACE and its individual component outcomes
- Compare of the rates of pre-specified immune-mediated events
- Estimate rates of medical events other than MACE or immune-mediated events

Most appropriate and feasible design to confirm overall safety as quickly as possible

- A sample size of 20,000 patients per group provides >99% power to rule out a 2-fold increase in the incidence of MACE if the background rate is 6 per 1000 person years.
- A sample size of 20,000 patients per group will provide approximately 87% power to detect a 2.5-fold increase in the incidence of immune-mediated diseases using a one-sided test at a level of significance of 0.025 if the background incidence rate is 1 per 1000 person years.
- Enables individuals immediate access to benefits of HEPLISAV-B for those in need.

To confirm the safety of HEPLISAV-B in medical practice as quickly as possible, a large observational post-marketing vaccine surveillance study is the most feasible and appropriate design. The post-marketing study in adults 18 years of age and older will determine the incidence of cardiovascular, immune-mediated, and other medical events. Dynavax proposes this observational electronic medical record review be conducted in an integrated health system/health maintenance organization (HMO) setting such as Kaiser Permanente Northern California (KPNC) and another Kaiser site. They have extensive experience in conducting vaccine safety studies. The study design will be finalized in consultation with FDA.

7.1 Objectives of the Post Marketing Study

The objectives of the post-marketing surveillance study are to:

- Compare the rates of 3-point MACE and its individual component outcomes in persons who receive HEPLISAV-B compared with persons who receive another hepatitis B vaccine;
- Compare the rates of pre-specified immune-mediated events in HEPLISAV-B recipients with the rates in persons who receive another hepatitis B vaccine; and
- Estimate the rates of medical events other than MACE or immune-mediated events.

7.2 Safety Data and Analyses

All MAEs, SAEs, and selected, pre-specified AESIs related to immune-mediated disorders following vaccination with HEPLISAV-B or another hepatitis B vaccine up to 1 year after last dose will be evaluated. Safety data will be collected on all women who are found to be pregnant at the time of vaccination or who become pregnant shortly after vaccination.

7.2.1 For the Analysis of MACE

- A comparison of event rates between 20,000 HEPLISAV-B recipients and 20,000 recipients of other hepatitis B vaccines.
- A sample size of 20,000 patients per group will provide > 99% power to rule out a 2-fold increase in the incidence of MACE if the background incidence rate is 6 per 1000 person years.

7.2.2 For the Analysis of Immune-mediated Events

- A comparison of rates of pre-specified immune-mediated medical event rates between 20,000 HEPLISAV-B recipients and 20,000 recipients of other hepatitis B vaccines.
- A sample size of 20,000 patients per group will provide approximately 87% power to detect a 2.5-fold increase in the incidence of immune-mediated diseases using a one-sided test at a level of significance of 0.025 if the background incidence rate is 1 per 1000 person years.

7.2.3 For the Analysis of Other Safety Events

- The analysis of events other than MACE or immune-mediated conditions is proposed to use a risk interval approach because it is well suited to analyses when there are no *a priori* hypotheses.

7.3 Overall Post-Marketing Surveillance Study Plan

It is anticipated that 20,000 patients will receive HEPLISAV-B and an equivalent number will receive another hepatitis B vaccine within 1 year of first use of HEPLISAV-B if the study is conducted at Kaiser or another similarly sized HMO. An interim analysis of all MACE outcomes as well as all immune-mediated AEs will be reviewed by an independent safety data monitoring committee to ensure that no major adverse safety differences emerge during the conduct of the study. Depending upon the rate of uptake, we estimate the first interim analysis will be conducted 12 months following initiation of the study.

8.0 BENEFIT/RISK CONCLUSIONS

Summary of Benefit/Risk Conclusions

Immunogenicity of HEPLISAV-B

- **Increased seroprotection:** SPRs in HEPLISAV-B (90% to 100%) were statistically significantly higher than those of Engerix-B of (65% to 94%) in all pre-specified populations including subpopulations with reduced SPRs from current vaccines, eg, in persons with diabetes, HEPLISAV-B was 90% vs.65.1% for Engerix-B.
- **Early onset of seroprotection:** 2 doses over 1 month of HEPLISAV-B induce seroprotection 5 months earlier than Engerix-B. Advantageous for those requiring rapid seroprotection, such as healthcare workers
- **Benefits of Higher Adherence Rates:** modelling the projected adherence benefit of HEPLISAV-B to extrapolate a CDC model to 50% of all unvaccinated persons with diabetes shows a 72% further reduction beyond Engerix-B resulting in preventing 29,000 additional persons from HBV infection

Safety of HEPLISAV-B

- In a racially diverse population of 10,038 subjects who received HEPLISAV-B and 4,200 subjects who received Engerix-B the safety profile of HEPLISAV-B was similar overall to that of Engerix-B
- HEPLISAV-B was well tolerated and PIRs in subjects who received HEPLISAV-B were balanced with those who received Engerix-B
- No clinically meaningful differences in AEs, MAEs, AESIs, SAEs, and deaths between the HEPLISAV-B and Engerix-B groups
    - Myocardial infarctions occurred in subjects in whom they would be expected at rates similar to lower than expected with no evidence for vaccine-induced immune etiologies. The small numerical imbalance in the single preferred term of *acute myocardial infarction* is likely the effect of random variation in small numbers of events. The totality of the data does not support a causal relationship between HEPLISAV-B and the safety of HEPLISAV-B will be confirmed in a large observational post-marketing surveillance study
- HEPLISAV-B was not associated with an increased rate of any specific immune-mediated diseases
- No contraindications to HEPLISAV-B were identified

Benefit/Risk Conclusion

- HEPLISAV-B can surmount limitations of currently licensed hepatitis B vaccines and meet an important public health need with statistically significantly higher seroprotection rates in all adults including adults historically associated with reduced seroprotection using just 2 doses over 1 month compared to 3 doses over 6 months
- HEPLISAV-B is well tolerated with an overall safety profile similar to that of Engerix-B.

The benefit of HEPLISAV-B outweighs the risks. HEPLISAV-B provides an opportunity to greatly improve the ability to directly protect more adults at risk of HBV infection, earlier, and with greater potential for adherence. In addition, there is an indirect medical benefit resulting from interrupting the chain of HBV transmission to others by inducing early and predictable seroprotection

8.1 Unmet Medical Need

The unmet medical need for a new hepatitis B vaccine for adults is defined by the morbidity and mortality caused by the virus, the low vaccine coverage rates in at-risk adult populations, and the limitations of currently approved vaccines. Such limitations include the following:

- Currently approved vaccines induce significantly lower antibody levels and rates of seroprotection in multiple important at-risk populations, including older adults, men, smokers, obese persons, and individuals with diabetes mellitus.4, 5, 20, 25, 58, 59, 69, 72, 74-78

- The prolonged time until reaching seroprotection after administration of a currently licensed vaccine (> 6 months) puts individuals in need of rapid seroprotection at risk – including healthcare workers, first responders, and individuals whose behaviors put them at high risk of exposure to HBV through sex or injection drug use (Appendix 1).

- Finally, most adults require all 3 doses of a currently approved vaccine over 6 months to develop seroprotection, leaving large proportions of populations with poor adherence rates, such as young adults, patients at STD clinics, and injection drug users, unprotected from infection.60, 96

8.2 Benefits of HEPLISAV-B

In the 3 pivotal clinical trials, 2 doses of HEPLISAV-B induced statistically significantly higher SPRs compared to 3 doses of Engerix-B measured at the primary endpoints. In addition, HEPLISAV-B demonstrated an ability to overcome the above limitations of the currently licensed vaccines. Evidence for this includes:

8.2.1 Increased Seroprotection

- At the primary endpoints, the SPRs induced by HEPLISAV-B were noninferior to and statistically significantly higher than the SPRs induced by Engerix-B.

- Peak seroprotection induced by HEPLISAV-B was statistically significantly higher than peak seroprotection induced by Engerix-B in all pre-specified subpopulations. HEPLISAV-B induced consistent SPRs across all adult subpopulations ranging from 90% to 100% while Engerix-B induced SPRs that were much more variable, ranging from 65% to 94%.

- In subpopulations with a higher incidence of HBV infection, including men, people of black race, and individuals with diabetes, HEPLISAV-B induced SPRs that were statistically significantly higher than the SPRs induced by Engerix-B.

- In subpopulations with reduced seroprotection rates from currently licensed vaccines (eg, older adults, men, obese subjects, smokers), HEPLISAV-B induced statistically significantly higher SPRs as well as among subpopulations who typically have high seroprotection rates from currently licensed hepatitis B vaccines (eg, younger adults, women, whites, blacks, non-obese subjects, nonsmokers).

- In individuals with diabetes mellitus, HEPLISAV-B induced statistically significantly higher seroprotection with 90% of subjects versus 65.1% for Engerix-B.

8.2.2 Early Onset of Seroprotection

- Unlike currently licensed vaccines that require 6 months to induce seroprotection, HEPLISAV-B induced seroprotection in a substantial proportion of individuals within 2 months after the first injection.

- Two months after the first dose of HEPLISAV-B, the SPR at Week 8 was statistically significantly higher than the SPR after 2 doses of Engerix-B at Week 8. The HEPLISAV-B Week 8 SPR was also higher than the peak Engerix-B SPR at Week 28.

- At 3 months after the first dose, HEPLISAV-B induced seroprotection in 92.0% of subjects and Engerix-B induced seroprotection in 20.9% of subjects.

- For individuals at high risk of infection who need rapid protection, and where the risk of exposure to HBV is imminent, the longer time to seroprotection with the currently approved vaccines leads to an increased risk of infection.

8.2.3 Benefits of Higher Adherence Rates

- Higher rates of adherence to 2 doses of vaccine over 1 month have been reported compared to adherence to a 3-dose schedule over 6 months.96 After 2 doses of HEPLISAV-B, 95% of subjects developed seroprotection in HBV-23, but after 2 doses of Engerix-B, only 20% to 50% of subjects developed seroprotection.

- Completing the 3-dose schedule of Engerix-B over 6 months is challenging for some adults who are at high risk for HBV infection. Many may only receive 1 dose of vaccine.60 For example, a study at a STD clinic in San Diego, California, which used an accelerated dosing schedule for Engerix-B of 0, 1 and 4 months, demonstrated that 36% of MSM did not receive 2 doses and 57% did not receive 3 doses.46

    - Using these adherence rates and SPRs in young men, 18 to 39 years of age, who would be most in need of seroprotection, the difference in seroprotection between HEPLISAV-B and Engerix-B increases nearly 3-fold, from 11.0% in men who receive all 3 doses of vaccine in clinical trials to 28.9% in projected actual use.

8.2.4 Modeling Improved Adherence

A particular benefit of HEPLISAV-B over Engerix-B is likely in persons with diabetes mellitus, notably, a population in whom the small number of myocardial infarction events was balanced between the HEPLISAV-B and Engerix-B groups. Poor implementation of the ACIP recommendation for routine hepatitis B vaccination of individuals with diabetes is aggravated by the limitations of Engerix-B. We modeled the use of HEPLISAV-B instead of using Engerix-B in an extrapolation of a hypothetical, 1-time vaccination program of adults diagnosed with diabetes (528,047 individuals) described by CDC[109] to 5,000,000 persons with diabetes, approximately half of those age ≤ 60 years who are unvaccinated (Table 8-1). Use of HEPLISAV-B would be expected to lead to a further 72% decrease in hepatitis-B related health outcomes compared with Engerix-B.

Table 8-1: Cases of Hepatitis B Infection and Complications Prevented in Hypothetical, 1-Time Hepatitis B Vaccination Program in Individuals With Diabetes Mellitus

Condition Prevented	CDC Estimates for Licensed Vaccine (n)	Estimates for HEPLISAV-B (n)[a]	Difference (HEPLISAV-B – Engerix-B) (n)	Difference Applied to 50% of Unvaccinated Persons with Diabetes ≤ age 60 years
Infection	4271	7359	3088	29,000
Hospitalization	467	805	338	3200
Chronic hepatitis B infection	256	441	185	1800
Hepatocellular carcinoma	33	57	24	220
Liver transplant	13	22	9	80
Death	130	224	94	900

CDC = Centers for Disease Control; n = number of individuals with condition prevented in each treatment group; SPR = seroprotection response rate.

[a] Estimates using HEPLISAV-B were calculated by multiplying the number of individuals with diabetes to be vaccinated (528,047) by the total effective SPR (HEPLISAV-B trial SPR data modified by adherence data from Nelson 2009[96]) for each vaccine and dividing the number of individuals with seroprotection from HEPLISAV-B (403,956) by the number of individuals with seroprotection from Engerix-B (234,981). The quotient (1.722973) was then multiplied by the number of cases prevented in the CDC estimates. These results were then extrapolated to apply to 5,000,000 persons.

8.3 Safety

Following the completion of HBV-23, the HEPLISAV-B safety database comprised a more racially diverse study population of 10,038 subjects who received HEPLISAV-B and 4,200 subjects who received Engerix-B. The safety profile of HEPLISAV-B was similar overall to that of Engerix-B. Specifically:

- Post-injection reactions in subjects who received HEPLISAV-B were characterized by a similar frequency of mild to moderate injection site pain and lower frequency of systemic reactions than in subjects who received Engerix-B.

- Across all of the HEPLISAV-B trials, there were no clinically meaningful differences in the times of onset, frequencies, or characteristics of AEs, MAEs, AESIs, SAEs, and deaths between the HEPLISAV-B and Engerix-B groups.

    - In a single study, HBV-23, the preferred term of *acute myocardial infarction* was reported in a higher proportion of HEPLISAV-B than Engerix-B recipients. A comprehensive evaluation found:

        - myocardial infarctions and MACE outcomes occurred in subjects in whom they would be expected at rates similar to or below background;

        - no evidence for theoretically plausible vaccine-induced immune etiologies;

        - the most reasonable conclusion is the numerical imbalance is likely due to random variation in small numbers of events, and

        - a large, observational, post-marketing surveillance study is proposed as the most feasible and appropriate design to confirm the safety of HEPLISAV-B.

- HEPLISAV-B, which includes a TLR9 agonist as adjuvant, shares its mechanism of action with currently approved, live-attenuated viral vaccines, such as yellow fever (YF-17D),42, 102 that have not been reported to be associated with an increased rate of immune-mediated disease. In the HEPLISAV-B development program, HEPLISAV-B was not associated with an increased rate of any specific immune-mediated disease. The phase 3 trial, HBV-23, was designed to increase the size of the HEPLISAV-B safety database to better assess serious immune-mediated diseases such as granulomatosis with polyangiitis and Tolosa Hunt syndrome. No such events occurred in the trial.

- The transient increase in nonspecific antiphospholipid antibodies in HEPLISAV-B subjects has also been reported with Engerix-B and other vaccines in the literature [80, 89, 32] and was not associated with clinical disease. There was no increased rate of ANA, ANCA, or anti-dsDNA production in subjects who received HEPLISAV-B compared with the rate of autoantibody production in subjects who received Engerix-B.

- No contraindications to HEPLISAV-B were identified. Although no cases of vaccine-associated anaphylaxis occurred in the HEPLISAV-B trials, individuals with allergies to the components of HEPLISAV-B should not receive the vaccine. Other identified risks may include bursitis in the injection arm due to poor injection technique, and syncope, which also occur with other vaccinations. No studies of HEPLISAV-B have been conducted in pregnant or lactating women, so its use in women with these conditions must be weighed against the benefit. Although not an identified risk, the use of HEPLISAV-B concomitantly with another vaccine (eg, zoster, pneumococcal) has not been studied. Dynavax plans to support a concomitant vaccine administration study post-approval.

8.4 Summary

HEPLISAV-B given at 0 and 1 month can surmount limitations of currently licensed hepatitis B vaccines by providing the following improvements:

- Statistically significantly higher proportion of adults achieving seroprotection,
- High levels of seroprotection in populations historically associated with reduced seroprotection rates and in populations with known higher seroprotection rates from hepatitis B vaccines,
- Earlier seroprotection,
- 2 doses over 1 month compared to 3 doses over 6 months.

HEPLISAV-B provides an opportunity to greatly improve the ability to directly protect more adults at risk of HBV infection, earlier, and with greater potential for adherence. In addition, there is an indirect medical benefit resulting from interrupting the chain of HBV transmission to others by inducing early and predictable seroprotection.

9.0 REFERENCES

1 K. Annunziata, A. Rak, H. Del Buono, M. DiBonaventura, and G. Krishnarajah, 'Vaccination Rates among the General Adult Population and High-Risk Groups in the United States', *PLoS One,* 7 (2012), e50553.

2 A. A. Ashkar, and K. L. Rosenthal, 'Toll-Like Receptor 9, Cpg DNA and Innate Immunity', *Curr Mol Med,* 2 (2002), 545-56.

3 F. Averhoff, F. Mahoney, P. Coleman, G. Schatz, E. Hurwitz, and H. Margolis, 'Immunogenicity of Hepatitis B Vaccines. Implications for Persons at Occupational Risk of Hepatitis B Virus Infection', *Am J Prev Med,* 15 (1998), 1-8.

4 R. Bazaz, H. M. Marriott, S. E. Francis, and D. H. Dockrell, 'Mechanistic Links between Acute Respiratory Tract Infections and Acute Coronary Syndromes', *J Infect,* 66 (2013), 1-17.

5 H. L. Bock, J. Kruppenbacher, R. Sanger, W. Hobel, R. Clemens, and W. Jilg, 'Immunogenicity of a Recombinant Hepatitis B Vaccine in Adults', *Arch Intern Med,* 156 (1996), 2226-31.

6 H. L. Bock, T. Loscher, N. Scheiermann, R. Baumgarten, M. Wiese, W. Dutz, R. Sanger, and R. Clemens, 'Accelerated Schedule for Hepatitis B Immunization', *J Travel Med,* 2 (1995), 213-17.

7 J. Bogefors, C. Rydberg, R. Uddman, M. Fransson, A. Månsson, M. Benson, M. Adner, and L. O. Cardell, 'Nod1, Nod2 and Nalp3 Receptors, New Potential Targets in Treatment of Allergic Rhinitis?', *Allergy,* 65 (2010), 1222-26.

8 H. M. Bolooki, and A. Askari, 'Acute Myocardial Infarction', Cleveland Clinic Center for Continuing Education, (2010) <http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/acute-myocardial-infarction/> Accessed 9/30/2016

9 M.G. Bruce, D. Bruden, D. Hurlburt, C. Zanis, G. Thompson, L. Rea, M. Toomey, L. Townshend-Bulson, K. Rudolph, L. Bulkow, P. R. Spradling, R. Baum, T. W. Hennessy, and B.J. McMahon, 'Antibody Levels and Protection after Hepatitis B Vaccine: Results of a 30-Year Follow-up Study and Response to a Booster Dose ', *J Infect Dis,* 214 (2016), 16-22.

10 K. L. Bucasas, L. M. Franco, C. A. Shaw, M. S. Bray, J. M. Wells, D. Nino, N. Arden, J. M. Quarles, R. B. Couch, and J. W. Belmont, 'Early Patterns of Gene Expression Correlate with the Humoral Immune Response to Influenza Vaccination in Humans', *J Infect Dis,* 203 (2011), 921-9.

11 C5Research, 'Dynavax Heplisav Clinical Trials Cec Charter', (Cleveland Clinic Coordinating Center for Clinical Research (C5Research) Clinical Events Committee 2016), 1-24.

12 J. D. Campbell, Y. Cho, M. L. Foster, H. Kanzler, M. A. Kachura, J. A. Lum, M. J. Ratcliffe, A. Sathe, A. J. Leishman, A. Bahl, M. McHale, R. L. Coffman, and E. M. Hessel, 'Cpg-Containing Immunostimulatory DNA Sequences Elicit Tnf-Alpha-Dependent Toxicity in Rodents but Not in Humans', *J Clin Invest,* 119 (2009), 2564-76.

13 Center for Biologics Evaluation and Research (CBER), 'Guidance for Industry: Non-Inferiority Clinical Trials', ed. by U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) (Rockville, MD: 2010), 1-66.

14 Centers for Disease Control and Prevention, 'Adult Vaccination Coverage — United States, 2010', *MMWR Morb Mortal Wkly Rep,* 61 (2012), 66-72.

15 Centers for Disease Control and Prevention, 'Diabetes Data and Trends: National Diabetes Surveillance System. Data from the National Health Interview Survey'2012) <http://www.cdc.gov/diabetes/statistics/incidence_national.htm> Accessed February 1, 2012

16 Centers for Disease Control and Prevention, 'Disease Burden from Viral Hepatitis a, B and C in the United States', Centers for Disease Control and Prevention,, (2011) <http://www.cdc.gov/hepatitis/hbv/statisticshbv.htm>

17 Centers for Disease Control and Prevention, 'Epidemiology and Prevention of Vaccine-Preventable Diseases', in *Epidemiology and Prevention of Vaccine-Preventable Diseases*, ed. by J. Hamborsky, A. Kroger and S. Wolfe (Washington DC: Public Health Foundation, 2015), 149-74.

18 Centers for Disease Control and Prevention, 'Healthcare-Associated Hepatitis B and C Outbreaks Reported to the Centers for Disease Control and Prevention (Cdc) 2008-2015', (Atlanta: Division of Viral Hepatitis and National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, 2017).

19 Centers for Disease Control and Prevention, 'Hepatitis B Virus: A Comprehensive Strategy for Eliminating Transmission in the United States through Universal Childhood Vaccination: Recommendations of the Immunization Practices Advisory Committee (Acip)', *MMWR,* 40 (1991), 1-22.

20 Centers for Disease Control and Prevention, 'Recommendation of the Immunization Practices Advisory Committee (Acip) Inactivated Hepatitis B Virus Vaccine', *MMWR,* 31 (1982), 317-22, 27-28.

21 Centers for Disease Control and Prevention, 'Sensitivity of the Test for Antibody to Hepatitis B Surface Antigen -- United States', *MMWR,* 42 (1993), 707-10.

22 Centers for Disease Control and Prevention, 'Summary of Trends in Viral Hepatitis – United States, 2015', (http://www.cdc.gov/hepatitis/statistics/2015surveillance/index.htm: 2017), 1-5.

23 Centers for Disease Control and Prevention, 'Underlying Cause of Death 1999-2014', (CDC WONDER Online Database: National Center for Health Statistics,, 2014).

24 Centers for Disease Control and Prevention, 'Viral Hepatitis and Young Persons Who Inject Drugs', Division of Viral Hepatitis and National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, (2017) Accessed April 26 2017.

25 D. Chaussabel, C. Quinn, J. Shen, P. Patel, C. Glaser, N. Baldwin, D. Stichweh, D. Blankenship, L. Li, I. Munagala, L. Bennett, F. Allantaz, A. Mejias, M. Ardura, E. Kaizer, L. Monnet, W. Allman, H. Randall, D. Johnson, A. Lanier, M. Punaro, K. M. Wittkowski, P. White, J. Fay, G. Klintmalm, O. Ramilo, A. K. Palucka, J. Banchereau, and V. Pascual, 'A Modular Analysis Framework for Blood Genomics Studies: Application to Systemic Lupus Erythematosus', *Immunity,* 29 (2008), 150-64.

26 T. C. Clayton, M. Thompson, and T. W. Meade, 'Recent Respiratory Infection and Risk of Cardiovascular Disease: Case-Control Study through a General Practice Database', *Eur Heart J,* 29 (2008), 96-103.

27 V. F. Corrales-Medina, M. Madjid, and D. M. Musher, 'Role of Acute Infection in Triggering Acute Coronary Syndromes', *Lancet Infect Dis,* 10 (2010), 83-92.

28 P. S. Creticos, J. T. Schroeder, R. G. Hamilton, S. L. Balcer-Whaley, A. P. Khattignavong, R. Lindblad, H. Li, R. Coffman, V. Seyfert, J. J. Eiden, D. Broide, and Immune Tolerance Network Group, 'Immunotherapy with a Ragweed-Toll-Like Receptor 9 Agonist Vaccine for Allergic Rhinitis', *N Engl J Med,* 355 (2006), 1445-55.

29 J. Danesh, J. G. Wheeler, G. M. Hirschfield, S. Eda, G. Eiriksdottir, A. Rumley, G. D. Lowe, M. B. Pepys, and V. Gudnason, 'C-Reactive Protein and Other Circulating Markers of Inflammation in the Prediction of Coronary Heart Disease', *N Engl J Med,* 350 (2004), 1387-97.

30 D. Daniels, S. Grytdal, and A. Wasley, 'Surveillance for Acute Viral Hepatitis - United States, 2007', *MMWR Surveill Summ,* 58 (2009), 1-27.

31 P. G. de Groot, and R. T. Urbanus, 'The Significance of Autoantibodies against Beta2-Glycoprotein I', *Blood,* 120 (2012), 266-74.

32 L. Dimitrijevic, I. Zivkovic, M. Stojanovic, V. Petrusic, and S. Zivancevic-Simonovic, 'Vaccine Model of Antiphospholipid Syndrome Induced by Tetanus Vaccine', *Lupus,* 21 (2012), 195-202.

33 Y. Doring, and A. Zernecke, 'Plasmacytoid Dendritic Cells in Atherosclerosis', *Front Physiol,* 3 (2012), 1-10.

34 C. Douvin, D. Simon, M. A. Charles, L. Deforges, P. Bierling, V. Lehner, A. Budkowska, and D. Dhumeaux, 'Hepatitis B Vaccination in Diabetic Patients. Randomized Trial Comparing Recombinant Vaccines Containing and Not Containing Pre-S2 Antigen', *Diabetes Care,* 20 (1997), 148-51.

35 O. Duramad, K. L. Fearon, J. H. Chan, H. Kanzler, J. D. Marshall, R. L. Coffman, and F. J. Barrat, 'Il-10 Regulates Plasmacytoid Dendritic Cell Response to Cpg-Containing Immunostimulatory Sequences', *Blood,* 102 (2003), 4487-92.

36 K. Edfeldt, J. Swedenborg, G. K. Hansson, and Z. Q. Yan, 'Expression of Toll-Like Receptors in Human Atherosclerotic Lesions: A Possible Pathway for Plaque Activation', *Circulation,* 105 (2002), 1158-61.

37 S. C. Eisenbarth, O. R. Colegio, W. O'Connor, F. S. Sutterwala, and R. A. Flavell, 'Crucial Role for the Nalp3 Inflammasome in the Immunostimulatory Properties of Aluminium Adjuvants [Letter]', *Nature,* 453 (2008), 1122-6.

38 A. K. Ekman, and L. O. Cardell, 'The Expression and Function of Nod-Like Receptors in Neutrophils', *Immunology,* 130 (2010), 55-63.

39 D. N. Fisman, D. Agrawal, and K. Leder, 'The Effect of Age on Immunologic Response to Recombinant Hepatitis B Vaccine: A Meta-Analysis', *Clin Infect Dis,* 35 (2002), 1368-75.

40 D. P. Francis, S. C. Hadler, S. E. Thompson, J. E. Maynard, D. G. Ostrow, N. Altman, E. H. Braff, P. O'Malley, D. Hawkins, F. N. Judson, K. Penley, T. Nylund, G. Christie, F. Meyers, J. N. Moore, Jr., A. Gardner, I. L. Doto, J. H. Miller, G. H. Reynolds, B. L. Murphy, C. A. Schable, B. T. Clark, J. W. Curran, and A. G. Redeker, 'The Prevention of Hepatitis B with Vaccine. Report of the Centers for Disease Control Multi-Center Efficacy Trial among Homosexual Men', *Ann Intern Med,* 97 (1982), 362-6.

41 J. W. Friedberg, H. Kim, M. McCauley, E. M. Hessel, P. Sims, D. C. Fisher, L. M. Nadler, R. L. Coffman, and A. S. Freedman, 'Combination Immunotherapy with a Cpg Oligonucleotide (1018 Iss) and Rituximab in Patients with Non-Hodgkin Lymphoma: Increased Interferon-Alpha/Beta-Inducible Gene Expression, without Significant Toxicity', *Blood,* 105 (2005), 489-95.

42 D. Gaucher, R. Therrien, N. Kettaf, B. R. Angermann, G. Boucher, A. Filali-Mouhim, J. M. Moser, R. S. Mehta, D. R. Drake, 3rd, E. Castro, R. Akondy, A. Rinfret, B. Yassine-Diab, E. A. Said, Y. Chouikh, M. J. Cameron, R. Clum, D. Kelvin, R. Somogyi, L. D. Greller, R. S. Balderas, P. Wilkinson, G. Pantaleo, J. Tartaglia, E. K. Haddad, and R. P. Sekaly, 'Yellow Fever Vaccine Induces Integrated Multilineage and Polyfunctional Immune Responses', *J Exp Med,* 205 (2008), 3119-31.

43 GlaxoSmithKline, 'Engerix-B [Hepatitis B Vaccine (Recombinant)] Prescribing Information', (REsearch Triangle Park, NC: 2016), 1-16.

44 GlaxoSmithKline, 'Engerix-B® [Hepatitis B Vaccine (Recombinant)] Prescribing Information', (Research Triangle Park, NC: 2013), 1-13.

45 D. C. Goff, Jr., D. M. Lloyd-Jones, G. Bennett, S. Coady, R. B. D'Agostino, Sr., R. Gibbons, P. Greenland, D. T. Lackland, D. Levy, C. J. O'Donnell, J. G. Robinson, J. S. Schwartz, S. T. Shero, S. C. Smith, Jr., P. Sorlie, N. J. Stone, P. W. Wilson, and Guidelines American College of Cardiology/American Heart Association Task Force on Practice, '2013 Acc/Aha Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines', *J Am Coll Cardiol,* 63 (2014), 2935-59.

46 R. A. Gunn, M. A. Lee, P. J. Murray, R. A. Gilchick, and H. S. Margolis, 'Hepatitis B Vaccination of Men Who Have Sex with Men Attending an Urban Std Clinic: Impact of an Ongoing Vaccination Program, 1998-2003', *Sex Transm Dis,* 34 (2007), 663-8.

47 G. K. Hansson, P. Libby, and I. Tabas, 'Inflammation and Plaque Vulnerability', *J Intern Med,* 278 (2015), 483-93.

48 G. K. Hansson, A. K. Robertson, and C. Soderberg-Naucler, 'Inflammation and Atherosclerosis', *Annu Rev Pathol,* 1 (2006), 297-329.

49 G. Hartmann, G. J. Weiner, and A. M. Krieg, 'Cpg DNA: A Potent Signal for Growth, Activation, and Maturation of Human Dendritic Cells', *Proc Natl Acad Sci U S A,* 96 (1999), 9305-10.

50 S. P. Henry, T.-W. Kim, K. Kramer-Stickland, T. A. Zanardi, Robert A. Fey, and Arthur A. Levin, 'Toxicologic Properties of 2'-O-Methoxyethyl Chimeric Antisense Inhibitors in Animals and Man', in *Antisense Drug Technology: Principles, Strategies, and Applications*, ed. by Stanley T. Crooke (Boca Raton, FL: CRC Press, Taylor & Francis Group, 2008), 327-63.

51 K. A. Hicks, J. E. Tcheng, B. Bozkurt, B. R. Chaitman, D. E. Cutlip, A. Farb, G. C. Fonarow, J. P. Jacobs, M. R. Jaff, J. H. Lichtman, M. C. Limacher, K. W. Mahaffey, R. Mehran, S. E. Nissen, E. E. Smith, and S. L. Targum, '2014 Acc/Aha Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards)', *Circulation,* 132 (2015), 302-61.

52 D. Higgins, J. D. Marshall, P. Traquina, G. Van Nest, and B. D. Livingston, 'Immunostimulatory DNA as a Vaccine Adjuvant', *Expert Rev Vaccines,* 6 (2007), 747-59.

53 V. Hornung, S. Rothenfusser, S. Britsch, A. Krug, B. Jahrsdorfer, T. Giese, S. Endres, and G. Hartmann, 'Quantitative Expression of Toll-Like Receptor 1-10 Mrna in Cellular Subsets of Human Peripheral Blood Mononuclear Cells and Sensitivity to Cpg Oligodeoxynucleotides', *J Immunol,* 168 (2002), 4531-7.

54 B. Hou, P. Saudan, G. Ott, M. L. Wheeler, M. Ji, L. Kuzmich, L. M. Lee, R. L. Coffman, M. F. Bachmann, and A. L. Defranco, 'Selective Utilization of Toll-Like Receptor and Myd88 Signaling in B Cells for Enhancement of the Antiviral Germinal Center Response', *Immunity,* 34 (2011), 375-84.

55 K. W. Howell, X. Meng, D. A. Fullerton, C. Jin, T. B. Reece, and J. C. Cleveland, Jr., 'Toll-Like Receptor 4 Mediates Oxidized Ldl-Induced Macrophage Differentiation to Foam Cells', *J Surg Res,* 171 (2011), e27-31.

56 G. N. Ioannou, 'Hepatitis B Virus in the United States: Infection, Exposure, and Immunity Rates in a Nationally Representative Survey', *Ann Intern Med,* 154 (2011), 319-28.

57 A. Iwasaki, and R. Medzhitov, 'Regulation of Adaptive Immunity by the Innate Immune System', *Science,* 327 (2010), 291-5.

58 A. D. Jack, A. J. Hall, N. Maine, M. Mendy, and H. C. Whittle, 'What Level of Hepatitis B Antibody Is Protective?', *J Infect Dis,* 179 (1999), 489-92.

59 N. Kadowaki, S. Ho, S. Antonenko, R. W. Malefyt, R. A. Kastelein, F. Bazan, and Y. J. Liu, 'Subsets of Human Dendritic Cell Precursors Express Different Toll-Like Receptors and Respond to Different Microbial Antigens', *J Exp Med,* 194 (2001), 863-9.

60 M. A. Kane, M. J. Alter, S. C. Hadler, and H. S. Margolis, 'Hepatitis B Infection in the United States. Recent Trends and Future Strategies for Control', *Am J Med,* 87 (1989), 11S-13S.

61 H. Kanzler, F. J. Barrat, E. M. Hessel, and R. L. Coffman, 'Therapeutic Targeting of Innate Immunity with Toll-Like Receptor Agonists and Antagonists', *Nat Med,* 13 (2007), 552-9.

62 T. Kawai, and S. Akira, 'The Role of Pattern-Recognition Receptors in Innate Immunity: Update on Toll-Like Receptors', *Nat Immunol,* 11 (2010), 373-84.

63 J. J. Kim, 'The Role of Cost-Effectiveness in U.S. Vaccination Policy', *N Engl J Med,* 365 (2011), 1760-1.

64 K. D. Kochanek, S. L. Murphy, J. Xu, and B. Tejada-Vera, 'Deaths: Final Data for 2014', *Natl Vital Stat Rep,* 65 (2016), 1-122.

65 H. C. Koenig, A. Sutherland, H. S. Izurieta, and D. McGonagle, 'Application of the Immunological Disease Continuum to Study Autoimmune and Other Inflammatory Events after Vaccination', *Vaccine,* 29 (2011), 913-9.

66 Y. Kondo, K. Tsukada, T. Takeuchi, T. Mitsui, K. Iwano, K. Masuko, T. Itoh, H. Tokita, H. Okamoto, F. Tsuda, and et al., 'High Carrier Rate after Hepatitis B Virus Infection in the Elderly', *Hepatology,* 18 (1993), 768-74.

67 M. Kool, T. Soullie, M. van Nimwegen, M. A. Willart, F. Muskens, S. Jung, H. C. Hoogsteden, H. Hammad, and B. N. Lambrecht, 'Alum Adjuvant Boosts Adaptive Immunity by Inducing Uric Acid and Activating Inflammatory Dendritic Cells', *J Exp Med,* 205 (2008), 869-82.

68 C. Koulis, Y. C. Chen, C. Hausding, I. Ahrens, T. S. Kyaw, C. Tay, T. Allen, K. Jandeleit-Dahm, M. J. Sweet, S. Akira, A. Bobik, K. Peter, and A. Agrotis, 'Protective Role for Toll-Like Receptor-9 in the Development of Atherosclerosis in Apolipoprotein E-Deficient Mice', *Arterioscler Thromb Vasc Biol,* 34 (2014), 516-25.

69 K. V. Kowdley, C. C. Wang, S. Welch, H. Roberts, and C. L. Brosgart, 'Prevalence of Chronic Hepatitis B among Foreign-Born Persons Living in the United States by Country of Origin', *Hepatology,* 56 (2012), 422-33.

70 A. M. Krieg, S. M. Efler, M. Wittpoth, M. J. Al Adhami, and H. L. Davis, 'Induction of Systemic Th1-Like Innate Immunity in Normal Volunteers Following Subcutaneous but Not Intravenous Administration of Cpg 7909, a Synthetic B-Class Cpg Oligodeoxynucleotide Tlr9 Agonist', *J Immunother,* 27 (2004), 460-71.

71 A. O. Krogmann, E. Lusebrink, M. Steinmetz, T. Asdonk, C. Lahrmann, D. Lutjohann, G. Nickenig, and S. Zimmer, 'Proinflammatory Stimulation of Toll-Like Receptor 9 with High Dose Cpg Odn 1826 Impairs Endothelial Regeneration and Promotes Atherosclerosis in Mice', *PLoS One,* 11 (2016), e0146326.

72 J. A. Kummer, R. Broekhuizen, H. Everett, L. Agostini, L. Kuijk, F. Martinon, R. van Bruggen, and J. Tschopp, 'Inflammasome Components Nalp 1 and 3 Show Distinct but Separate Expression Profiles in Human Tissues Suggesting a Site-Specific Role in the Inflammatory Response', *J Histochem Cytochem,* 55 (2007), 443-52.

73 E. Leuridan, and P. Van Damme, 'Hepatitis B and the Need for a Booster Dose', *Clin Infect Dis,* 53 (2011), 68-75.

74 P. Libby, 'Mechanisms of Acute Coronary Syndromes and Their Implications for Therapy', *N Engl J Med,* 368 (2013), 2004-13.

75 P. Libby, A. H. Lichtman, and G. K. Hansson, 'Immune Effector Mechanisms Implicated in Atherosclerosis: From Mice to Humans', *Immunity,* 38 (2013), 1092-104.

76 P. Libby, I. Tabas, G. Fredman, and E. A. Fisher, 'Inflammation and Its Resolution as Determinants of Acute Coronary Syndromes', *Circ Res,* 114 (2014), 1867-79.

77 A. H. Lichtman, C. J. Binder, S. Tsimikas, and J. L. Witztum, 'Adaptive Immunity in Atherogenesis: New Insights and Therapeutic Approaches', *J Clin Invest,* 123 (2013), 27-36.

78 F. J. Mahoney, and M. A. Kane, 'Hepatitis B Vaccine', in *Vaccines*, ed. by S. A. Plotkin and W. A. Orenstein (Philadelphia: W.B. Saunders Company, 1999), 158-82.

79 J. D. Marshall, K. Fearon, C. Abbate, S. Subramanian, P. Yee, J. Gregorio, R. L. Coffman, and G. Van Nest, 'Identification of a Novel Cpg DNA Class and Motif That Optimally Stimulate B Cell and Plasmacytoid Dendritic Cell Functions', *J Leukoc Biol,* 73 (2003), 781-92.

80 J. Martinuc Porobic, T. Avcin, B. Bozic, M. Kuhar, S. Cucnik, M. Zupancic, K. Prosenc, T. Kveder, and B. Rozman, 'Anti-Phospholipid Antibodies Following Vaccination with Recombinant Hepatitis B Vaccine', *Clin Exp Immunol,* 142 (2005), 377-80.

81 E. E. Mast, H. S. Margolis, A. E. Fiore, E. W. Brink, S. T. Goldstein, S. A. Wang, L. A. Moyer, B. P. Bell, and M. J. Alter, 'A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee

on Immunization Practices (Acip) Part 1: Immunization of Infants, Children, and Adolescents', *MMWR,* 54 (2005), 1-31.

82 E. E. Mast, C. M. Weinbaum, A. E. Fiore, M. J. Alter, B. P. Bell, L. Finelli, L. E. Rodewald, J. M. Douglas, Jr., R. S. Janssen, and J. W. Ward, 'A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices (Acip) Part Ii: Immunization of Adults', *MMWR Recomm Rep,* 55 (2006), 1-25.

83 E. Mast, and J. L. Ward, 'Hepatitis B Vaccines', in *Vaccines*, ed. by S. A. Plotkin, W. A. Orenstein and P. A. Offit (Philadelphia: WB Saunders, 2008), 205-41.

84 S. H. McCall, M. Sahraei, A. B. Young, C. S. Worley, J. A. Duncan, J. P. Ting, and I. Marriott, 'Osteoblasts Express Nlrp3, a Nucleotide-Binding Domain and Leucine-Rich Repeat Region Containing Receptor Implicated in Bacterially Induced Cell Death', *J Bone Miner Res,* 23 (2008), 30-40.

85 A. McGrogan, H. E. Seaman, J. W. Wright, and C. S. de Vries, 'The Incidence of Autoimmune Thyroid Disease: A Systematic Review of the Literature', *Clin Endocrinol (Oxf),* 69 (2008), 687-96.

86 G. M. McQuillan, P. J. Coleman, D. Kruszon-Moran, L. A. Moyer, S. B. Lambert, and H. S. Margolis, 'Prevalence of Hepatitis B Virus Infection in the United States: The National Health and Nutrition Examination Surveys, 1976 through 1994', *Am J Public Health,* 89 (1999), 14-8.

87 M. Mendy, I. Peterson, S. Hossin, T. Peto, M. L. Jobarteh, A. Jeng-Barry, M. Sidibeh, A. Jatta, S. E. Moore, A. J. Hall, and H. Whittle, 'Observational Study of Vaccine Efficacy 24 Years after the Start of Hepatitis B Vaccination in Two Gambian Villages: No Need for a Booster Dose', *PLoS One,* 8 (2013), e58029.

88 Merck & Co., Inc., 'Summary for Basis of Approval, Merck Sharp & Dohme (Mds), Recombivax Hb, No. 88-0192', (1987), 1-9.

89 A. Meyer, P. Rotman-Pikielny, A. Natour, and Y. Levy, 'Antiphospholipid Syndrome Following a Diphtheria-Tetanus Vaccination: Coincidence Vs. Causality', *Isr Med Assoc J,* 12 (2010), 638-9.

90 K. S. Michelsen, M. H. Wong, P. K. Shah, W. Zhang, J. Yano, T. M. Doherty, S. Akira, T. B. Rajavashisth, and M. Arditi, 'Lack of Toll-Like Receptor 4 or Myeloid Differentiation Factor 88 Reduces Atherosclerosis and Alters Plaque Phenotype in Mice Deficient in Apolipoprotein E', *Proc Natl Acad Sci U S A,* 101 (2004), 10679-84.

91 Y. I. Miller, S. Viriyakosol, D. S. Worrall, A. Boullier, S. Butler, and J. L. Witztum, 'Toll-Like Receptor 4-Dependent and -Independent Cytokine Secretion Induced by Minimally Oxidized Low-Density Lipoprotein in Macrophages', *Arterioscler Thromb Vasc Biol,* 25 (2005), 1213-9.

92 D. Mozaffarian, E. J. Benjamin, A. S. Go, D. K. Arnett, M. J. Blaha, M. Cushman, S. de Ferranti, J. P. Despres, H. J. Fullerton, V. J. Howard, M. D. Huffman, S. E. Judd, B. M. Kissela, D. T. Lackland, J. H. Lichtman, L. D. Lisabeth, S. Liu, R. H. Mackey, D. B. Matchar, D. K. McGuire, E. R. Mohler, 3rd, C. S. Moy, P. Muntner, M. E. Mussolino, K. Nasir, R. W. Neumar, G. Nichol, L. Palaniappan, D. K. Pandey, M. J. Reeves, C. J. Rodriguez, P. D. Sorlie, J. Stein, A. Towfighi, T. N. Turan, S. S. Virani, J. Z. Willey, D. Woo, R. W. Yeh, M. B. Turner, and Committee and Stroke Statistics Subcommittee American Heart Association Statistics, 'Heart Disease and Stroke

Statistics--2015 Update: A Report from the American Heart Association', *Circulation,* 131 (2015), e29-e322.

93 A. E. Mullick, P. S. Tobias, and L. K. Curtiss, 'Modulation of Atherosclerosis in Mice by Toll-Like Receptor 2', *J Clin Invest,* 115 (2005), 3149-56.

94 M. Mutsch, W. Zhou, P. Rhodes, M. Bopp, R. T. Chen, T. Linder, C. Spyr, and R. Steffen, 'Use of the Inactivated Intranasal Influenza Vaccine and the Risk of Bell's Palsy in Switzerland', *N Engl J Med,* 350 (2004), 896-903.

95 National Academy of Sciences, 'A National Strategy for the Elimination of Hepatitis B and C: Phase Two Report', ed. by G. J. Buckley and B. L. Strom (Washington, DC: The National Acadenies of Sciences, Engineering, Medicine, 2017), 1-253.

96 J. C. Nelson, R. C. Bittner, L. Bounds, S. Zhao, J. Baggs, J. G. Donahue, S. J. Hambidge, S. J. Jacobsen, N. P. Klein, A. L. Naleway, K. M. Zangwill, and L. A. Jackson, 'Compliance with Multiple-Dose Vaccine Schedules among Older Children, Adolescents, and Adults: Results from a Vaccine Safety Datalink Study', *Am J Public Health,* 99 Suppl 2 (2009), S389-97.

97 G. Nicolaou, A. H. Goodall, and C. Erridge, 'Diverse Bacteria Promote Macrophage Foam Cell Formation Via Toll-Like Receptor-Dependent Lipid Body Biosynthesis', *J Atheroscler Thromb,* 19 (2012), 137-48.

98 A. Niessner, K. Sato, E. L. Chaikof, I. Colmegna, J. J. Goronzy, and C. M. Weyand, 'Pathogen-Sensing Plasmacytoid Dendritic Cells Stimulate Cytotoxic T-Cell Function in the Atherosclerotic Plaque through Interferon-Alpha', *Circulation,* 114 (2006), 2482-9.

99 A. Niessner, and C. M. Weyand, 'Dendritic Cells in Atherosclerotic Disease', *Clin Immunol,* 134 (2010), 25-32.

100 M. B. Pepys, and G. M. Hirschfield, 'C-Reactive Protein: A Critical Update', *J Clin Invest,* 111 (2003), 1805-12.

101 L. B. Polish, C. N. Shapiro, F. Bauer, P. Klotz, P. Ginier, R. R. Roberto, H. S. Margolis, and M. J. Alter, 'Nosocomial Transmission of Hepatitis B Virus Associated with the Use of a Spring-Loaded Finger-Stick Device', *N Engl J Med,* 326 (1992), 721-5.

102 T. D. Querec, R. S. Akondy, E. K. Lee, W. Cao, H. I. Nakaya, D. Teuwen, A. Pirani, K. Gernert, J. Deng, B. Marzolf, K. Kennedy, H. Wu, S. Bennouna, H. Oluoch, J. Miller, R. Z. Vencio, M. Mulligan, A. Aderem, R. Ahmed, and B. Pulendran, 'Systems Biology Approach Predicts Immunogenicity of the Yellow Fever Vaccine in Humans', *Nat Immunol,* 10 (2009), 116-25.

103 M. Reilly, 'Acute Hepatitis B Incidence among Adults with and without Diabetes-Updated Estimate. ', in *ACIP meeting, CDC* (Atlanta, GA: 2011), 1-9.

104 P. Rendi-Wagner, M. Kundi, H. Stemberger, G. Wiedermann, H. Holzmann, M. Hofer, K. Wiesinger, and H. Kollaritsch, 'Antibody-Response to Three Recombinant Hepatitis B Vaccines: Comparative Evaluation of Multicenter Travel-Clinic Based Experience', *Vaccine,* 19 (2001), 2055-60.

105 M. Renshaw, J. Rockwell, C. Engleman, A. Gewirtz, J. Katz, and S. Sambhara, 'Cutting Edge: Impaired Toll-Like Receptor Expression and Function in Aging', *J Immunol,* 169 (2002), 4697-701.

106 A. J. Roome, S. J. Walsh, M. L. Cartter, and J. L. Hadler, 'Hepatitis B Vaccine Responsiveness in Connecticut Public Safety Personnel', *JAMA,* 270 (1993), 2931-4.

107 L. Ruane, T. Buckley, S. Y. S. Hoo, P. S. Hansen, C. McCormack, E. Shaw, J. Fethney, and G. H. Tofler, 'Triggering of Acute Myocardial Infarction by Respiratory Infection', *Intern Med J,* 47 (2017), 522-29.

108 B. Salvador, A. Arranz, S. Francisco, L. Cordoba, C. Punzon, M. A. Llamas, and M. Fresno, 'Modulation of Endothelial Function by Toll Like Receptors', *Pharmacol Res,* 108 (2016), 46-56.

109 M. Sawyer, and T. J. Hoerger, 'Use of Hepatitis B Vaccination for Adults with Diabetes Mellitus: Recommendations of the Advisory Committee on Immunization Practices (Acip)', *MMWR,* 60 (2011), 1709-11.

110 B. M. Scirica, D. L. Bhatt, E. Braunwald, P. G. Steg, J. Davidson, B. Hirshberg, P. Ohman, R. Frederich, S. D. Wiviott, E. B. Hoffman, M. A. Cavender, J. A. Udell, N. R. Desai, O. Mosenzon, D. K. McGuire, K. K. Ray, L. A. Leiter, I. Raz, Savor-Timi Steering Committee, and Investigators, 'Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus', *N Engl J Med,* 369 (2013), 1317-26.

111 F. A. Sharp, D. Ruane, B. Claass, E. Creagh, J. Harris, P. Malyala, M. Singh, D. T. O'Hagan, V. Petrilli, J. Tschopp, L. A. O'Neill, and E. C. Lavelle, 'Uptake of Particulate Vaccine Adjuvants by Dendritic Cells Activates the Nalp3 Inflammasome', *Proc Natl Acad Sci U S A,* 106 (2009), 870-5.

112 J. B. Sims, J. A. de Lemos, P. Maewal, J. J. Warner, G. E. Peterson, and D. K. McGuire, 'Urinary Tract Infection in Patients with Acute Coronary Syndrome: A Potential Systemic Inflammatory Connection', *Am Heart J,* 149 (2005), 1062-5.

113 L. Smeeth, S. L. Thomas, A. J. Hall, R. Hubbard, P. Farrington, and P. Vallance, 'Risk of Myocardial Infarction and Stroke after Acute Infection or Vaccination', *N Engl J Med,* 351 (2004), 2611-8.

114 SmithKline Biologicals, 'Summary for Basis of Approval, Smithkline. Biologicals: Engerix B, No. 87- 0556', (US Food and Drug Administration, 1989), 1-10.

115 W. Szmuness, C. E. Stevens, E. A. Zang, E. J. Harley, and A. Kellner, 'A Controlled Clinical Trial of the Efficacy of the Hepatitis B Vaccine (Heptavax B): A Final Report', *Hepatology,* 1 (1981), 377-85.

116 W. Szmuness, C.E. Stevens, E.A. Zang, E.J. Harley, P.E. Taylor, and A. Kellner, 'Hepatitis B Vaccine: A Controlled Clinical Trial in Homosexual Men', in *Viral Hepatitis* (1982), 467-86.

117 K. Tobinai, Y. Kobayashi, M. Narabayashi, M. Ogura, Y. Kagami, Y. Morishima, T. Ohtsu, T. Igarashi, Y. Sasaki, T. Kinoshita, and T. Murate, 'Feasibility and Pharmacokinetic Study of a Chimeric Anti-Cd20 Monoclonal Antibody (Idec-C2b8, Rituximab) in Relapsed B-Cell Lymphoma. The Idec-C2b8 Study Group', *Ann Oncol,* 9 (1998), 527-34.

118 R. A. Tohme, D. Awosika-Olumo, C. Nielsen, S. Khuwaja, J. Scott, J. Xing, J. Drobeniuc, D. J. Hu, C. Turner, T. Wafeeg, U. Sharapov, and P. Spradling, 'Evaluation of Hepatitis B Vaccine Immunogenicity among Older Adults During an Outbreak Response in Assisted Living Facilities', *Vaccine,* 29 (2011), 9316-20.

119 M. E. Tosti, V. Alfonsi, E. Lacorte, A. Mele, C. Galli, A. R. Zanetti, L. Romano, and Seieva Collaborating Group, 'Acute Hepatitis B after the Implementation of Universal Vaccination in Italy: Results from 22 Years of Surveillance (1993-2014)', *Clin Infect Dis,* 62 (2016), 1412-8.

120 G. Trinchieri, and A. Sher, 'Cooperation of Toll-Like Receptor Signals in Innate Immune Defence', *Nat Rev Immunol,* 7 (2007), 179-90.

121 P. Valenzuela, A. Medina, W. J. Rutter, G. Ammerer, and B. D. Hall, 'Synthesis and Assembly of Hepatitis B Virus Surface Antigen Particles in Yeast', *Nature,* 298 (1982), 347-50.

122 M. Van der Wielen, P. Van Damme, R. Chlibek, J. Smetana, and F. von Sonnenburg, 'Hepatitis a/B Vaccination of Adults over 40 Years Old: Comparison of Three Vaccine Regimens and Effect of Influencing Factors', *Vaccine,* 24 (2006), 5509-15.

123 C. Warren-Gash, L. Smeeth, and A. C. Hayward, 'Influenza as a Trigger for Acute Myocardial Infarction or Death from Cardiovascular Disease: A Systematic Review', *Lancet Infect Dis,* 9 (2009), 601-10.

124 D. J. Weber, W. A. Rutala, G. P. Samsa, J. E. Santimaw, and S. M. Lemon, 'Obesity as a Predictor of Poor Antibody Response to Hepatitis B Plasma Vaccine', *JAMA,* 254 (1985), 3187-9.

125 D. Westmoreland, V. Player, D. C. Heap, and A. Hammond, 'Immunization against Hepatitis B--What Can We Expect? Results of a Survey of Antibody Response to Immunization in Persons 'at Risk' of Occupational Exposure to Hepatitis B', *Epidemiol Infect,* 104 (1990), 499-509.

126 W. W. Williams, P. J. Lu, A. O'Halloran, D. K. Kim, L. A. Grohskopf, T. Pilishvili, T. H. Skoff, N. P. Nelson, R. Harpaz, L. E. Markowitz, A. Rodriguez-Lainz, and A. P. Fiebelkorn, 'Surveillance of Vaccination Coverage among Adult Populations - United States, 2015', *MMWR Surveill Summ,* 66 (2017), 1-28.

127 P. J. Wismans, J. van Hattum, G. C. de Gast, K. P. Bouter, R. J. Diepersloot, T. Maikoe, and G. C. Mudde, 'A Prospective Study of in Vitro Anti-Hbs Producing B Cells (Spot-Elisa) Following Primary and Supplementary Vaccination with a Recombinant Hepatitis B Vaccine in Insulin Dependent Diabetic Patients and Matched Controls', *J Med Virol,* 35 (1991), 216-22.

128 B. Wolters, U. Junge, S. Dziuba, and M. Roggendorf, 'Immunogenicity of Combined Hepatitis a and B Vaccine in Elderly Persons', *Vaccine,* 21 (2003), 3623-8.

129 R. C. Wood, K. L. MacDonald, K. E. White, C. W. Hedberg, M. Hanson, and M. T. Osterholm, 'Risk Factors for Lack of Detectable Antibody Following Hepatitis B Vaccination of Minnesota Health Care Workers', *JAMA,* 270 (1993), 2935-9.

130 X. H. Xu, P. K. Shah, E. Faure, O. Equils, L. Thomas, M. C. Fishbein, D. Luthringer, X. P. Xu, T. B. Rajavashisth, J. Yano, S. Kaul, and M. Arditi, 'Toll-Like Receptor-4 Is Expressed by Macrophages in Murine and Human Lipid-Rich Atherosclerotic Plaques and Upregulated by Oxidized Ldl', *Circulation,* 104 (2001), 3103-8.

131 A. Yilmaz, M. Lochno, F. Traeg, I. Cicha, C. Reiss, C. Stumpf, D. Raaz, T. Anger, K. Amann, T. Probst, J. Ludwig, W. G. Daniel, and C. D. Garlichs, 'Emergence of Dendritic Cells in Rupture-Prone Regions of Vulnerable Carotid Plaques', *Atherosclerosis,* 176 (2004), 101-10.

132 H. R. Yu, H. C. Huang, H. C. Kuo, J. M. Sheen, C. Y. Ou, T. Y. Hsu, and K. D. Yang, 'Ifn-Alpha Production by Human Mononuclear Cells Infected with Varicella-Zoster Virus through Tlr9-Dependent and -Independent Pathways', *Cell Mol Immunol,* 8 (2011), 181-8.

10.0 APPENDICES

APPENDIX 1: INDIVIDUALS WITH 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 with diabetes
- Individuals with end-stage renal disease, including predialysis, hemodialysis, and peritoneal dialysis
- Healthcare 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 ≥ 2%
- Individuals with chronic liver disease
- Individuals with HIV infection
- All other individuals seeking protection from HBV infection

Data Source: ([82, 109])
HBsAg = hepatitis B virus surface antigen; HIV = human immunodeficiency virus; N = number of subjects in the population; n = number of subjects in the group.

APPENDIX 2: COMPLETED CLINICAL TRIALS OF HEPLISAV-B

Phase/ Trial No.	Trial Design	HEPLISAV-B Dose/Schedule/N	Comparator Dose/Schedule/N	Key Immunogenicity/Safety Endpoint(s)
Primary Safety Population - Pivotal Trials				
Phase 3 HBV-23 Completed 16 October 2015	Observer-blinded, randomized, active-controlled, parallel-group, multicenter trial in subjects 18 to 70 years of age conducted in the US	HEPLISAV-B: 20 mcg HBsAg 3 mg 1018 Schedule: 0, 4 weeks (placebo at 24 weeks) N = 5592	Engerix-B: 20 mcg HBsAg 0.5 mg alum Schedule = 0, 4, 24 weeks N = 2782	Primary Endpoints SPR at Week 28 in subjects with type 2 diabetes mellitus Overall safety with respect to clinically significant events Safety Assessments MAEs (56 weeks) SAEs (56 weeks) Thrombotic/Thromboembolic events (56 weeks)
Phase 3 HBV-16 Completed 25 May 2011	Observer-blind, randomized, active-controlled, parallel-group, multicenter trial in healthy adults 40 to 70 years of age conducted in the United States and Canada	HEPLISAV-B: 20 mcg HBsAg 3 mg 1018 Schedule: 0, 4 weeks (placebo at 24 weeks) N = 1969	Engerix-B: 20 mcg HBsAg 0.5 mg alum Schedule = 0, 4, 24 weeks N = 483	Primary Endpoints SPR at Week 12 for HEPLISAV-B and Week 32 for Engerix-B Lot consistency of HEPLISAV-B measured by GMC at Week 8 Safety Assessments Local and systemic post-injection reactions (7 days following each injection) AEs (28 weeks) SAEs (52 weeks) Active surveillance and external adjudication of AESIs by SEAC (52 weeks) Clinical laboratory tests (serum chemistry, hematology, ANA, and anti-dsDNA)
Phase 3 HBV-10 [a] Completed 17 March 2008	Observer-blind, randomized, active-controlled, parallel-group, multicenter trial in healthy subjects 11 to 55 years of age conducted in Canada and Germany	HEPLISAV-B: 20 mcg HBsAg 3 mg 1018 Schedule: 0, 4 weeks (placebo at 24 weeks) N = 1820 (n=11, aged less than 18 years)	Engerix-B: 20 mcg HBsAg 0.5 mg alum Schedule = 0, 4, 24 weeks N = 608 (n=2, aged less than 18 years)	Primary Endpoint SPR at Week 12 for HEPLISAV-B and Week 28 for Engerix-B Safety Assessments Local and systemic post-injection reactions (7 days following each injection) AEs (28 weeks) SAEs (28 weeks) Clinical laboratory tests (serum chemistry, hematology, ANA, and anti-dsDNA)

Phase/ Trial No.	Trial Design	HEPLISAV-B Dose/Schedule/N	Comparator Dose/Schedule/N	Key Immunogenicity/Safety Endpoint(s)
Supportive Trials that Used the Current Formulation of HEPLISAV-B				
Phase 1 HBV-22 Completed 9 December 2014	Systems biology study of HEPLISAV-B in adults 50 to 70 years of age conducted in the US	HEPLISAV-B: 20 mcg HBsAg 3 mg 1018 Schedule: 0, 4 weeks N = 25	None	Primary Endpoints Changes in cellular responses and gene expression Correlate changes with seroprotection SPR at Weeks 4, 8, 12 Safety Assessments AEs (12 weeks) SAEs (56 weeks) Immune-mediated AEs (56 weeks)
Phase 2 HBV-14[b] Completed 6 March 2008	Open-label trial in healthy subjects 11 to 55 years of age conducted in the US	HEPLISAV-B: 20 mcg HBsAg 3 mg 1018 Schedule: 0, 4 weeks N = 207	None	Primary Endpoints The percentage of subjects with post-injection local and systemic reactions reported during Days 0 through 6 following each injection The percentage of subjects with AEs through Week Concomitant medication usage through Week 8 Secondary Endpoints SPR at Weeks 4, 8, 12, and 28 GMC at Weeks 4, 8, 12, and 28 Safety Assessments AEs (28 weeks) SAEs (28 weeks)
Supportive Trials that Used a Previous Formulation of HEPLISAV-B or Different Dosing				
Phase 1 HBV0001 Completed 9 May 2002	Observer-blind, randomized, dose-escalation trial of the 1018 and rHBsAg components of vaccine in healthy, seronegative adults 18 to 55 years of age conducted in Canada	1018 alone or with HBsAg 0.3 mg, alone or plus HBsAg 0.65 mg, alone or plus HBsAg 1 mg, alone or plus HBsAg 3 mg, alone or plus HBsAg HBsAg: constant at 20 mcg Schedule: 0, 8 weeks N = 32	HBsAg alone: 20 mcg Schedule: 0, 8 weeks N = 8 1018 alone: 0.3 mg, 0.65 mg, 1 mg, 3 mg Schedule: 0, 8 weeks N = 8	Primary Endpoint Anti-HBs measured after vaccinations Safety Assessments Local and systemic post-injection reaction (7 days following each injection) AEs (62 weeks) SAEs (62 weeks) Clinical laboratory tests (serum chemistry, hematology, urinalysis, ANA, and anti-dsDNA, anti-ssDNA, ESR, and C3/C4)

Phase/ Trial No.	Trial Design	HEPLISAV-B Dose/Schedule/N	Comparator Dose/Schedule/N	Key Immunogenicity/Safety Endpoint(s)
Phase 2 HBV-03 Completed 20 May 2004	Observer-blind, randomized, parallel-group trial in adults 18 to 28 years of age conducted in Canada	HEPLISAV-B: 20 mcg HBsAg 3 mg 1018 Schedule: 0, 8 weeks (placebo/meningo-coccal vaccine at 24 weeks) N = 48	Engerix-B: 20 mcg HBsAg 0.5 mg alum Schedule: 0, 8, 24 weeks N = 51	Primary Endpoint SPR at Week 8 Safety Assessments Local and systemic post-injection reaction (7 days following each injection) AEs (28 weeks) SAEs (60 weeks) Clinical laboratory tests (serum chemistry, hematology, urinalysis, ANA, anti-dsDNA, anti-ssDNA, ESR, and C3/C4,)
Phase 3 HBV-04 Completed 4 January 2007	Double-blind, randomized, parallel-group trial in adults 40 to 70 years of age conducted in South Korea, Philippines, and Singapore	HEPLISAV-B 20 mcg HBsAg 3 mg 1018 Schedule: 0, 8, 24 weeks (placebo at 4 weeks) N = 206	Engerix-B 20 mcg HBsAg 0.5 mg alum Schedule: 0, 4, 24 weeks (placebo at 8 weeks) N = 206	Primary Endpoint SPR at Week 28 Safety Assessments Local and systemic post-injection reactions (7 days following each injection) AEs (28 weeks) SAEs (50 weeks) Clinical laboratory tests (serum chemistry, hematology, urinalysis)
Phase 2 HBV-05 Completed 24 August 2005	Double-blind, randomized, parallel-group trial in adults 40 to 70 years of age conducted in Singapore	HEPLISAV-B 20 mcg HBsAg 3 mg 1018 Schedule; 0, 8, 24 weeks (placebo at 4 weeks) N = 48	Engerix-B 20 mcg HBsAg 0.5 mg alum Schedule: 0, 4, 24 weeks (placebo at 8 weeks) N = 47	Primary Endpoint SPR at Week 28 Safety Assessments Local and systemic post-injection reaction (7 days following each injection) AEs (24 weeks) SAEs (50 weeks) Clinical laboratory tests (serum chemistry, hematology, ANA, and anti-dsDNA)
Phase 2 HBV-08 Completed 6 September 2006	Double-blind, randomized, parallel-group trial in adults 18 to 39 years of age conducted in Canada	HEPLISAV-B Half Dose (10 mcg/1.5 mg) Schedule: 0, 4 weeks Schedule: 0, 4 weeks and 0, 8 weeks N = 61	None	Primary Endpoint SPR at 4 weeks after 2nd dose Safety Assessments Local and systemic post-injection reaction (7 days following each injection) AEs (12 weeks) SAEs (32 weeks) Clinical laboratory tests (serum chemistry, hematology, urinalysis, ANA)

Phase/ Trial No.	Trial Design	HEPLISAV-B Dose/Schedule/N	Comparator Dose/Schedule/N	Key Immunogenicity/Safety Endpoint(s)
Nonresponder Trial that Used a Previous Formulation of HEPLISAV-B or Different Dosing				
Phase 2 HBV-02 Completed 28 August 2004	Observer-blind, randomized, parallel-group trial of hypo- and non-responders to licensed hepatitis B vaccine in adults 18 to 65 years of age conducted in Canada	HEPLISAV-B: 20 mcg HBsAg 3 mg 1018 Schedule: single injection N = 30	Engerix-B: 20 mcg HBsAg 0.5 mg alum Schedule: single injection N = 29	Primary Endpoint SPR at Week 4 Safety Assessments Local and systemic post-injection reaction (7 days following each injection) AEs (4 weeks) SAEs (52 weeks) Clinical laboratory tests (serum chemistry, hematology, urinalysis, ANA, and anti-dsDNA, anti-ssDNA, and ESR)

AEs = adverse events; AESIs = adverse events of special interest; ANA = antinuclear antibody; anti-dsDNA = antibody to double-stranded DNA; anti-ssDNA = antibody to single-stranded DNA; DNA = deoxyribonucleic acid; Engerix-B = 20 mcg recombinant HBsAg and 0.5 mg aluminum hydroxide unless otherwise indicated; ESR = erythrocyte sedimentation rate; GMC = geometric mean concentration; HBsAg = hepatitis B virus surface antigen; HEPLISAV-B = 20 mcg recombinant HBsAg subtype *adw* and 3 mg 1018 unless otherwise indicated; MAEs = medically attended adverse events; N = number of randomized subjects; SAE = serious adverse events; schedule = number and timing of vaccine doses; SEAC = Safety Evaluation and Adjudication Committee; SPR = seroprotection rate; US = United States.

[b] There was a misdosed subject in HBV-10 who was randomized to receive Engerix-B but received HEPLISAV-B. This subject was analyzed as HEPLISAV-B in the Safety Population.

[b] No subject less than 18 years of age was enrolled in HBV-14.

APPENDIX 3: IMMUNE-MEDIATED ADVERSE EVENTS OF SPECIAL INTEREST PREFERRED TERMS

AESIs in the analyses represent autoimmune, inflammatory, and hypersensitivity disorders included in the list of AESIs provided to Dynavax by the FDA for HBV-23, dated 15 May 2014.

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 (added by Dynavax)
- Immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy)
- Multiple sclerosis
- 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
- 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

APPENDIX 4: DEATHS

Trial	Age (At Study Entry)	Sex	Race	Smoking Status	MedDRA Preferred Term	Study Day	Number of Active Injections	Days Since Last Active Dose[a]	Relationship to Treatment
HEPLISAV-B									
HBV-23	58	F	Black or African American	Smoker	Victim of Homicide	2	1	(b) (6)	Not Related
HBV-23	50	M	Black or African American	Nonsmoker	Acute Coronary Syndrome	8	1		Not Related
HBV-23	49	M	Black or African American	Smoker	Toxicity To Various Agents	32	2		Not Related
HBV-23	67	M	White	Nonsmoker	Acute Respiratory Failure	45	2		Not Related
HBV-23	68	M	White	Nonsmoker	Hepatic Cirrhosis	56	2		Not Related
HBV-23	56	M	White	Smoker	Hepatitis C	60	2		Not Related
HBV-23	38	M	White	Smoker	Toxicity To Various Agents	65	2		Not Related
HBV-16	45	M	White	Nonsmoker	Pulmonary Embolism	75	2		Not related
HBV-23	69	M	White	Smoker	Acute Myocardial Infarction	85	2		Not Related
HBV-23	61	F	White	Smoker	Death	85	2		Not Related
HBV-23	57	M	White	Nonsmoker	Hypertensive Heart Disease	92	2		Not Related
HBV-23	62	M	White	Smoker	Overdose	112	2		Not Related
HBV-23	61	M	Black or African American	Smoker	Acute Respiratory Distress Syndrome	149	2		Not Related
HBV-23	44	M	White	Smoker	Toxicity To Various Agents	188	2		Not Related
HBV-23	49	M	White	Smoker	Toxicity To Various Agents	190	2		Not Related
HBV-23	46	F	White	Nonsmoker	Hypoxic-Ischaemic Encephalopathy[b]	219	2		Not Related
HBV-23	62	M	White	Nonsmoker	Hypertensive Heart Disease	240	2		Not Related
HBV-23	58	F	Black or African American	Smoker	Hypertensive Heart Disease	254	2		Not Related
HBV-23	70	F	White	Nonsmoker	Cardiac Arrest	275	2		Not Related

Trial	Age (At Study Entry)	Sex	Race	Smoking Status	MedDRA Preferred Term	Study Day	Number of Active Injections	Days Since Last Active Dose[a]	Relationship to Treatment
HBV-23	49	M	White	Nonsmoker	Lung Cancer Metastatic	273	2	(b) (6)	Not Related
HBV-23	42	F	Black or African American	Nonsmoker	Gun Shot Wound	310	2		Not Related
HBV-23	49	M	White	Smoker	Accident	315	2		Not Related
HBV-23	47	M	Black or African American	Nonsmoker	Myocardial Infarction	320	2		Not Related
HBV-23	55	F	White	Smoker	Cardio-Respiratory Arrest	323	2		Not Related
HBV-23	43	F	White	Smoker	Small Cell Lung Cancer Metastatic	329	2		Not Related
HBV-23	51	F	White	Smoker	Death	379	2		Not Related
Engerix-B									
HBV-23	52	M	White	Smoker	Myocardial Infarction	13	1		Not Related
HBV-23	44	M	Black or African American	Nonsmoker	Craniocerebral Injury	18	1		Not Related
HBV-23	48	M	Black or African American	Nonsmoker	Hypertensive Heart Disease	189	3		Not Related
HBV-16	64	M	Black or African American	Nonsmoker	Cardiac Failure	73	2		Not related
HBV-23	69	M	Black or African American	Nonsmoker	Cardio-Respiratory Arrest	257	3		Not Related
HBV-23	55	M	Black or African American	Smoker	Toxicity To Various Agents	128	2		Not Related
HBV-23	33	F	Asian	Nonsmoker	Head Injury	330	3		Not Related
HBV-23	67	M	White	Nonsmoker	Pancreatic Carcinoma Metastatic	348	3		Not Related

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

[a] Number of days to onset of the MedDRA Preferred Term event.

[b] The event of hypoxic-ischaemic encephalopathy was secondary to an accidental overdose.

APPENDIX 5: TREATMENT EMERGENT SAEs BY SYSTEM ORGAN CLASS AND PREFERRED TERM (PRIMARY SAFETY POPULATION)

System Organ Class Preferred Term	HEPLISAV-B (N = 9365) % (n)	Engerix-B (N = 3867) % (n)
Subjects with at least 1 qualifying adverse event	4.8% (449)	4.8% (184)
Blood And Lymphatic System Disorders	0.04% (4)	0.08% (3)
Anaemia	0.02% (2)	0.05% (2)
Anaemia Vitamin B12 Deficiency	0	0.03% (1)
Leukocytosis	0.01% (1)	0
Microcytic Anaemia	0.01% (1)	0
Cardiac Disorders	0.63% (59)	0.54% (21)
Acute Coronary Syndrome	0.01% (1)	0
Acute Myocardial Infarction	0.17% (16)	0.05% (2)
Angina Pectoris	0.04% (4)	0.03% (1)
Angina Unstable	0.01% (1)	0.03% (1)
Atrial Fibrillation	0.07% (7)	0.10% (4)
Atrial Flutter	0.02% (2)	0.03% (1)
Bradycardia	0.02% (2)	0
Cardiac Arrest	0.03% (3)	0
Cardiac Failure	0.02% (2)	0.03% (1)
Cardiac Failure Acute	0.01% (1)	0
Cardiac Failure Congestive	0.06% (6)	0.08% (3)
Cardiac Ventricular Thrombosis	0.01% (1)	0.03% (1)
Cardio-Respiratory Arrest	0.01% (1)	0.03% (1)
Cardiogenic Shock	0.01% (1)	0
Cardiomyopathy	0.01% (1)	0.03% (1)
Coronary Artery Disease	0.09% (8)	0.08% (3)
Coronary Artery Occlusion	0.01% (1)	0.03% (1)
Coronary Artery Stenosis	0.02% (2)	0.03% (1)
Hypertensive Heart Disease	0.04% (4)	0.03% (1)
Myocardial Infarction	0.02% (2)	0.03% (1)
Myocardial Ischaemia	0.01% (1)	0
Pulseless Electrical Activity	0.01% (1)	0
Supraventricular Tachycardia	0.01% (1)	0.03% (1)
Ventricular Fibrillation	0.01% (1)	0
Ventricular Tachycardia	0.02% (2)	0
Congenital, Familial And Genetic Disorders	0.03% (3)	0.03% (1)

System Organ Class Preferred Term	HEPLISAV-B (N = 9365) % (n)	Engerix-B (N = 3867) % (n)
Atrial Septal Defect	0.01% (1)	0
Ebstein's Anomaly	0.01% (1)	0.03% (1)
Sickle Cell Anaemia With Crisis	0.01% (1)	0
Ear And Labyrinth Disorders	0.03% (3)	0.03% (1)
Vertigo	0.02% (2)	0
Vertigo Positional	0.01% (1)	0.03% (1)
Endocrine Disorders	0.01% (1)	0.05% (2)
Inappropriate Antidiuretic Hormone Secretion	0.01% (1)	0
Pituitary-Dependent Cushing's Syndrome	0	0.03% (1)
Thyroid Mass	0	0.03% (1)
Eye Disorders	0	0
Gastrointestinal Disorders	0.49% (46)	0.47% (18)
Abdominal Hernia	0.02% (2)	0
Abdominal Pain	0.02% (2)	0.05% (2)
Appendix Disorder	0.01% (1)	0
Barrett's Oesophagus	0	0.03% (1)
Colitis	0.02% (2)	0
Colitis Ulcerative	0.01% (1)	0
Constipation	0.02% (2)	0.03% (1)
Cyclic Vomiting Syndrome	0.01% (1)	0
Diarrhoea	0.01% (1)	0
Diverticular Perforation	0.02% (2)	0.03% (1)
Diverticulum Intestinal Haemorrhagic	0.01% (1)	0
Duodenal Ulcer Haemorrhage	0	0.03% (1)
Enteritis	0	0
Erosive Oesophagitis	0.01% (1)	0
Gastric Haemorrhage	0	0.03% (1)
Gastric Ulcer	0.01% (1)	0.03% (1)
Gastric Ulcer Haemorrhage	0.01% (1)	0
Gastritis	0.03% (3)	0
Gastritis Alcoholic	0.01% (1)	0
Gastritis Alcoholic Haemorrhagic	0.01% (1)	0
Gastritis Haemorrhagic	0.01% (1)	0
Gastrointestinal Haemorrhage	0.02% (2)	0.03% (1)
Gastrooesophageal Reflux Disease	0.04% (4)	0.03% (1)
Haematemesis	0.01% (1)	0

System Organ Class Preferred Term	HEPLISAV-B (N = 9365) % (n)	Engerix-B (N = 3867) % (n)
Ileus	0.01% (1)	0
Ileus Paralytic	0.01% (1)	0
Impaired Gastric Emptying	0	0.03% (1)
Inguinal Hernia	0.01% (1)	0.03% (1)
Intestinal Obstruction	0	0.03% (1)
Large Intestine Perforation	0.01% (1)	0.03% (1)
Lower Gastrointestinal Haemorrhage	0	0.03% (1)
Oesophageal Spasm	0.01% (1)	0
Oesophagitis	0.01% (1)	0
Pancreatitis	0.02% (2)	0.03% (1)
Pancreatitis Acute	0.01% (1)	0.05% (2)
Rectal Haemorrhage	0.01% (1)	0.05% (2)
Rectal Prolapse	0.01% (1)	0
Small Intestinal Obstruction	0.07% (7)	0.05% (2)
Upper Gastrointestinal Haemorrhage	0.02% (2)	0
Varices Oesophageal	0.01% (1)	0
General Disorders And Administration Site Conditions	0.19% (18)	0.28% (11)
Chest Pain	0.02% (2)	0.05% (2)
Death	0.02% (2)	0
Device Dislocation	0.01% (1)	0
Device Failure	0.01% (1)	0
Drug Withdrawal Syndrome	0	0.03% (1)
Hernia Obstructive	0	0
Non-Cardiac Chest Pain	0.13% (12)	0.21% (8)
Hepatobiliary Disorders	0.17% (16)	0.26% (10)
Bile Duct Stone	0.02% (2)	0.03% (1)
Cholecystitis	0.06% (6)	0.05% (2)
Acute Cholecystitis	0.01% (1)	0.05% (2)
Chronic Cholecystitis	0.01% (1)	0.05% (2)
Cholelithiasis	0.04% (4)	0.10% (4)
Hepatic Cirrhosis	0.01% (1)	0.03% (1)
Ischaemic Hepatitis	0.01% (1)	0
Immune System Disorders	0.01% (1)	0.05% (2)
Anti-Neutrophil Cytoplasmic Antibody Positive Vasculitis	0	0.03% (1)
Hypersensitivity	0.01% (1)	0.03% (1)
Infections And Infestations	0.83% (78)	0.91% (35)

System Organ Class Preferred Term	HEPLISAV-B (N = 9365) % (n)	Engerix-B (N = 3867) % (n)
Abscess Limb	0.01% (1)	0
Abscess Neck	0.01% (1)	0
Appendicitis	0.03% (3)	0.03% (1)
Appendicitis Perforated	0.02% (2)	0
Arthritis Bacterial	0.01% (1)	0
Bacteraemia	0.01% (1)	0
Bronchitis	0.03% (3)	0
Cavernous Sinus Thrombosis	0.01% (1)	0
Cellulitis	0.07% (7)	0.10% (4)
Cellulitis Of Male External Genital Organ	0.01% (1)	0
Cellulitis Orbital	0	0.03% (1)
Cholecystitis Infective	0.01% (1)	0
Clostridium Difficile Colitis	0.01% (1)	0
Dengue Fever	0	0
Device Related Infection	0.01% (1)	0
Diabetic Foot Infection	0.02% (2)	0.03% (1)
Diverticulitis	0.02% (2)	0.05% (2)
Erysipelas	0	0.03% (1)
Gastroenteritis	0.04% (4)	0.03% (1)
Gastroenteritis Salmonella	0	0.03% (1)
Gastroenteritis Viral	0	0.03% (1)
Groin Abscess	0.01% (1)	0.03% (1)
Hepatitis C	0.02% (2)	0
Infectious Colitis	0.02% (2)	0
Influenza	0.02% (2)	0.03% (1)
Latent Tuberculosis	0.01% (1)	0
Liver Abscess	0	0.03% (1)
Lobar Pneumonia	0.02% (2)	0
Localised Infection	0.01% (1)	0
Meningitis	0.02% (2)	0
Mycobacterium Avium Complex Infection	0.01% (1)	0
Osteomyelitis	0.01% (1)	0.03% (1)
Otitis Media Bacterial	0.01% (1)	0
Periorbital Cellulitis	0.01% (1)	0
Perirectal Abscess	0.02% (2)	0.03% (1)
Pneumonia	0.17% (16)	0.21% (8)

System Organ Class Preferred Term	HEPLISAV-B (N = 9365) % (n)	Engerix-B (N = 3867) % (n)
Pneumonia Escherichia	0.01% (1)	0
Pneumonia Staphylococcal	0.01% (1)	0
Post Procedural Infection	0.01% (1)	0.03% (1)
Postoperative Wound Infection	0	0.03% (1)
Pyelonephritis	0.02% (2)	0.03% (1)
Pyelonephritis Acute	0.02% (2)	0
Salpingo-Oophoritis	0	0.03% (1)
Sepsis	0.05% (5)	0.03% (1)
Septic Shock	0	0.03% (1)
Splenic Abscess	0.01% (1)	0
Staphylococcal Abscess	0.01% (1)	0.03% (1)
Staphylococcal Infection	0.01% (1)	0
Staphylococcal Osteomyelitis	0	0.03% (1)
Tonsillitis	0.01% (1)	0
Upper Respiratory Tract Infection	0.01% (1)	0
Urinary Tract Infection	0	0.03% (1)
Urinary Tract Infection Enterococcal	0.01% (1)	0
Urosepsis	0.04% (4)	0.05% (2)
Viral Sepsis	0.01% (1)	0
Wound Infection	0	0.03% (1)
Wound Infection Staphylococcal	0.01% (1)	0
Injury, Poisoning And Procedural Complications	0.68% (64)	0.57% (22)
Accident	0.01% (1)	0
Accidental Overdose	0.01% (1)	0
Alcohol Poisoning	0.02% (2)	0
Ankle Fracture	0.04% (4)	0.03% (1)
Arterial Injury	0.01% (1)	0
Cervical Vertebral Fracture	0.01% (1)	0.03% (1)
Concussion	0.01% (1)	0
Contusion	0.01% (1)	0
Craniocerebral Injury	0	0.03% (1)
Delayed Recovery From Anaesthesia	0	0.03% (1)
Facial Bones Fracture	0	0.03% (1)
Fall	0.01% (1)	0
Femoral Neck Fracture	0	0.05% (2)
Femur Fracture	0.02% (2)	0.03% (1)

System Organ Class Preferred Term	HEPLISAV-B (N = 9365) % (n)	Engerix-B (N = 3867) % (n)
Fibula Fracture	0.01% (1)	0
Foot Fracture	0.02% (2)	0
Forearm Fracture	0	0.03% (1)
Fracture	0	0
Fractured Sacrum	0	0
Gastrointestinal Anastomotic Leak	0	0.03% (1)
Gun Shot Wound	0.04% (4)	0
Hand Fracture	0.01% (1)	0
Head Injury	0	0.03% (1)
Hip Fracture	0.02% (2)	0
Humerus Fracture	0.02% (2)	0
Intentional Overdose	0.01% (1)	0
Jaw Fracture	0.03% (3)	0
Joint Dislocation	0	0.03% (1)
Joint Injury	0.01% (1)	0.03% (1)
Laceration	0.01% (1)	0.03% (1)
Ligament Rupture	0	0
Lower Limb Fracture	0.01% (1)	0
Lumbar Vertebral Fracture	0.02% (2)	0
Meniscus Injury	0.02% (2)	0.03% (1)
Muscle Strain	0.01% (1)	0
Overdose	0.01% (1)	0
Patella Fracture	0.03% (3)	0
Peripheral Nerve Injury	0.01% (1)	0
Post Procedural Complication	0.01% (1)	0
Post Procedural Haematoma	0.02% (2)	0
Postoperative Fever	0.01% (1)	0.03% (1)
Postoperative Ileus	0.01% (1)	0.03% (1)
Procedural Intestinal Perforation	0.01% (1)	0
Procedural Pain	0	0.05% (2)
Rib Fracture	0.02% (2)	0
Scapula Fracture	0.01% (1)	0
Seroma	0.01% (1)	0
Spinal Column Injury	0	0
Spinal Fracture	0.01% (1)	0
Stab Wound	0.01% (1)	0

System Organ Class Preferred Term	HEPLISAV-B (N = 9365) % (n)	Engerix-B (N = 3867) % (n)
Sternal Fracture	0.01% (1)	0
Tendon Rupture	0.01% (1)	0
Thermal Burn	0.01% (1)	0
Tibia Fracture	0.02% (2)	0
Toxicity To Various Agents	0.05% (5)	0.03% (1)
Traumatic Haemothorax	0	0.03% (1)
Ulna Fracture	0.01% (1)	0
Urinary Retention Postoperative	0	0.03% (1)
Wrist Fracture	0	0.03% (1)
Investigations	0.02% (2)	0.03% (1)
Electrophoresis Protein Abnormal	0.01% (1)	0
Foetal Heart Rate Abnormal	0	0.03% (1)
International Normalised Ratio Increased	0.01% (1)	0
Metabolism And Nutrition Disorders	0.21% (20)	0.23% (9)
Dehydration	0.01% (1)	0.10% (4)
Diabetes Mellitus Inadequate Control	0.02% (2)	0.03% (1)
Diabetic Ketoacidosis	0.06% (6)	0.03% (1)
Dyslipidaemia	0.01% (1)	0
Hyperglycaemia	0.01% (1)	0
Hypoglycaemia	0.01% (1)	0
Hypokalaemia	0.03% (3)	0.05% (2)
Hyponatraemia	0.04% (4)	0
Type 2 Diabetes Mellitus	0.01% (1)	0.03% (1)
Water Intoxication	0.01% (1)	0
Musculoskeletal And Connective Tissue Disorders	0.45% (42)	0.41% (16)
Back Pain	0.01% (1)	0.03% (1)
Bursitis	0.02% (2)	0.03% (1)
Costochondritis	0	0.03% (1)
Flank Pain	0	0.03% (1)
Gouty Arthritis	0.01% (1)	0
Intervertebral Disc Degeneration	0.02% (2)	0.05% (2)
Intervertebral Disc Protrusion	0.05% (5)	0.03% (1)
Loose Body In Joint	0.01% (1)	0
Lumbar Spinal Stenosis	0.03% (3)	0.03% (1)
Muscular Weakness	0.01% (1)	0
Musculoskeletal Chest Pain	0.02% (2)	0

System Organ Class Preferred Term	HEPLISAV-B (N = 9365) % (n)	Engerix-B (N = 3867) % (n)
Myositis	0	0.03% (1)
Neck Pain	0.01% (1)	0.03% (1)
Osteoarthritis	0.17% (16)	0.13% (5)
Rhabdomyolysis	0.02% (2)	0
Rotator Cuff Syndrome	0	0.03% (1)
Spinal Column Stenosis	0.03% (3)	0
Spinal Osteoarthritis	0.02% (2)	0
Spondylolisthesis	0.02% (2)	0
Vertebral Foraminal Stenosis	0.01% (1)	0
Neoplasms Benign, Malignant And Unspecified (Includes Cysts And Polyps)	0.49% (46)	0.49% (19)
Adenocarcinoma Of Colon	0.01% (1)	0.03% (1)
Brain Neoplasm	0.01% (1)	0
Brain Neoplasm Benign	0.01% (1)	0
Breast Cancer	0.05% (5)	0.03% (1)
Breast Cancer Recurrent	0.01% (1)	0
Cervix Carcinoma	0	0.03% (1)
Cholangiocarcinoma	0	0.03% (1)
Clear Cell Renal Cell Carcinoma	0.01% (1)	0
Colon Adenoma	0.04% (4)	0
Colon Cancer Stage Iv	0.01% (1)	0
Ductal Adenocarcinoma Of Pancreas	0.01% (1)	0
Endometrial Cancer	0.01% (1)	0
Hodgkin's Disease	0.01% (1)	0
Inflammatory Carcinoma Of The Breast	0.01% (1)	0
Intraductal Papillary Mucinous Neoplasm	0.01% (1)	0
Intraductal Proliferative Breast Lesion	0.02% (2)	0
Invasive Ductal Breast Carcinoma	0.02% (2)	0.03% (1)
Lung Adenocarcinoma	0.01% (1)	0
Lung Cancer Metastatic	0.01% (1)	0
Malignant Melanoma	0.01% (1)	0
Marrow Hyperplasia	0	0
Meningioma	0.01% (1)	0
Metastatic Renal Cell Carcinoma	0.01% (1)	0
Non-Small Cell Lung Cancer Metastatic	0.01% (1)	0
Oesophageal Adenocarcinoma	0	0.03% (1)

System Organ Class **Preferred Term**	**HEPLISAV-B** **(N = 9365)** **% (n)**	**Engerix-B** **(N = 3867)** **% (n)**
Ovarian Cancer Stage Iii	0	0.03% (1)
Ovarian Germ Cell Teratoma	0	0.03% (1)
Pancreatic Carcinoma	0.01% (1)	0
Pancreatic Carcinoma Metastatic	0.01% (1)	0.03% (1)
Papillary Thyroid Cancer	0.01% (1)	0.03% (1)
Pelvic Neoplasm	0.01% (1)	0
Plasma Cell Myeloma	0.01% (1)	0
Prostate Cancer	0.04% (4)	0.18% (7)
Prostate Cancer Stage Ii	0.01% (1)	0
Rectal Adenocarcinoma	0.01% (1)	0
Small Cell Lung Cancer Metastatic	0.01% (1)	0
Squamous Cell Carcinoma Of The Cervix	0.01% (1)	0
Squamous Cell Carcinoma Of The Oral Cavity	0.01% (1)	0
Uterine Leiomyoma	0.02% (2)	0.05% (2)
Nervous System Disorders	0.45% (42)	0.44% (17)
Benign Intracranial Hypertension	0	0.03% (1)
Carotid Artery Stenosis	0.02% (2)	0.03% (1)
Carotid Sinus Syndrome	0	0.03% (1)
Cauda Equina Syndrome	0.01% (1)	0
Cerebral Ischaemia	0.01% (1)	0
Cerebrovascular Accident	0.07% (7)	0.08% (3)
Cervical Myelopathy	0.01% (1)	0.03% (1)
Complex Partial Seizures	0.01% (1)	0.03% (1)
Convulsion	0.04% (4)	0.03% (1)
Dizziness	0.02% (2)	0
Embolic Stroke	0.01% (1)	0
Grand Mal Convulsion	0	0
Guillain-Barré Syndrome	0.01% (1)	0
Haemorrhagic Stroke	0	0.03% (1)
Headache	0.01% (1)	0
Hepatic Encephalopathy	0.01% (1)	0
Hypoaesthesia	0	0.03% (1)
Hypoxic-Ischaemic Encephalopathy	0.02% (2)	0
Ischaemic Stroke	0.02% (2)	0.03% (1)
Lacunar Infarction	0.01% (1)	0
Lumbar Radiculopathy	0.01% (1)	0

System Organ Class Preferred Term	HEPLISAV-B (N = 9365) % (n)	Engerix-B (N = 3867) % (n)
Migraine	0.01% (1)	0
Neuropathy Peripheral	0.01% (1)	0
Radial Nerve Palsy	0.01% (1)	0
Spondylitic Myelopathy	0.01% (1)	0.03% (1)
Subarachnoid Haemorrhage	0.02% (2)	0
Syncope	0.02% (2)	0.10% (4)
Thalamic Infarction	0.01% (1)	0
Thrombotic Stroke	0	0.03% (1)
Transient Global Amnesia	0.01% (1)	0
Transient Ischaemic Attack	0.04% (4)	0.03% (1)
VIIth Nerve Paralysis	0	0
Pregnancy, Puerperium And Perinatal Conditions	0.06% (6)	0.08% (3)
Abortion Spontaneous	0.03% (3)	0.05% (2)
Foetal Growth Restriction	0.01% (1)	0
Gestational Diabetes	0.01% (1)	0
Oligohydramnios	0	0.03% (1)
Placenta Praevia	0.01% (1)	0
Psychiatric Disorders	0.28% (26)	0.18% (7)
Bipolar Disorder	0.03% (3)	0.03% (1)
Bipolar I Disorder	0.04% (4)	0
Confusional State	0	0.03% (1)
Delirium	0.01% (1)	0
Delirium Tremens	0	0.03% (1)
Depression	0.07% (7)	0.03% (1)
Depression Suicidal	0.01% (1)	0
Major Depression	0.01% (1)	0
Mental Status Changes	0.03% (3)	0.03% (1)
Schizoaffective Disorder	0.01% (1)	0
Schizophrenia	0.01% (1)	0
Substance-Induced Psychotic Disorder	0	0.03% (1)
Suicidal Ideation	0.03% (3)	0.03% (1)
Suicide Attempt	0.03% (3)	0.03% (1)
Renal And Urinary Disorders	0.15% (14)	0.23% (9)
Acute Prerenal Failure	0.01% (1)	0
Bladder Disorder	0	0.03% (1)
Calculus Ureteric	0.04% (4)	0.05% (2)

System Organ Class Preferred Term	HEPLISAV-B (N = 9365) % (n)	Engerix-B (N = 3867) % (n)
Nephrolithiasis	0	0.03% (1)
Prerenal Failure	0.01% (1)	0
Renal Failure	0.01% (1)	0.03% (1)
Renal Failure Acute	0.04% (4)	0.08% (3)
Renal Failure Chronic	0.02% (2)	0
Tubulointerstitial Nephritis	0.01% (1)	0
Urinary Incontinence	0	0
Urinary Retention	0	0.05% (2)
Reproductive System And Breast Disorders	0.05% (5)	0.18% (7)
Adenomyosis	0	0.05% (2)
Cystocele	0.01% (1)	0
Dysfunctional Uterine Bleeding	0.01% (1)	0
Endometriosis	0.01% (1)	0
Haemorrhagic Ovarian Cyst	0	0.03% (1)
Menorrhagia	0	0.03% (1)
Menstruation Irregular	0.01% (1)	0
Ovarian Cyst	0	0.03% (1)
Postmenopausal Haemorrhage	0	0.03% (1)
Prostatitis	0.01% (1)	0.03% (1)
Vaginal Haemorrhage	0	0.03% (1)
Respiratory, Thoracic And Mediastinal Disorders	0.48% (45)	0.39% (15)
Acute Respiratory Distress Syndrome	0.01% (1)	0.03% (1)
Acute Respiratory Failure	0.06% (6)	0.03% (1)
Asthma	0.07% (7)	0.05% (2)
Bronchial Hyperreactivity	0	0.03% (1)
Chronic Obstructive Pulmonary Disease	0.11% (10)	0.10% (4)
Diaphragmatic Paralysis	0.01% (1)	0
Diaphragmatic Rupture	0.01% (1)	0
Dyspnoea	0.02% (2)	0
Haemothorax	0.01% (1)	0
Hiccups	0.01% (1)	0
Hypoxia	0.03% (3)	0
Lung Infiltration	0.01% (1)	0
Nasal Polyps	0.01% (1)	0
Nasal Septum Deviation	0	0
Pleural Effusion	0.02% (2)	0

System Organ Class **Preferred Term**	**HEPLISAV-B** **(N = 9365)** **% (n)**	**Engerix-B** **(N = 3867)** **% (n)**
Pleuritic Pain	0.01% (1)	0
Pneumonia Aspiration	0.01% (1)	0.03% (1)
Pneumothorax	0.05% (5)	0.03% (1)
Pneumothorax Spontaneous	0.01% (1)	0
Pulmonary Embolism	0.09% (8)	0.05% (2)
Pulmonary Oedema	0.01% (1)	0
Respiratory Arrest	0	0.03% (1)
Respiratory Failure	0.01% (1)	0.05% (2)
Skin And Subcutaneous Tissue Disorders	0.02% (2)	0.05% (2)
Diabetic Foot	0.01% (1)	0.05% (2)
Hidradenitis	0.01% (1)	0
Social Circumstances	0.01% (1)	0
Victim Of Homicide	0.01% (1)	0
Surgical And Medical Procedures	0	0
Abortion Induced Complete	0	0
Hip Arthroplasty	0	0
Vascular Disorders	0.22% (21)	0.23% (9)
Aortic Aneurysm	0.02% (2)	0
Aortic Stenosis	0	0.03% (1)
Deep Vein Thrombosis	0.06% (6)	0.10% (4)
Granulomatosis With Polyangiitis	0.01% (1)	0
Hypertension	0.06% (6)	0.08% (3)
Hypertensive Crisis	0.02% (2)	0
Hypotension	0.02% (2)	0.05% (2)
Peripheral Vascular Disorder	0.01% (1)	0
Thrombophlebitis Superficial	0.01% (1)	0

APPENDIX 6: NARRATIVES OF POTENTIAL MYOCARDIAL INFARCTIONS

HEPLISAV-B Group

1. HBV-23 Subject: ST elevation myocardial infarction [Preferred Term: Acute Myocardial Infarction]

A 62-year-old white man with a relevant medical history of coronary artery disease with an old lateral myocardial infarction (MI), dyslipidemia, multiple prior coronary stents, and obesity experienced an ST elevation myocardial infarction 319 days after the second HEPLISAV-B injection. The subject had developed chest pain while mowing his lawn and was taken to the emergency room (ER). He had an ECG and was diagnosed with acute MI/ ST segment elevation myocardial infarction (STEMI) with a junctional rhythm at a rate of 47 beats per minute (bpm). The subject underwent left heart catheterization with selective coronary angiography and ventriculography and percutaneous coronary intervention (PCI) of the circumflex which revealed the following: intermediate stenosis (45%) of the proximal left anterior descending (LAD), which was not angiographically significant; STEMI, proximal circumflex occluded (100%) and successful angioplasty with drug-eluting stent of the proximal circumflex. Ejection fraction was 55%. A repeat ECG revealed atrial fibrillation with rapid ventricular response, inferior infarct, possible anterior infarct, left axis deviation, and a ventricular rate of 119 bpm. Intravenous (IV) amiodarone was administered and he converted to sinus bradycardia and maintained sinus rhythm. The day after event onset, the subject's ECG revealed normal sinus rhythm, inferior infarct, and possible anterolateral infarct at a ventricular rate of 62 bpm. Laboratory results included elevated troponin, and an echocardiogram showed left ventricular ejection fraction of 60%, mild inferolateral hypokinesis, left ventricular hypertrophy, and mild mitral regurgitation. Two days after the event onset, the subject was discharged home with no further chest pain, mild elevation in troponins, and normal left ventricular ejection fraction (LVEF), and the event was considered resolved.

C5 adjudicated this as a myocardial infarction event.

2. HBV-23 Subject: Non-ST elevation myocardial infarction [Preferred Term: Acute Myocardial Infarction]

A 69-year-old white woman with a relevant medical history of obesity and dyslipidemia experienced a non-ST elevation myocardial infarction 208 days after the second HEPLISAV-B injection. On the day the event occurred, the subject presented to the ER following 3 hours of chest pain. Troponin I was elevated and an ECG showed sinus bradycardia with borderline first degree atrioventricular (AV) block and low QRS voltages in the precordial leads. The subject had no recurrence of chest pain overnight. The subject's repeat troponin I, creatine phosphokinase (CPK), and CK-MB were elevated. She was admitted to the hospital and underwent cardiac catheterization. There was diffuse non-obstructive atherosclerotic coronary artery disease with preserved left ventricular systolic function. It was thought that

the first diagonal branch was most likely the culprit vessel corresponding with anterolateral wall motion abnormalities by pre-catheterization echocardiogram, only moderate ostial stenosis on angiography with good flow, and no evidence of an active lesion. Two days after event onset, the subject was discharged from the hospital, at which time the event of non-ST elevation MI was considered resolved. Discharge diagnoses included coronary artery disease and non-ST elevated myocardial infarction, with diffuse non-obstructive atherosclerotic coronary artery disease and moderate ostial stenosis of the first diagonal branch.

C5 adjudicated this as a myocardial infarction event.

3. HBV-23 Subject: Acute myocardial infarction [Preferred Term: Acute Myocardial Infarction]

A 46-year-old white man with a relevant medical history of sleep apnea, hyperlipidemia, hypertension, and obesity experienced an acute MI 175 days after the second HEPLISAV-B injection. Upon presentation to the ER, an ECG showed sinus tachycardia and possible left atrial enlargement. Troponin I was elevated. A computed tomography (CT) evaluation of the heart without contrast showed an Agatston score of 91. Repeat ECGs showed sinus rhythm without sinus tachycardia.

The day after event onset, the subject underwent selective coronary angiography, left heart catheterization with hemodynamics, and left ventriculogram. The cardiac catheterization revealed: 1) normal left main; 2) ectasia of the left circumflex and left anterior descending with signs of recently ruptured plaque in the proximal left anterior descending, but non-obstructive; 3) normal distal left anterior descending and diagonal branch; 4) patent obtuse marginal branches; 5) patent right coronary artery with minimal plaque in the mid right coronary artery non-obstructive; 6) patent posterior descending artery and posterolateral branch; and 7) preserved left ventricular function. Given the results of the catheterization, aggressive medical management and risk reduction were recommended. Post catheterization ECG showed normal sinus rhythm and no significant changes. The subject was discharged from the hospital that same day, and the event of acute MI was considered resolved. Discharge diagnoses included acute MI, hyperlipidemia, leukocytosis, and sleep apnea.

C5 adjudicated this as a myocardial infarction event.

4. HBV-23 Subject: Coronary artery occlusion [Preferred Term: Coronary Artery Occlusion]

A 64-year-old white woman with a relevant medical history of type 2 diabetes mellitus, dyslipidemia, hypertension, heart palpitations, and sleep apnea experienced an event of coronary artery occlusion 14 days after the first HEPLISAV-B injection.

Thirty days after the first HEPLISAV-B injection, the subject was seen by a cardiologist for evaluation of a 3-day history of worsening heart palpitations. Treatment with Imdur ER (isosorbide mononitrate) and *heart monitoring* were started.

The subject received the second injection of HEPLISAV-B 3 days after being evaluated by her cardiologist. On an undetermined date close to event onset, a PCI of a presumed chronic total occlusion was attempted but was unsuccessful. Approximately 1 month later, the subject notified the site that that she discontinued Imdur ER due to significant fatigue and dizziness. Fourteen days later, a nuclear perfusion test was performed and revealed inferior ischemia. The subject continued to have chest pain and underwent left heart catheterization. The catheterization revealed a 60% lesion in the proximal right coronary artery, a totally occluded third obtuse marginal (OM) artery and smaller second OM artery, and posterior descending artery (PDA). She had 3 drug-eluting stents placed to her right coronary artery and 1 stent placed in the second OM artery. The PCI's were successful, with TIMI-3 flow. Discharge diagnoses included obstructive coronary artery disease, atherosclerotic coronary artery disease, hypertension, dyslipidemia and diabetes mellitus type 2. The event was considered resolved.

C5 adjudicated this as a not a myocardial infarction event.

5. HBV-23 Subject: Non-ST elevation MI [Preferred Term: Acute Myocardial Infarction]

A 53-year-old white man with a relevant medical history that included erythrocytosis, hypertension, hyperlipidemia, metabolic syndrome, type 2 diabetes mellitus, and right renal cyst experienced an acute MI 64 days after the second HEPLISAV-B injection. The subject presented to the ER complaining of abdominal pain that had been progressing for a week. He also complained of intermittent episodes of crampy-like pain, nausea, decreased oral intake, and multiple episodes of diarrhea. He denied chest pain, palpitations, diaphoresis or shortness of breath. The subject was found to be in acute renal failure and was significantly dehydrated. An x-ray of the abdomen was suspicious for mid to distal small bowel obstruction. An abdominal CT showed a small bowel obstruction as a result of left lateral abdominal wall hernia. There was evidence of prior partial colectomy. The subject was hydrated aggressively and started on empiric antibiotics. The subject was diagnosed with acute kidney injury most likely of pre-renal etiology, metabolic acidosis, and non-anion gap most likely secondary to diarrhea. The subject was treated with bicarbonate to correct the metabolic acidosis and hydralazine was added to control the subject's blood pressure. Diarrhea and kidney functions improved. Subsequently while the subject was still in the hospital, he developed chest pain along with palpitations. ECG showed sinus rhythm, incomplete right bundle branch block, and borderline ST depressions laterally. Troponin was elevated. The CK-MB fraction peaked at 7.4% on a total CK of 87 IU/L (35-232) on the same day. He was diagnosed with non-ST elevation MI. The subject underwent cardiac catheterization which revealed multi-vessel coronary artery disease. The left anterior descending artery (LAD) had a significant sequential stenosis and there was moderate diffuse disease distally. Diagonal branch artery had 2 sequential lesions. Circumflex artery had a tight narrowing in the proximal segment. Due to the diffuse disease of the LAD, PCI was recommended.

Two days later, the subject underwent balloon angioplasty of LAD, and 3 stents were placed. He was started on Effient (prasugrel). After the procedure, the subject was hemodynamically stable. The subject was discharged on the same day, at which time the event of non ST elevation MI was considered resolved. Discharge diagnoses were abdominal pain and small bowel obstruction resolved, hypertension, acute kidney injury resolved, metabolic acidosis resolved, diabetes with Hg A1c of 6.8, left kidney cyst, adrenal adenoma, non-ST elevation MI, multi vessel coronary artery disease status post PCI, and obesity.

C5 adjudicated this as a myocardial infarction event.

6. HBV-23 Subject: Interrupted inferior myocardial infarction [Preferred Term: Myocardial Infarction]

A 68-year-old white woman with a relevant medical history that included chronic obstructive pulmonary disease (COPD), hyperlipidemia, and 1 pack per day tobacco use experienced an MI 53 days after the second HEPLISAV-B injection. On the day of event onset, the subject experienced substernal chest pain that radiated to her neck and left arm and was brought to the ER. An ECG revealed inferior ST elevation. She was taken directly for right coronary artery dilatation and stenting, and 3 stents were deployed. The cardiac catheterization findings were consistent with an acute inferior myocardial infarction due to acute occlusion of the right coronary artery with minimal decrease in left ventricular function and with corresponding segmental wall motion abnormality. Cardiac enzymes were in the normal range. Following the procedure her chest pain resolved and the ST segments returned to normal, at which time the event of interrupted inferior myocardial infarction was considered resolved. The subject did well throughout her hospitalization without any recurrent chest pain.

C5 adjudicated this as a myocardial infarction event.

7. HBV-23 Subject: Non-ST elevation myocardial infarction [Preferred Term: Acute Myocardial Infarction]

A 68-year-old white man with a relevant medical history that included obesity, type 2 diabetes mellitus, hypertension, hyperlipidemia, chronic sinusitis, and previous smoking history experienced an acute MI 309 days after the second HEPLISAV-B injection. On the day of event onset, the subject was brought to the ER with complaints of left-sided chest pain associated with palpitations, nausea, diaphoresis, and shortness of breath. An ECG revealed wide complex tachycardia with a heart rate of 168 bpm; a repeat ECG revealed sinus tachycardia, narrow complex with a heart rate of 101 bpm; and a third ECG revealed ventricular tachycardia, wide complex tachycardia, and right bundle branch block with a heart rate of 124 bpm. Laboratory results included elevated glucose, troponin I, point of care (POC) troponin, natriuretic peptide, and CK-MB relative index 3.6. Since the subject was experiencing persistent atrial fibrillation with rapid ventricular response and was not responding to maximum medical therapy, he had multiple attempts of unsuccessful

cardioversion. The subject underwent left heart catheterization, selective coronary angiography, left ventriculography, PCI of left circumflex artery, and thrombectomy of left circumflex artery. Angiographic results showed left main near normal, short nonexistent; no significant disease was present in the proximal, mid, or distal left anterior descending artery or any branches; left circumflex artery was a dominant vessel that gave rise to early obtuse marginal branch that had ostial 30% to 40% stenosis and subtotal occlusion of left circumflex artery with thrombus distal to obtuse marginal origin; right coronary artery was a diffusely diseased vessel with 1-1.5 mm diameter and it had 70 to 80% lesion in its mid portion; left ventriculography showed ejection fraction in the range of 35 to 40%; however, wall motion abnormality could not be determined since it was a hand injection. Final impression included severe single-vessel coronary artery disease with thrombus requiring thrombectomy and PCI of the bifurcation of the left circumflex artery, and obtuse marginal branch. Balloon angioplasty of the ostium of left circumflex artery and obtuse marginal branch was followed by across the lesion, stent placement, and left circumflex artery with slight pinching of the vessel without physiological changes in the form of ST elevations or chest pain; drug-eluting stent placement with 3.5 post dilated to 4.01 and 99% lesion to 0% with removal of thrombus. There was significant disease in the non-dominant diffusely diseased right coronary artery. After cardiac catheterization, the event of non-ST elevation MI was considered resolved. Three days after acute MI onset, the event of ventricular tachycardia was considered resolved and the subject was discharged. Final diagnoses included ventricular tachycardia, hypertensive urgency, type 2 diabetes mellitus, dyslipidemia, acute coronary syndrome with elevated cardiac enzymes, hyperlipidemia, and tobacco abuse disorder.

C5 adjudicated this as a myocardial infarction event.

8. HBV-23 Subject: ST elevation myocardial infarction [Preferred Term: Acute Myocardial Infarction]

A 60-year-old white man with a relevant medical history that included hypertension experienced an acute MI 329 days after the second HEPLISAV-B injection. On the day of event onset, the subject experienced left shoulder pain, left arm pain, and difficulty walking without shortness of breath. The next day, the subject developed severe chest pressure and went to the ER. An ECG showed ST elevations inferiorly, Troponin I was elevated, and the subject was diagnosed with an inferior STEMI. The subject was taken for an emergency cardiac catheterization and percutaneous coronary intervention. Findings from the procedure were as follows: the left main was normal; the left anterior descending long type 3 vessel extending around the apex of the heart had a high-grade 90% lesion, which was quite lengthy extending from just beyond the ostium to just distal to the takeoff of a small first diagonal branch. Following intervention, there was no significant residual stenosis. The circumflex was a medium size vessel giving off marginal branches. The first obtuse marginal branch had a 95% stenosis following intracoronary stenting, and there was no residual stenosis. The right coronary artery was the culprit vessel per his infarct; it had a 99% flow-limiting lesion. Following intervention, there was no residual stenosis and TIMI-3 flow was reestablished. A

left ventriculogram was performed in the right anterior oblique projection and demonstrated mild inferior wall hypokinesis. Overall, the ejection fraction was well preserved and estimated at 55%. The subject had 3 stents placed and was admitted to the intensive care unit.

Two days after event onset, echocardiogram revealed the presence of left ventricular diastolic dysfunction but was otherwise normal. The subject was discharged and the event was considered resolved. Discharge diagnoses were: inferior STEMI, three-vessel coronary artery disease, hypertension, elevated hemoglobin A1c (question early diabetes), and dyslipidemia.

C5 adjudicated this as a myocardial infarction event.

9. HBV-23 Subject: Unstable angina [Preferred Term: Angina Unstable]

A 56-year-old white man with a relevant medical history that included hypertension, water retention, hypercholesterolemia, septic shock (approximately 1 year prior to study entry), deep vein thrombosis, paroxysmal atrial fibrillation, morbid obesity, and a former smoker experienced an unstable angina event 96 days after the second HEPLISAV-B injection.

Ninety-two days after having received the second HEPLISAV-B injection, the subject underwent a cardiac evaluation. A perfusion scan revealed a partially reversible defect in the inferolateral wall, with a reversible component primarily in the distal inferior wall. Left ventricular ejection fraction was normal at 53%. There was moderate left ventricular dilatation but no wall motion abnormality on gated SPECT. An echocardiogram showed an ejection fraction of 50-55% and septal wall abnormal wall motion consistent with left bundle branch block.

Ninety-six days after the second HEPLISAV-B injection, the subject returned to the hospital with complaints of shortness of breath and chest pain. The subject reported that the chest pain had been on and off for the past 3 weeks and had been worse with activity. He described the pain as a squeezing sensation and a deep dull pain that “grabs him” and was 6-7/ 10 on a pain scale. He was admitted for evaluation of unstable angina pectoris. Cardiac enzymes were all within normal limits. An ECG showed normal sinus rhythm, bifascicular block (right bundle branch block, left anterior fascicular block), and ST depression and lateral leads (possible lateral infarct, age undetermined) that were unchanged from an ECG 10 days prior. Three days after admission, a left heart catheterization showed no significant coronary artery disease; the left ventricular end diastolic pressure was normal. The subject was discharged and the event of unstable angina was considered resolved. Discharge diagnoses included latent tuberculosis by skin test, atrial fibrillation, chest pain, hypertension, unstable angina, and obstructive sleep apnea.

C5 adjudicated this as not a myocardial infarction event.

10. HBV-23: Myocardial infarction [Preferred Term: Myocardial Infarction]

A 47-year-old black or African American man with a relevant medical history that included type 2 diabetes mellitus, peripheral vascular disease, gangrene left leg, left leg below knee amputation, and right leg edema experienced a fatal MI (b) (6) days after receiving the second injection of HEPLISAV-B. The death certificate noted that the subject died in the hospital; cause of death per the death certificate was an MI and the manner of death was noted as natural. An autopsy was not performed. Medical records could not be obtained.

C5 adjudicated this as unable to determine whether it was a myocardial infarction event and unable to determine cause of death.

11. HBV-23 Subject: ST-Elevation Myocardial Infarction [Preferred Term: Acute Myocardial Infarction]

A 53-year-old black or African-American man with a relevant medical history that included prior heroin addiction and hypertension was hospitalized for an ST-elevated myocardial infarction (STEMI).

Two hundred and ninety-five days after receiving the first HEPLISAV-B injection, the subject presented to the hospital with a chief complaint of left-sided "pressure-like" chest pain that radiated to his back as well as dyspnea on exertion. The chest pain started the night before, woke him from sleep, and persisted throughout the next day. The subject reported intermittent episodes of chest pain previously but was not able to associate it with anything. In the ER, serial troponins and brain natriuretic peptide were elevated. An ECG showed the following: normal sinus rhythm with T wave abnormality; consider anterior ischemia; prolonged QT interval and T wave inversion more evident in the anterior leads. The subject underwent a coronary angiogram. Findings included a 99% complex tubular lesion of the mid left anterior descending (LAD) coronary artery, which was considered a culprit subtotal occlusion with possible spontaneous recannulation, and 75% discrete lesion of the left circumflex (LCX) coronary artery; the right coronary artery was normal. A bare metal stent was placed in the LAD artery with post stenosis of 0%. The subject was subsequently admitted to the coronary care unit with an admitting diagnosis of an ST-elevation myocardial infarction (STEMI). The following day, the subject's troponin levels were still elevated.

Two days after admission, he underwent a second coronary catheterization; the LAD stent was noted to be patent, and the LCX lesion was seen, with 48% occlusion. No stent was placed. An echocardiogram showed a systolic ejection fraction of 35-40% and grade I diastolic dysfunction with moderate hypokinesis. The following day, the subject was discharged in stable condition, at which time the event was considered resolved. Discharge diagnoses included anterior wall ST-elevation myocardial infarction, hypertension, hyperlipidemia, prostate cancer status post radiation.

C5 adjudicated this as a myocardial infarction event.

12. HBV-23 Subject: Acute myocardial infarction [Preferred Term: Acute Myocardial Infarction]

A 68-year-old white man with relevant medical that included high cholesterol, coronary artery disease, heart attack, hypertension, chest pain, angioplasty for chest pain, stent placement of the circumflex, and paroxysmal atrial fibrillation was hospitalized for an acute MI 85 days after receiving the second HEPLISAV-B injection. Symptoms of ischemia began around 6:30 am on the morning of admission and he arrived at the emergency room at 2:32 pm. Cardiac catheterization showed an ejection fraction of 15% with severe anterior apical hypokinesis and akinesis and left ventricular end diastolic pressure (LVEDP) of 30 with no aortic valve gradient. Left main trunk distal eccentric stenosis was estimated at 50 to 60%. The left anterior descending (LAD) was occluded with collateral large vessels wrapped around the apex, with TIMI flow of 0. The circumflex was found to have proximal eccentric 80% calcified lesion that was passed by the wire but could not be removed by thrombectomy and was not stented since it was not the infarct vessel. The right coronary proximal showed 60% stenosis down the vessel. The interventional procedures included wiring of the circumflex into the LAD. The LAD was approached first and export catheter taken to the circumflex to see if the proximal lesion was a clot. The lesion appeared to be chronic and calcified and was left alone in the LAD. The wire initially went into the diagonal, which looked like it was the LAD distribution, but turned out not to be, and a 2 mm balloon restored TIMI grade 1 flow. An export manual thrombectomy restored TIMI grade 2 flow and a large clot was removed. Two bare-metal stents were placed into the diagonal, integrity 2.75 x 12 and 2.5 x 8, restoring TIMI grade 3 flow. There was a catheter dissection between the stents that appeared to be stable and was left alone. Flush mid LAD occlusions then became apparent, which were crossed with a wire and ballooning was done. The export catheter did not remove much clot; this was a large vessel that was then stented with bare-metal stents all the way back to the diagonal branch restoring TIMI grade 3 flow. The stenting resulted in the release of pain. The following morning, the subject was found to be dyspneic with pulmonary edema. Atrial flutter was present and he was shocked 3 times and given amiodarone. The subject converted spontaneously to sinus rhythm. The subject was then taken back to the catheterization lab and his arteries were re-visualized. The right coronary appeared to be a least 80 to 90% stenotic and there was bidirectional flow in the distal LAD indicating collaterals. An intra-aortic balloon pump was placed and pumping was stared at 1:1. About 36 hours after the acute MI, creatine phosphokinase values exceeded 3,843. The next day, the subject was doing well with runs of atrial fibrillation despite amiodarone. Cardizem (diltiazem) was administered and helped restore sinus rhythm. The intra-aortic balloon pump was tapered to 2:1. Liver functions tests were found to be abnormal and B-type natriuretic peptide was found to be 398. Three days after admission, the subject developed pulmonary edema and had chest pressure. It was determined that the subject was balloon dependent and needed a left ventricular assist devise (LVAD) bridge if necessary. The subject was transferred to another hospital with a LVAD team. At time of transfer, the subject was in good spirits; systolic blood pressure was 110 mmHg, and he was being supported with vasopressors and on the balloon pump. An echocardiogram showed an ejection fraction that

was felt to be 20 to 25% with some asymmetrical left ventricular hypertrophy, total anteroseptal apical akinesis with no clot in the apex, and grade III diastolic dysfunction with restricted filling and mild to moderate insufficiency. Final diagnoses at transfer included acute anterior MI with cardiogenic shock, prior inferior infarction, factor V Leiden mutation, paroxysmal atrial flutter, acute kidney injury, status post-acute stenting of the left anterior descending and diagonal left anterior descending with bare metal stents, status post angioplasty of the left anterior descending and circumflex in 2002, combined systolic and diastolic failure (class IV), and fever. Eighty-eight days after receiving the second HEPLISAV-B injection, the subject arrived at the transfer hospital. An Impella ventricular assist device for treatment of cardiogenic shock was placed. Two days post transfer, notable laboratory results were: total creatine kinase 550, creatine kinase MB 3.2, troponin I 41.45, and bilirubin 0.6 (units and normal ranges not provided). Eleven days post transfer, a right heart catheterization showed upper normal right heart filling pressures with normal wedge pressure, normal cardiac output and cardiac index, systolic congestive heart failure, and cardiomyopathy. Four days later, an echocardiogram showed normal left ventricle cavity size and wall thickness. Systolic function was severely reduced with an estimated ejection fraction in the range of 20 to 25%. There was severe diffuse hypokinesis with regional variations and akinesis of the anteroseptal, anterior, and apical myocardium. Features were consistent with a pseudonormal left ventricular filling pattern, with concomitant abnormal relaxation and increased filling pressure (grade 2 diastolic dysfunction). The mitral valve showed moderate regurgitation, the left and right atriums were mildly to moderately dilated, and systolic pressure in the pulmonary arteries was markedly increased (estimated to be 70 mmHg). The subject was ambulating and was discharged home with home health care. Discharge diagnoses included acute systolic heart failure, cardiogenic shock supported by Impella, acute anterior MI, coronary artery disease status post PCI to LAD with BMS, ischemic cardiomyopathy (EF 15%), hypoxic respiratory failure, and obstructive sleep apnea on CPAP. The events of acute MI, hypoxic respiratory failure, acute systolic heart failure, and cardiogenic shock were considered resolved at the time of discharge.

C5 adjudicated this as a myocardial infarction event.

13. HBV-23 Subject: Non-ST elevation myocardial infarction [Preferred Term: Acute Myocardial Infarction]

A 64-year-old white woman with relevant medical history that included type 2 diabetes mellitus, hypertension, peripheral vascular disease, and chronic kidney disease was hospitalized for a non-ST elevation MI 319 days after receiving the second injection of HEPLISAV-B. The subject presented to the emergency room (ER) with chest pain. Two days later, she was transferred to a different facility for worsening shortness of breath where she was diagnosed with a non-ST elevation myocardial infarction. Serial troponins peaked at 0.767. The subject underwent a cardiac catheterization, which revealed severe 2-vessel coronary artery disease. There was mild left main coronary artery disease and 20% stenosis in the distal left main coronary artery. Successful PCI was undertaken with stenting (drug-

eluting) of the 70% stenosis in the mid left circumflex artery and angioplasty and stenting (drug-eluting x 2) of the 90% stenosis in the proximal to mid-right coronary artery. The left ventricular ejection fraction was > 60%. She tolerated the procedure well with no complications. Results of a transthoracic echocardiogram were normal. Hemoglobin A1c was 9.9%. The subject was discharged from the hospital and the event was considered resolved. Discharge diagnoses included non-ST segment elevation myocardial infarction, coronary artery disease, type 2 diabetes (uncontrolled with complications), diabetic nephropathy (chronic kidney disease), peripheral arterial disease, hypertension, and anxiety.

C5 adjudicated this as a myocardial infarction event.

14. HBV-23 Subject: Acute coronary syndrome [Preferred Term: Acute Coronary Syndrome]

A 50-year-old black or African American man with a relevant medical history that included colon cancer, hypertension, mitral valve prolapse and prior mitral valve replacement surgery, coronary atherosclerosis, cardiomyopathy, left ventricular hypertrophy, alcohol abuse, and urine toxicology that was "positive for cocaine" while on study, died (b)(days after receiving the first HEPLISAV-B injection due to acute coronary syndrome. The study staff was notified of the subject's death by a family member. According to the EMS records, the subject was found by his family lying supine on the couch and unresponsive and upon EMS arrival was noted to have no signs of life. The cause of death per the death certificate was acute coronary syndrome secondary to coronary atherosclerosis. Other conditions noted on the death certificate as contributing to the death included cardiomyopathy, left ventricular hypertrophy, and alcohol abuse. An autopsy was not performed.

C5 adjudicated this as not a myocardial infarction event but was confirmed as a cardiovascular death (sudden cardiac death).

15. **HBV-23 Subject: Acute myocardial infarction [Preferred Term: Acute Myocardial Infarction]**

A 69-year-old black or African American man with a relevant medical history that included hypertension, congestive heart failure, abdominal aortic aneurysm, and neuropathy experienced a fatal acute myocardial infarction (b) (6) days after receiving the second injection of HEPLISAV-B. The subject was found dead in his home, slumped over in a chair. He was last known to be alive 2 days prior. Resuscitative measures were not attempted. The cause of death, per the death certificate, was acute MI due to atherosclerosis. Other factors noted as contributing to the subject's death were tobacco use and chronic obstructive pulmonary disease (COPD). An autopsy was not performed.

C5 adjudicated this as a non-myocardial infarction event and as undetermined cause of death.

16. HBV-23 Subject: Acute ST elevation myocardial infarction [Preferred Term: Acute Myocardial Infarction]

A 64-year-old white man with relevant medical history of hyperlipidemia, hypertension, and tobacco abuse was hospitalized for an acute ST elevation MI 62 days after receiving the second injection of HEPLISAV-B. The subject presented to the hospital with chest pain, and an ECG revealed an anterior MI, ST elevation MI. Serial troponins, CK, and CKMB were elevated. The subject underwent an emergency left cardiac catheterization with bilateral selective coronary angiography, left ventriculography, and had an angioplasty with 3 drug-eluting stents successfully placed in the left anterior descending artery. The subject was discharged 3 days after event onset, at which time the event of acute ST elevation myocardial infarction was considered resolved. Discharge diagnoses included acute ST elevation MI, coronary artery disease, hypertension, hyperlipidemia, and a history of tobacco abuse.

C5 adjudicated this as a myocardial infarction event.

17. HBV-23 Subject: Non-ST segment elevation myocardial infarction [Preferred Term: Acute myocardial Infarction]

A 39-year-old white woman with a relevant medical history of that included tobacco abuse (current use and smoked 1 pack per day for approximately 20 years), and hypertension experienced a life-threatening non-ST segment elevation MI and was hospitalized 174 days after receiving the second injection of HEPLISAV-B. The subject presented to the ER with a complaint of ongoing symptoms of intermittent left sided chest pain radiating to her arm and associated with dyspnea which had been getting worse over the previous 24 hours. The pain was exertional and improved with "sitting and resting" but was worse when lying down. She reported the pain had been progressively worse over the past 6 months and now precipitated at rest as well as with minimal activity. Initial vital signs included a blood pressure of 178/106 mmHg. An initial ECG showed sinus tachycardia with inferolateral ST depression; repeat ECG showed resolution of the ST changes. Nitroglycerin was administered, her chest pain dissipated, and her ST depression went away. Serial troponins were increasing. The subject was admitted for treatment of a non ST segment elevation MI. Results of an echocardiogram showed a dilated inferior vena cava with poor inspiratory collapse consistent with elevated right atrial pressures; right ventricular pressure was 34.2 mmHg and estimated right atrial pressure was 15 mmHg and was otherwise normal. Cardiac catheterization revealed 2-vessel coronary disease. A long, 50% narrowing of the proximal segment of the left anterior descending coronary artery with good distal runoff was seen. In the right coronary artery, a 90% obstruction proximally before the acute margin and an approximately 50% narrowing at the acute margin were noted. Angioplasty was performed, and 2 drug eluting stents were placed in the right proximal coronary artery. The subject was discharged and the event of non ST segment elevation myocardial infarction was considered resolved. Discharge diagnoses included acute coronary syndrome (non-ST myocardial infarction) and coronary artery disease with 2 left anterior descending stents (clarified by the investigator to be noted in error as the stents were placed in the right proximal coronary artery).

C5 adjudicated this as a myocardial infarction event.

18. HBV-23 Subject: Acute coronary syndrome, ST elevation myocardial infarction [Preferred Term: Acute Myocardial Infarction]

A 66-year-old white man with a relevant medical history that included borderline hypertension, extensive smoking history, and occult coronary artery disease experienced an acute coronary syndrome and was hospitalized for ST elevation MI 64 days after receiving the second HEPSLIAV-B injection. The subject presented to the ER complaining of chest pain and abdominal pain for 2 to 3 days prior to his admission. The pain was rated 10/10, gradual in onset, substernal and achy in nature and did not improve with rest or nitroglycerin. ECG revealed sinus tachycardia with a heart rate of 108 per minute, extensive anterior infarct, and acute ST elevation considered inferior injury. The pain had not improved with nitroglycerin or rest. Troponin I was elevated at >40.00 ng/ml (normal range ≤ 0.04). A chest x-ray showed no acute cardiopulmonary abnormality. An echocardiogram revealed mild concentric left ventricular hypertrophy, with proximal septal thickening and an ejection fraction of 25 to 30%. A bright echodensity was noted at the apex; thrombus could not be ruled out. Akinesis was noted in the entire apex. There was a mild mid lateral wall hypokinesis with severe mid septal hypokinesis. Left ventricle, aorta, aortic valve, and tricuspid were normal, pulmonary valve was not well visualized, and there was no pulmonary regurgitation. Grade I diastolic dysfunction was noted; there was no pericardial effusion. The subject was taken immediately for left cardiac catheterization which showed a 100% discrete stenosis in the proximal left anterior descending artery and the first diagonal artery. The lesion was an acute occlusion and was the cause of the acute MI. Thrombus was present. Angioplasty was performed with a standard angioplasty balloon in the proximal anterior left descending artery and the first diagonal artery. A bare metal stent was placed in the proximal left anterior descending artery, and a second bare metal stent was placed in the mid left anterior descending artery. Nitroglycerin was used in the proximal left anterior descending artery; nicardipine was used in the left anterior descending artery. The left circumflex artery gave rise to 2 obtuse marginal arteries; there was a 10% discrete stenosis in the proximal left circumflex artery. The right coronary artery (RCA) was dominant to the posterior circulation; there was a 10% diffuse stenosis in the mid-RCA. Five days later, a repeat ECG showed normal sinus rhythm with a heart rate of 84 beats per minute and anterolateral infarct with recent persistent ST elevation. The subject was discharged home and the event was considered recovered with sequelae. The sequelae were described as cardiomyopathy with low ejection fraction. Discharge diagnoses included acute coronary syndrome, ST elevation MI, hypertension, abnormal glucose levels/diabetes, and “smoking cessation”.

C5 adjudicated this as a myocardial infarction event.

19. HBV-23 Subject: Non-ST elevation myocardial infarction [Preferred Term: Acute myocardial infarction]

A 61-year-old white woman with relevant medical history of chest pain, coronary artery disease, and hypertension experienced a non-ST elevation myocardial infarction and was hospitalized 2 days after receiving the second injection of HEPLISAV-B. The subject went to the ER with complaints of dull chest pain which was radiating towards the right arm and shortness of breath. The subject also reported having numbness and tingling in the right arm, diaphoresis, and nausea. She stated that a cardiac work up performed about 1 year prior had been normal. Troponins were initially negative but trended up to 1.15. An initial ECG was normal. A second ECG demonstrated a sinus rhythm, nonspecific T abnormalities, and a heart rate of 60. A subsequent ECG revealed a heart rate of 79, sinus rhythm and abnormal T waves, and probable ischemia. A cardiac catheterization was performed due to increasing chest pain with enzyme abnormalities consistent with acute coronary syndrome and/or non-ST elevated MI. The subject was found to have: 1) a severe left anterior descending (LAD) stenosis, bifurcation disease involving the origin of the diagonal artery which was the cause of the subject's presenting acute coronary syndrome and non-ST elevation myocardial infarction; 2) otherwise normal coronaries; 3) mild to moderate impairment of left ventricular contractility, ejection fraction 40%; and 4) successful stent angioplasty of the left anterior descending artery. Additional plain balloon angioplasty of the stented first diagonal artery was performed leaving 30% residual ostial stenosis. Post stent placement the subject was doing well. The events of LAD stenosis and non-ST myocardial infarction were considered resolved 2 days after event onset and the subject was discharged.

C5 adjudicated this as a myocardial infarction event.

20. HBV-16 Subject: Myocardial infarction- non-ST segment elevation [Preferred Term: Myocardial infarction]

A 63-year-old white woman with a relevant medical history that included hypertension, ischemic cardiomyopathy, previous MI, and hypercholesterolemia that was not treated with statins due to elevated liver enzymes experienced an MI- non-ST segment elevation and was hospitalized 15 days after the first HEPLISAV-B injection. She had an elevated troponin level, and cardiac catheterization showed 80% stenosis of the mid right coronary artery and non-obstructive disease in the diagonal branch. She underwent percutaneous coronary intervention of the proximal-to-mid right coronary artery with a 4 × 18 mm vision stent. During her hospitalization she was also found to have ischemic cardiomyopathy with an ejection fraction of 30-35%; treatment with metoprolol tartrate was initiated. The subject was discharged 2 days after hospital admission, and the event was considered resolved with sequelae (ischemic cardiomyopathy with an ejection fraction of 30 - 35%).

C5 adjudicated this as a myocardial infarction event.

21. HBV-16 Subject: Non-ST segment elevation myocardial infarction [Preferred Term: Acute myocardial infarction]

A 58-year-old white man with no relevant medical history experienced a non-ST segment elevation MI and was admitted to the hospital 22 days after the first HEPLISAV-B injection. On the day of hospital admission, the subject reported a 2-week history of episodic non-radiating retrosternal chest pain associated with shortness of breath precipitated by activity and relieved with rest. The longest episode of pain, which lasted 15 to 20 minutes, was noted to be *very significant for unstable angina*. He reported that he had a stress test done 2 years previously due to palpitations but had no known coronary disease. An ECG and a chest x-ray were both normal. Serial troponin levels were mildly elevated. Angiography revealed severe stenosis of the left anterior descending (LAD) artery and right coronary artery (RCA). The subject underwent a percutaneous coronary intervention to 3 areas; 2 in the LAD artery and 1 in the RCA. The subject was discharged from the hospital the next day, at which time the event of non-ST-segment-elevation MI was considered resolved.

C5 adjudicated this as a myocardial infarction event.

Engerix-B Group

1. **HBV-23 Subject: Non-ST elevation myocardial infarction [Preferred Term: Acute myocardial infarction]**

A 66-year-old white man with a relevant medical history that included hyperlipidemia, type 2 diabetes mellitus, chest tightness, mild renal artery stenosis, chronic kidney disease stage III (eGFR of 67), systolic murmur, and coronary artery disease experienced a non-ST elevation MI and severe multivessel coronary artery disease and was hospitalized 115 days after receiving the third injection of Engerix-B. The subject had complaints for months of short-lived burning in his chest upon exertion which would go away quickly. A nuclear medicine stress test performed was abnormal and he was recommended to have a coronary angiogram.

On the day of event onset and hospitalization, the subject experienced a syncopal episode and denied any chest pain or shortness of breath. An ECG in the ER showed normal sinus rhythm with left axis deviation with ST depressions in the anterior leads (V2, V3, V4, V5, V6 and leads II). A coronary computed tomography angiogram (CTA) showed CA+ score of 498 and extensive triple vessel coronary artery disease; the test was noted as technically limited. Serial troponin values were elevated. The next day, a non-ST elevation MI was diagnosed. A left heart catheterization and left ventriculogram were performed and revealed severe multivessel coronary artery disease (proximal left anterior descending artery had diffuse calcific disease that extended into mid segment of about 75% to 80% severity; ramus intermediate branch had about 85% diffuse calcific disease in the proximal segment; mid left circumflex artery had 90% focal stenosis, obtuse marginal 4 had 85% stenosis; right coronary artery: mid right coronary artery had 90-95% stenosis, likely the culprit lesion, distal right coronary artery had about 70% narrowing). Ejection fraction was 50% with mild inferior

hypokinesia, but global function was low normal. End-diastolic pressure was borderline elevated. The subject underwent emergent coronary artery bypass grafting x 6; left internal mammary artery to left anterior descending artery, saphenous vein graft to diagonal artery, saphenous vein graft to obtuse marginal only to the circumflex artery is a sequential graft, saphenous vein graft to right coronary, the posterior descending artery, the sequential graft along with endoscopic vein harvesting, and epiaortic ultrasound guidance. The subject tolerated the procedure well and the events of non-ST elevation MI and severe multivessel coronary artery disease were considered resolved the day after event onset.

The subject was discharged in stable condition with discharge diagnoses of acute respiratory failure, non-ST elevation MI, paroxysmal atrial fibrillation, and coronary artery disease status post coronary artery bypass graft.

C5 adjudicated this as a myocardial infarction event.

2. HBV-23 Subject: Myocardial infarction [Preferred Term: Myocardial Infarction]

A 52-year-old white man with a history of marijuana and regular tobacco use experienced ventricular fibrillation arrest due to an acute MI and died (b) (6) days after receiving the first injection of Engerix-B. The subject was found *down* in a hotel parking lot. A bystander performed cardiopulmonary resuscitation (CPR) until emergency medical services (EMS) arrived. The subject underwent continued CPR and countershock to break the arrhythmia. An echocardiogram was negative for a pericardial effusion. An ECG revealed an inferior MI. The subject was prepped for a cardiac catheterization, but the subject lost his pulse again and CPR was resumed. His lactate level was 8.3 and troponin was 0.1 (unit of measure and normal ranges not provided) and 2 ampules of sodium bicarbonate were given. The subject was shocked again and was considered to be in refractory ventricular fibrillation; treatment was administered, all of which were unsuccessful in resuscitating the subject, and further efforts were not attempted. Resuscitative measures were stopped. Cause of death was reported by the investigator as a ventricular fibrillation arrest due to acute MI with refractory ventricular fibrillation. A death certificate was not available. Urine testing was positive for THC COOH, cotinine, and ranitidine breakdown, but was otherwise negative. An autopsy report noted the final post mortem diagnosis was atherosclerotic cardiovascular disease with cardiomegaly, coronary atherosclerosis, moderate aortic atherosclerosis, a remote 0.5 cm anterior left ventricular MI, and passive hepatic congestion. It was the opinion of the medical examiner that the subject died as a result of atherosclerotic cardiovascular disease; the manner of death was determined to be natural.

C5 adjudicated this not as a myocardial infarction event but was confirmed as a cardiovascular death (sudden cardiac death).

3. HBV-23 Subject: Coronary artery blockage [Preferred Term: Coronary Artery Occlusion]

A 55-year-old black or African American man with a relevant medical history that included angina due to possible arterial blockage, dyslipidemia, former alcohol and cocaine dependency, on an unspecified date, underwent a pre-operative stress test for a knee surgery that revealed a 40% perfusion defect. One hundred ninety-four days after receiving the third dose of Engerix-B, the subject underwent a cardiac catheterization that revealed 50% proximal, 80% mid left anterior descending (LAD), 90% first diagonal, 80% second diagonal, 100% first marginal, and 99% proximal right coronary artery (RCA) stenosis. Two hundred 3 days after receiving the third dose of Engerix-B, the subject experienced chest pain, was admitted to the hospital, and underwent a 5-vessel, off-pump coronary artery bypass grafting surgery: skeletonized left internal mammary artery to the distal left anterior descending, free skeletonized right internal mammary artery to the first obtuse marginal branch, reversed saphenous vein graft to the second diagonal branch, reversed saphenous vein graft to the posterior descending artery, and reverse saphenous vein graft to the posterolateral obtuse marginal branch. Endoscopic saphenous vein harvesting was performed to the right lower extremity. The procedure was uncomplicated and he was extubated that same evening. The subject was stable and was discharged 5 days after event onset, at which time the event was considered resolved.

C5 adjudicated this as not a myocardial infarction event.

4. HBV-16 Subject: Non ST segment elevation myocardial infarction; Unstable angina [Preferred Terms: Acute Myocardial Infarction; Angina Unstable]

A 60-year-old white man with a relevant medical history that included hypertension and dyslipidemia experienced events of acute MI and unstable angina 11 days after the second Engerix-B injection. The subject presented to the ER with chest pain, severe arm pain, and severe headache and was hypertensive upon arrival. The subject reported a several month history of exertional chest pain that was relieved with rest. The pain had been increasing in frequency and severity. Serial cardiac isoenzymes showed a mild troponin elevation and normal CK-MB. His treatment included an ACE inhibitor and beta blocker therapy for blood pressure control. The subject had some relief of his chest pain after treatment of his blood pressure, but the chest pain continued intermittently overnight. Because his brain natriuretic peptide was 9 ng/L, the subject underwent a cardiac catheterization and was found to have severe multivessel coronary artery disease. He underwent a successful percutaneous transluminal coronary angioplasty with 2 stents deployed in the proximal to mid and the mid right coronary artery. His ejection fraction was normal. The subject was discharged from the hospital 2 days after admission, at which time the events were considered resolved.

C5 adjudicated this as a myocardial infarction event.

APPENDIX 7: NARRATIVES FOR RARE, SERIOUS IMMUNE-MEDIATED EVENTS

HEPLISAV-B Group

1. HBV-10 Subject: c-ANCA positive vasculitis [Preferred Term: Granulomatosis With Polyangiitis]

A 55-year-old white woman from Northern Europe with a medical history of menopause, eleven days after her second study injection, presented with vocal hoarseness and approximately 8 weeks later, the subject reported symptoms of sinusitis. She reported never having had similar episodes before. Approximately 1 month later, she was hospitalized for 3 days for sinusitis on the left side. During this hospitalization, the subject underwent septal plastic surgery with drainage of the left paranasal sinus. Discharge medications were levofloxacin, diclofenac, and antihistamine to be taken for 1 week. Shortly after discharge, the sinusitis was considered resolved.

Five and a half months after her second study injection, the subject was hospitalized for surgery for a relapse of sinusitis. During this hospitalization, the subject developed a pericardial effusion and had pulmonary infiltrates and bilateral pleural effusions. She was had proteinuria with possible glomerulonephritis. Six and a half months after her second study injection, an ELISA test was positive for c-ANCA (titer of 1:128, positive for proteinase-3). She was diagnosed with granulomatosis with polyangiitis and was started on corticosteroids and cyclophosphamide.

The investigator assessed the event as serious, severe, and possibly related to study treatment.

2. HBV-10 Subject: Guillain-Barré Syndrome [Preferred Term: Guillain-Barré Syndrome]

A 36-year-old white woman with a medical history of splenectomy in 1985 for unknown reasons, approximately 3.5 months after the second HEPLISAV-B injection, and 5 days after an influenza vaccination, experienced the onset of Guillain-Barré syndrome. The subject was hospitalized complaining of progressive weakness that progressed to respiratory failure. The subject's hospitalization was prolonged by the diagnosis of a follicular variant of papillary carcinoma (thyroid) and bilateral pulmonary embolism. While hospitalized, she was treated with anticoagulants, antibiotics, immunoglobulins, and plasmapheresis, resulting in noticeable improvement. She was discharged approximately 10 weeks after onset of Guillain-Barré syndrome. This subject had a positive pre-vaccination ANA titer of 1:160 and a negative pre-vaccination anti-dsDNA result. No post-vaccination ANA or anti-dsDNA results were obtained. The Guillain-Barré Syndrome was considered by the investigator to be severe and probably not related to study vaccine but instead related to influenza vaccination. The subject was discontinued from the study due to the Guillain-Barré Syndrome.

3. HBV-16 Subject: Cavernous sinus syndrome [Preferred Term: Cavernous Sinus Thrombosis]

A 69 year white man who experienced an event that was not considered by the investigator to be potentially autoimmune and was not adjudicated by the SEAC was randomized to HEPLISAV-B, received 3 study injections, and experienced an SAE of cavernous sinus syndrome. The subject experienced transient amblyopia 5 months after the last dose of HEPLISAV-B, headaches 2 months later, and painful ophthalmoplegia 8.5 months after the last dose of HEPLISAV-B. The subject improved while on corticosteroid therapy and did not have a recurrence of symptoms in the subsequent 2 years. The initial working diagnosis was Tolosa Hunt Syndrome (THS), a granulomatous inflammatory disorder. Extensive workup revealed no evidence of a thrombotic, vascular, neoplastic, or infectious etiology. There was also no laboratory evidence of autoimmune disorder based on a negative test results for ANA, c-ANCA, p-ANCA, Sjogren's syndrome-A (SS-A), Sjogren's syndrome-B (SS-B), ribonuclear protein (RNP), and Smith antibodies. In the absence of inflammation on the orbital MRI and normal autoantibody test results, the diagnosis of cavernous sinus syndrome was felt to be most appropriate by the treating neurologist. This event was assessed by the investigator as not related to study treatment. Dynavax sought an independent evaluation by a noted neuroophthalmologist at a U.S. academic medical center who could not make a definitive diagnosis but noted that a normal MRI essentially excluded inflammation or signs of THS. His clinical suspicion was that the patient had a microvascular, ischemic third nerve palsy. The FDA sought consultation from 4 physicians who all felt the subject had THS.

Engerix-B Group

1. HBV-10 Subject: p-ANCA Positive Vasculitis [Preferred Term: P-ANCA Associated Vasculitis]

A 44-year-old white woman with a history of mixed connective tissue disease since approximately 1998, approximately 4 months following her second Engerix-B injection, experienced onset of an SAE of p-ANCA associated vasculitis with symptoms of severe dyspnea, hemoptysis, and pleuritic pain. She was hospitalized and admitted to the intensive care unit, where she required intubation and mechanical ventilation. A bronchoscopy showed pulmonary hemorrhage. She was discharged from the intensive care unit after 17 days on oxygen therapy. During the hospitalization a blood test revealed positive myeloperoxidase-p-ANCA (no titer reported). The subject was then given a provisional diagnosis of p-ANCA associated vasculitis and started on pulse methylprednisolone and cyclophosphamide. On a further review of the subject's history it was determined that she demonstrated some features of scleroderma but was considered to have a possible crossover syndrome. The subject was discharged from the hospital after 4 weeks when the event of p-ANCA associated vasculitis was considered to be resolved. This subject had a positive pre-vaccination ANA result of greater than 1:5120 and a negative pre-vaccination anti-dsDNA result. No post vaccination ANA or anti-dsDNA results were obtained. The p-ANCA associated vasculitis was considered by the investigator to be severe, serious, and not related to study vaccine.