Dynavax Technologies Corporation

HEPLISAV™
Hepatitis B Vaccine

Vaccines and Related Biological Products Advisory Committee (VRBPAC)
Briefing Document
for the
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LIST OF ABBREVIATIONS

Abbreviation	Term
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AESI	adverse event of special interest
AI	autoimmune
AIAE	autoimmune adverse event
ANA	antinuclear antibody
ANCA	anti-neutrophil cytoplasmic antibody
anti-HBs	antibody to hepatitis B surface antigen
BMI	body mass index
cANCA	cytoplasmic staining anti-neutrophil cytoplasmic antibody
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CpG	cytosine phosphoguanosine
CSR	clinical study report
DNA	deoxyribonucleic acid
dsDNA	double-stranded deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ELISA	enzyme-linked immunosorbent assay
GMC	geometric mean concentration
GPA	granulomatosis with polyangiitis (Wegener's granulomatosis)
HBsAg	hepatitis B surface antigen
HBcAg	hepatitis B core antigen
HBV	hepatitis B virus
HEPLISAV	HBsAg *adw* subtype in a single vial presentation
HEPLISAV (All)	refers to all formulations of HEPLISAV, Formulations 1, 2, and 3
HEPLISAV (F1)	HEPLISAV Formulation 1, comprised HBsAg subtype *adw* and 3000 mcg 1018 ISS Adjuvant in a 2-vial presentation
HEPLISAV (F2)	HEPLISAV Formulation 2, comprised 20 mcg HBsAg subtype *adr* and 3000 mcg 1018 ISS Adjuvant in a single- or 2-vial presentation. HBsAg subtype *adr* was used in trials DV2-HBV-04, DV2-HBV-05, and DV2-HBV-08
HEPLISAV (F3)	The proposed commercial formulation of HEPLISAV, also known as Formulation 3, comprises 20 mcg HBsAg subtype *adw* and 3000 mcg 1018 ISS Adjuvant in a single-vial presentation. HEPLISAV was used in the following trials: DV2-HBV-10, DV2-HBV-14, and DV2-HBV-16
HIV	human immunodeficiency virus
IFA	immunofluorescence assay

Abbreviation	Term
IFN	interferon
Ig	immunoglobulin
IL	interleukin
IM	intramuscular
inj	injection
ITT	intent-to-treat
mITT	modified intent-to-treat
MSM	men who have sex with men
ODN	oligodeoxynucleotide
p-ANCA	perinuclear-staining anti-neutrophil cytoplasmic antibody
pDC	plasmacytoid dendritic cell
PEAI	pre-existing event of autoimmune disease
PIR	post-injection reaction
PP	per protocol
PR3	proteinase 3
PRR	pattern recognition receptors
rHBsAg	recombinant hepatitis B surface antigen
RR	relative risk
SAE	serious adverse event
SEAC	safety evaluation and adjudication committee
SLE	systemic lupus erythematosus
SPR	seroprotection rate
STD	sexually transmitted disease
Th1	T helper cell 1
Th2	T helper cell 2
TLR	Toll-like receptor
TSH	thyroid-stimulating hormone
T4	thyroxine-4
VSD	Vaccine Safety Datalink
1018 ISS	Dynavax's adjuvant used in HEPLISAV

1.0 EXECUTIVE SUMMARY

HEPLISAV™ is a recombinant hepatitis B vaccine designed to meet the medical need in adults for improved immunogenicity and a simpler dosing regimen than the currently available vaccines. The proposed indication is for immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 through 70 years old.

The HEPLISAV clinical program demonstrated the safety and immunogenicity of HEPLISAV compared with Engerix-B®, the most widely used hepatitis B vaccine in the United States. The 2 pivotal phase 3 trials both met their primary endpoints, demonstrating that seroprotection with HEPLISAV is noninferior to that of Engerix-B. The trials showed that the HEPLISAV seroprotection is higher than that of Engerix-B across all subpopulations, including those with a diminished response to the currently available vaccines. HEPLISAV's 2-dose, 1-month regimen has the potential to improve adherence over the 3-dose, 6-month regimen of the current vaccines. The combination of the higher immunogenicity and potential to improve adherence should result in higher effective seroprotection rates in actual use across all populations at risk for hepatitis B infection.

The safety of HEPLISAV has been demonstrated in an integrated analysis of the clinical trials. The trials showed that HEPLISAV has a safety profile similar to that of Engerix-B. There were 2 unexpected findings of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, 1 case of cytoplasmic staining anti-neutrophil cytoplasmic antibody (c-ANCA) vasculitis in the HEPLISAV group and 1 case of perinuclear staining anti-neutrophil cytoplasmic antibody (p-ANCA) vasculitis in the Engerix-B group. A comprehensive analysis of autoimmune events showed similar rates of events in the HEPLISAV and Engerix-B treatment groups. Other AEs occurred at similar rates in both treatment groups.

1.1 Hepatitis B Infection

Hepatitis B virus (HBV) infection is a serious infectious disease that can result in significant morbidity and mortality. After infection, up to 20% of persons will develop the chronic carrier state and will be subject to severe sequelae including chronic active hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma. Chronic carriers of HBV are also the source of transmission to others. Currently, up to 2.2 million persons are estimated to be living with HBV infection in the United States.

The first plasma-derived hepatitis B vaccine was approved in 1981 and recombinant hepatitis B vaccines were approved in 1987. These vaccines are adjuvanted with an aluminum salt and administered as a series of 3 to 4 doses over 6 to 12 months.

Current hepatitis B vaccines have been recommended for persons with risk factors for exposure to HBV since 1982. These risk factors include: (1) persons at risk through sexual exposure, including men who have sex with men (MSM), persons with more than 1 sex partner in the previous 6 months, and persons with a sexually transmitted disease (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 higher risk for HBV infection such as those with diabetes, travelers to countries with a high prevalence of chronic HBV infection, persons with chronic liver disease, and those with HIV infection.

Recognizing the difficulties of immunizing adults, in 1991 the Advisory Committee on Immunization Practices (ACIP) recommended including hepatitis B vaccine in universal vaccinations for infants, catch-up use in adolescents, and reiterated the need for hepatitis B vaccination for adults with risk factors for HBV infection. Over the ensuing 2 decades, the incidence of HBV infection in the United States decreased 82% from 1990 through 2007, but the incidence of infection in older adults declined much less than in children and young.

1.2 Medical Need for an Improved Hepatitis B Vaccine

The universal childhood hepatitis B immunization program has been very successful due to a well-established immunization infrastructure and the fact that over 90% of infants and adolescents develop a seroprotective antibody response to hepatitis B vaccine. However, HBV infection continues to be a significant public health problem in adults, in whom approximately 90% of the new cases of HBV infection occur each year. The major modes of transmission of HBV in adults are sexual exposure, particularly among heterosexuals with multiple sex partners and MSM, and injection-drug use. The CDC estimates the annual incidence of HBV infection is highest in men 30 to 45 years old (38.9 per 100000 population), and among racial groups it is highest in blacks (17.6 per 100000 population). The incidence in persons with diabetes is also high (18.9 per 100000).

Most adults today did not receive hepatitis B vaccination as an infant or adolescent. The challenge of vaccinating adults against HBV is multifactorial and 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 schedule. And finally, the vaccine must provide seroprotection. The first obstacle continues to be a challenge to health care providers and public health authorities. The second 2 obstacles can be overcome with an improved hepatitis B vaccine.

The currently approved hepatitis B vaccines (Engerix-B and Recombivax®) have provided significant benefits, but they have limitations that reduce their effectiveness in adults, both in terms of their administration and. These limitations include:

- Reduced immunologic responsiveness to a complete vaccine regimen in certain hyporesponsive populations including older adults, men, individuals with diabetes mellitus, obese individuals, and smokers
- Requirement for adherence to a complete 3-dose vaccination schedule over 6 months; and
- Prolonged time (> 6 months) before development of seroprotection because only 20% to 30% of individuals are protected after receiving 2 doses.

1.2.1 Hyporesponsive Populations

One of the potential reasons for ongoing HBV transmission in adults is that some groups of adults do not respond as well as others to the currently licensed HBV vaccines. Among individuals 40 years of age and older, the proportion who achieve seroprotection after a 3-dose regimen of the currently licensed hepatitis B vaccines declines below 90%, and by age 60 years seroprotection develops in less than 75% of those vaccinated.

Men have reduced immune responses to currently licensed hepatitis B vaccines compared with women and have a higher incidence of HBV infection. The higher incidence is largely due to behaviors that put men at risk for infection such as multiple heterosexual sex partners, MSM, and injecting drugs.

Persons with diabetes mellitus have reduced immune responses to current hepatitis B vaccines and a high incidence of HBV infection. The CDC estimates that 4000 cases of hepatitis B infection occur in individuals with diabetes each year in the United States, which is more than 10% of all reported cases of hepatitis B infections. Individuals with diabetes who contract HBV have a higher rate of symptomatic acute hepatitis, chronic HBV infection, and death compared with individuals without diabetes. The case fatality rate following acute symptomatic HBV infection among individuals with diabetes can be as high as 5% to 18%. Outbreaks of acute hepatitis B in long-term care facilities led to the recent recognition that persons with diabetes are at increased risk of HBV infection due to improper use of devices that monitor blood glucose. Because of the increased incidence of HBV infection in individuals with diabetes and outbreaks of hepatitis B infection in individuals with diabetes in long-term care facilities, the ACIP recently released new recommendations for adults with diabetes: (1) hepatitis B vaccine should be routinely administered to all unvaccinated adults with diabetes 19 to 59 years of age; and (2) hepatitis B vaccine may be administered at the discretion of the treating clinician to unvaccinated adults with diabetes who are 60 years of age and older.

1.2.2 Adherence to Vaccination in Adults

In actual use, not all individuals receive the complete 3-dose vaccine regimen, leaving them susceptible to HBV infection. Older adults have been found to be more adherent to the vaccination schedule but demonstrate a lower immune response to currently licensed vaccines, while younger adults have a good immune response to vaccine but are less adherent. In a large retrospective Vaccine Safety Datalink (VSD) Study of 88711 hepatitis B vaccine recipients ≥ 18 years old, 81% received 2 or more doses and only 64% of those vaccinated received all 3 doses of vaccine during an 8-year study period.

1.2.3 Time to Seroprotection

In addition to the variable antibody response in many adults with the currently licensed vaccines, most persons do not achieve seroprotection until after the third dose at 6 months. Because of the prolonged time to receive the complete vaccination series, 75% to 80% of individuals remain at risk for HBV infection until after receiving the third dose. The long time needed to achieve seroprotection may be an issue for individuals at risk of imminent exposure to HBV, including health-care workers and emergency first-responders, older adults with diabetes entering long-term care facilities, travelers to countries with a high prevalence of chronic hepatitis B, and those with behavioral risk factors for infection including heterosexuals with multiple sex partners, MSM, and injection-drug users.

1.3 HEPLISAV and Scientific Rationale

HEPLISAV combines a yeast-derived recombinant hepatitis B surface antigen (rHBsAg) with Dynavax's 1018 ISS Adjuvant, a Toll-like receptor 9 (TLR9) agonist. The goal of using 1018 ISS Adjuvant is to increase the immunogenicity of rHBsAg, including increasing the immunogenicity in populations hyporesponsive to the current vaccines. This vaccine is a sterile liquid dosage form supplied in 0.5 mL dose vials and contains 20 mcg of HBsAg and 3000 mcg of 1018 ISS Adjuvant given in a 2-dose series over 1 month by intramuscular (IM) injection.

The 1018 ISS Adjuvant used in HEPLISAV resulted from more than a decade of research on specific immumodulators. Beginning in 1999, Dynavax Technologies conducted preclinical and toxicity studies with 1018 ISS. Acting mechanistically in a very different manner from aluminum-based adjuvants, 1018 ISS stimulates TLR9, predominantly in plasmacytoid dendritic cells (pDCs). The activated pDCs then present the hepatitis B surface antigen (HBsAg) to CD4+ cells, leading to production of HBsAg-specific antibodies (anti-HBs) against the hepatitis B virus. In contrast, alum adjuvants used in the currently licensed hepatitis B vaccines stimulate a more general inflammatory response to mechanical disruption of cell membranes that is not as specific to the production of anti-HBs.

The clinical development of HEPLISAV included an extensive panel of nonclinical studies of rHBsAg combined with 1018 ISS and 1018 ISS alone performed both in vitro and in several diverse animal models. Seven supporting clinical trials of HEPLISAV were conducted and 20 mcg HBsAg + 3000 mcg 1018 ISS was determined to be the effective clinical dose. These trials were followed by the 2 pivotal phase 3 trials, DV2-HBV-10 and DV2-HBV-16.

The proposed indication for HEPLISAV is for immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 through 70 years old. For this indication, Dynavax enrolled 5870 subjects in 9 completed clinical trials of HEPLISAV, including 4425 adult subjects who received HEPLISAV and 1420 adult subjects who received the comparator vaccine, Engerix-B, manufactured by GlaxoSmithKline.

Near the end of the first pivotal trial (DV2-HBV-10), a rare autoimmune event of Wegener's granulomatosis (granulomatosis with polyangiitis) was reported as a possibly related serious adverse event, leading to a clinical hold on the HEPLISAV development program. Details of this case and the clinical hold are discussed in detail later in this Briefing Document. After a thorough safety investigation and analysis of autoimmune events, the clinical hold was lifted and the second phase 3 pivotal trial (DV2-HBV-16) was conducted. In this trial, intensive prospective surveillance for autoimmune disorders was put in place including an autoimmune signs and symptoms questionnaire administered to every subject at each clinic visit, testing for autoantibodies, expert independent evaluation of any suspected autoimmune event, establishment of an independent Safety Evaluation and Adjudication Committee (SEAC) for confirmation of each possible autoimmune event, and an independent Data and Safety Monitoring Board (DSMB) for evaluation of safety. Following these additional safety measures in DV2-HBV-16, HEPLISAV was found to have a safety profile similar to Engerix-B.

1.4 Immunogenicity

Based on the results from early hepatitis B vaccine trials where HBV infection was the clinical endpoint, achieving a post-vaccination anti-HBs concentration of 10 mIU/mL or greater has been shown to correlate with protection against HBV infection. Thus, the HEPLISAV clinical development program, like other clinical development programs for hepatitis B vaccines, has used the seroprotection rate (SPR), the proportion of individuals achieving an anti-HBs concentration of 10 mIU/mL or greater after vaccination, as the immune correlate of protection.

The immunogenicity of HEPLISAV has been established in 2 pivotal trials, both of which met their primary endpoints, demonstrating that the rates of seroprotection with HEPLISAV were noninferior to seroprotection achieved with Engerix-B. The immunogenicity of HEPLISAV was consistently higher across all subpopulations, including subpopulations hyporesponsive to the currently available vaccines.

1.4.1 Phase 3 Pivotal Trials

The immunogenicity of HEPLISAV was assessed in 2 phase 3 pivotal trials, DV2-HBV-10 and DV2-HBV-16. Both pivotal trials were randomized, subject- and observer-blinded, active-controlled, parallel-group, multicenter trials to compare immune responses following injection with either 2 doses of HEPLISAV and 1 dose of placebo or 3 doses of Engerix-B.

In DV2-HBV-10, the randomization was 3:1 for HEPLISAV versus Engerix-B, while in DV2-HBV-16 it was 4:1. DV2-HBV-10 was a 28-week trial and DV2-HBV-16 was 52 weeks in duration. Eligible subjects in both trials were generally healthy volunteers (no clinically debilitating illnesses) who were serum negative for HBsAg, anti-HBs, and antibody to hepatitis B core antigen (anti-HBc); had no history of HBV infection; and had no prior immunization with any hepatitis B vaccine. HEPLISAV was given in both trials as a 2-dose regimen at 0 and 1 month (plus a placebo injection at 6 months); Engerix-B, the active licensed comparator vaccine, was given using the approved 3-dose regimen at 0, 1, and 6 months.

The subjects and study personnel conducting clinical safety evaluations were blind to treatment assignment. Study drug was not packaged in a blinded manner. Therefore, designated study site personnel with no other trial conduct responsibilities were not blinded so they could prepare and/or administer the study injections. In addition, an unblinded study monitor with no other trial responsibilities confirmed drug accountability. In both trials, designated unblinded staff members were not involved in assessing safety and were instructed not to communicate treatment assignments to the personnel responsible for safety assessments.

1.4.1.1 Noninferiority Objective

The demonstration of seroprotection in the 2 pivotal trials relied on head-to-head comparisons between HEPLISAV and Engerix-B. Both trials employed a noninferiority trial design and were powered to demonstrate noninferiority of HEPLISAV compared to Engerix-B (SPR for HEPLISAV minus SPR for Engerix-B) with a pre-specified noninferiority margin of -10%.

1.4.1.2 Primary Endpoint for Pivotal Trials

The primary immunogenicity objective for DV2-HBV-10 was:

- To demonstrate noninferiority of the SPR at Week 12 following injection with HEPLISAV at Weeks 0 and 4 to the SPR at Week 28 following injection with Engerix-B at Weeks 0, 4, and 24.

The primary immunogenicity objective for DV2-HBV-16 was:

- To demonstrate the noninferiority of the immune response to HEPLISAV vaccination as measured by 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).

1.4.2 Immunogenicity of HEPLISAV

The immunogenicity of hepatitis B vaccines is expressed in terms of the SPR, defined as the proportion of individuals achieving an anti-HBs level ≥10 mIU/mL after vaccination. In the 2 pivotal trials, DV2-HBV-10 and DV2-HBV-16, HEPLISAV was administered to a total of 3778 subjects over 18 years of age; 1089 subjects received Engerix-B. Of those randomized, 3564 (94.3%) HEPLISAV subjects and 1039 (95.4%) Engerix-B subjects completed the trial.

In both pivotal trials HEPLISAV demonstrated noninferiority to Engerix-B as measured by the SPRs at the primary endpoints. In addition, the peak SPR in the HEPLISAV group was significantly higher than in the Engerix-B group in each trial.

In DV2-HBV-10 in subjects aged 18 to 55 years, the SPR with HEPLISAV at the primary endpoint (Week 12 for HEPLISAV versus Week 28 for Engerix-B) was 95.0% compared to an SPR of 81.1% with Engerix-B. The difference between SPRs (HEPLISAV minus Engerix-B) was 13.9% (95% confidence interval [CI]: 10.6%, 17.6%), which met the prospectively-defined criterion for the primary endpoint of noninferiority (lower limit of the 95% CI > -10%).

In the second pivotal trial (DV2-HBV-16) in subjects 40 to 70 years old, the SPR with HEPLISAV at the primary endpoint (Week 12 for HEPLISAV versus Week 32 for Engerix-B) was 90.0% compared to an SPR of 70.5% with Engerix-B. The difference between SPRs (HEPLISAV minus Engerix-B) was 19.6% (95% CI: 14.7%, 24.7%), which met the pre-specified criterion for the primary endpoint of noninferiority (lower limit of the 95% CI > -10%).

1.4.2.1 Peak Seroprotection

In both pivotal trials, the peak SPR in the HEPLISAV group occurred at Week 24, 20 weeks after the last dose of HEPLISAV, and was significantly higher than the peak SPR in the Engerix-B group which occurred at Week 28, 4 weeks after the last dose of Engerix-B. In the DV2-HBV-10 per protocol (PP) population, the peak SPR induced by HEPLISAV, which occurred at Week 24, was 98.3%. The peak SPR induced by Engerix-B, which occurred at Week 28, was 81.1%. The difference in SPRs was 17.2% (95% CI: 14.0%, 20.8%). Over the course of the DV2-HBV-10 study, the SPR in the HEPLISAV group remained significantly higher than the SPR in the Engerix-B group. In the DV2-HBV-16 PP population, the peak SPR induced by HEPLISAV, which occurred at Week 24, was 95.1%. The peak SPR induced by Engerix-B, which occurred at Week 28, was 72.8%. The difference in SPRs was 22.3%

(95% CI: 17.7%, 27.2%). Over the course of the DV2-HBV-16 study, the SPR in the HEPLISAV group remained significantly higher than the SPR in the Engerix-B group.

1.4.2.2 Seroprotection at Early Time Points

HEPLISAV provided earlier seroprotection after administration. After 2 study injections, at Week 8, in DV2-HBV-10, the SPR in the HEPLISAV group (88.5%) was not only higher than the SPR in the Engerix-B group at Week 8 (26.4%; difference = 62.1%, 95% CI: 58.0%, 66.0%), but was also higher than the peak SPR in the Engerix-B group at Week 28 (81.1%). At Week 8, in DV2-HBV-16, the SPR in the HEPLISAV group was 76.6% and was not only significantly higher than the SPR in the Engerix-B group at Week 8 (20.3%; difference = 56.2%, 95% CI: 51.1%, 60.7%), but was also significantly higher than the peak SPR in the Engerix-B group at Week 28 (72.8%).

1.4.2.3 Seroprotection by Age Groups

In all age groups the peak SPR with HEPLISAV was significantly higher than with Engerix-B. For subjects 18 to 29, 30 to 39, 40 to 49, 50 to 59, and 60 to 70 years old, the peak SPR for HEPLISAV (at Week 24) ranged from 91.6% to 99.7% while the peak SPR for Engerix-B subjects (at Week 28) ranged from 67.7% to 92.7%. The percent difference in SPRs (HEPLISAV SPR minus Engerix-B SPR) ranged from 6.8% in 18 to 29 years old to 23.9% in those 60 years and older.

1.4.2.4 Seroprotection in Persons With and Without Diabetes Mellitus

In subjects with type 2 diabetes, the peak SPR induced by HEPLISAV, which occurred at Week 28, was 89.3% and the peak SPR induced by Engerix-B, which occurred at Week 28 was 61.8% with a difference in SPRs of 27.5% (95% CI: 15.0%, 41.1%). In subjects without diabetes, the peak SPR induced by HEPLISAV, which occurred at Week 24, was 96.9% and the peak SPR induced by Engerix-B, which occurred at Week 28, was 77.5% with a difference in SPRs of 19.3% (95% CI: 16.8%, 22.1%).

1.4.2.5 Seroprotection in Hyporesponsive Groups

HEPLISAV induced significantly higher peak SPRs than Engerix-B across all subpopulations analyzed, including subpopulations known to be hyporesponsive to currently licensed hepatitis B vaccines: Older adults, men, obese subjects, and smokers; as well as in subpopulations with a good response to licensed vaccines: Young adults, women, whites, blacks, non-obese subjects, and nonsmokers.

Immunogenicity Summary

HEPLISAV, administered as 2 doses over 1 month, compared to Engerix-B, administered as 3 doses over 6 months, demonstrated:

- Noninferiority of the seroprotection rate at the primary endpoint;
- Significantly higher seroprotection using fewer doses;
- Higher seroprotection in all subpopulations analyzed;
- Significantly higher seroprotection in populations hyporesponsive to currently licensed HBV vaccines (older adults, men, diabetics, obese, and smokers); and
- Earlier seroprotection.

1.5 Safety

The safety and tolerability of HEPLISAV was similar to that of Engerix-B. The majority of AEs were mild to moderate, self-limited, and did not lead to discontinuation. Standard safety evaluations of HEPLISAV included local and systemic reactogenicity, AEs, and serious adverse events (SAEs), which demonstrated that HEPLISAV was generally well tolerated, with a safety profile similar to that of Engerix-B. The post-injection reaction profile of HEPLISAV included a similar rate of systemic reactions (32% for HEPLISAV versus 37% for Engerix-B), and a similar rate of local reactions (43% for HEPLISAV and 41% for Engerix-B). The type and frequency of AEs, SAEs, deaths, and withdrawals were similar for HEPLISAV and Engerix-B.

There is a theoretical concern that any adjuvanted vaccine might induce autoimmune disease or exacerbate pre-existing autoimmune disease (PEAI). In the HEPLISAV clinical development program, safety findings related to autoimmune diseases were analyzed on an individual basis and by treatment group. A pre-specified list of autoimmune and inflammatory disorders from multiple organ systems was used to programmatically search the safety database for Adverse Events of Special Interest (AESIs) across all trials. And in DV2-HBV-16, all possible new-onset autoimmune diseases were evaluated by a SEAC for confirmation and relatedness.

Using these methods, the incidence of autoimmune events was low in the HEPLISAV clinical development program. In the 2 pivotal trials, the relative risk (RR) of an AESI in the HEPLISAV group was 0.57 (95% CI: 0.17, 1.91), indicating a similar rate of AESIs in the HEPLISAV group compared to the Engerix-B group.

Two additional autoimmune events were adjudicated by the SEAC that were not already identified as AESIs in the HEPLISAV group (2 of 1968 subjects or 0.1%) and zero in the Engerix-B group (0 of 481 subjects or 0.0%). In DV2-HBV-10 and DV2-HBV-16, the RR of AESI and SEAC adjudicated autoimmune events was 0.72 (95% CI: 0.23, 2.29). For all recipients of 1018 ISS throughout the HEPLISAV clinical development program (4425 subjects in the HEPLISAV group compared to 1420 subjects in the Engerix-B group), the incidence of autoimmune events was 0.27% in the HEPLISAV group and 0.35% in the Engerix-B group, giving a RR of 0.77 (95% CI: 0.27, 2.18). In an analysis of autoantibodies, similar rates of autoantibody development (antinuclear antibody [ANA], anti-double-stranded deoxyribonucleic acid [anti-dsDNA], or anti-neutrophil cytoplasmic antibody [ANCA]) were observed for HEPLISAV subjects and Engerix-B subjects.

In DV2-HBV-10, 2 cases of ANCA-associated vasculitis occurred: 1 case of c-ANCA vasculitis or granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) in a subject who received HEPLISAV; and, 1 case of p-ANCA vasculitis or microscopic polyangiitis in a subject who received Engerix-B. Both cases occurred in older adults, in whom the incidence of ANCA-associated vasculitis is highest. The case of p-ANCA vasculitis occurred 3 months after receiving the second dose of Engerix-B and was considered not related to study treatment by the site investigator. The case of c-ANCA vasculitis occurred 1 month after the third injection (placebo) and 5 months after receiving the second injection of HEPLISAV. This case was considered possibly related to study treatment by the site investigator. In light of the serious nature of this AE, the theoretical risk of autoimmunity with adjuvanted vaccines, and the low incidence of ANCA-associated vasculitis in the general population, the HEPLISAV clinical development program was put on clinical hold and the safety of HEPLISAV was further evaluated. During the clinical hold, AEs from all subjects from the entire clinical development program were reviewed for other cases that might represent ANCA-associated vasculitis. Cases of possible vasculitis or associated conditions were investigated, but no additional cases of ANCA-associated vasculitis were identified. Thus, the rate of ANCA-associated vasculitis in DV2-HBV-10 was 1 of 1809 (0.06%) subjects for HEPLISAV recipients and 1 of 606 (0.17%) subjects for Engerix-B recipients. In the entire HEPLISAV program, the rate was 1 of 2500 (0.04%) subjects for HEPLISAV recipients and 1 of 930 (0.11%) subjects for Engerix-B recipients.

All available serum samples from baseline, Month 3 (2 months after the last HEPLISAV dose) and Month 7 (1 month after the last Engerix-B dose) from 2024 subjects in DV2-HBV-10 and 2 prior trials were tested for ANCA. The testing algorithm used enzyme immunoassay assessment for myeloperoxidase, the target for p-ANCA antibodies, and proteinase-3 (PR3), the target for c-ANCA antibodies. Positive enzyme immunoassay samples were then tested by an immunofluorescence assay (IFA) for confirmation. There were no c-ANCA or p-ANCA positive samples by IFA in any of the subjects tested other than the 2 initially reported.

None of the known mechanisms of action of cytosine phosphoguanosine oligodeoxynucleotide (CpG-ODN) provide any potential links to autoimmune disease. However, there remains a theoretical concern that adjuvanted vaccines might increase the risk of autoimmune disease without preference for a specific autoimmune disease. To explore this possibility, Dynavax reviewed all AEs of autoimmune disease in DV2-HBV-10, and in the entire HEPLISAV development program. In DV2-HBV-10, the rates of autoimmune adverse events (AIAEs) were 2 of 1809 (0.11%) subjects in HEPLISAV recipients and 1 of 606 (0.17%) subjects in Engerix-B recipients and in the entire program, the rates of AIAEs were 7 of 2500 (0.28%) subjects in HEPLISAV recipients and 4 of 930 (0.43%) subjects in Engerix-B recipients (RR: 0.65; 95% CI: 0.19, 2.22).

Finally, Dynavax had considered anti-dsDNA to be a potentially useful safety biomarker during the development program because 1018 ISS, as an oligonucleotide, could potentially act as an antigen and induce cross-reactive antibodies to dsDNA. In addition, anti-dsDNA has a strong correlation with systemic lupus erythematosus (SLE), and SLE is among the more common autoimmune diseases. In DV2-HBV-10, the number of subjects who went from anti-dsDNA negative to positive was 9 of 1730 (0.52%) subjects in the HEPLISAV group and 3 of 580 (0.52%) subjects in the Engerix-B group. Within the entire program, the rates were 46 of 3918 (1.17%) subjects and 11 of 1122 (0.98%) subjects, respectively.

Based on these assessments and the plan to conduct enhanced surveillance for autoimmune diseases in the next phase 3 pivotal trial, DV2-HBV-16, the clinical hold was lifted and the HEPLISAV clinical development program resumed.

1.5.1 Summary of Safety

Safety data from the 2 phase 3 pivotal trials, DV2-HBV-10 and DV2-HBV-16, demonstrated a similar safety profile for HEPLISAV when compared with Engerix-B. HEPLISAV and Engerix-B had similar rates of post-injection reactions (HEPLISAV: 55.1%; Engerix-B: 57.1%) and most injection reactions were self-limited and mild or moderate in severity. HEPLISAV and Engerix-B had similar rates of local post-injection reactions (HEPLISAV: 42.8%; Engerix-B: 41.1%) with the most frequent local post-injection reaction being injection-site pain (HEPLISAV: 41.7%; Engerix-B: 40.5%). The frequency of systemic post-injection reactions was similar for HEPLISAV subjects (32.3%) and Engerix-B subjects (37.4%).

AEs occurred at similar rates in both treatment groups (HEPLISAV: 55.3%; Engerix-B: 58.0%). The majority of AEs in both groups were mild or moderate in severity. The 3 most frequently reported AEs in each treatment group were the same: Nasopharyngitis, headache, and back pain. Study withdrawals due to AEs were infrequent and occurred at similar rates between treatment groups (HEPLISAV: 0.08%; Engerix-B: 0.18%). SAEs were reported with similar frequency in both HEPLISAV and Engerix-B subjects (HEPLISAV: 2.8%; Engerix-B: 3.3%) with the majority of SAEs considered by investigators to be unrelated to vaccination. In each group, 1 related SAE occurred.

The RR of an SAE for HEPLISAV compared with Engerix-B had a point estimate of 0.83 (95% CI: 0.57, 1.21). The frequencies of SAEs from previous trials including all subjects who received 1018 ISS Adjuvant [HEPLISAV (ALL)] were similar in both treatment groups (HEPLISAV [ALL]: 2.7%; Engerix-B: 3.7%). The RR of an SAE in the HEPLISAV (ALL) group compared with the Engerix-B group was 0.74 (95% CI: 0.54, 1.03).

No deaths were reported in the supportive clinical trials or DV2-HBV-10. In DV2-HBV-16, there were 2 deaths: 1 in the HEPLISAV group and 1 in the Engerix-B group. Both of these deaths were considered by the investigator to be unrelated to vaccination.

AESIs were infrequent (HEPLISAV: 0.21%; Engerix-B: 0.37%). HEPLISAV and Engerix-B had similar rates of exacerbation of pre-existing events of special interest (HEPLISAV: 2.3%; Engerix-B: 4.3%). Two new-onset SEAC-adjudicated autoimmune events, not already counted in the AESIs, were identified in HEPLISAV subjects (N = 1969) and 0 in Engerix-B subjects (N = 483) in DV2-HBV-16. All events were non-serious and consisted of commonly occurring medical conditions in older adults.

1.6 Benefit/Risk

HEPLISAV has a favorable benefit/risk profile for the vaccination of adults at risk for hepatitis B infection. The HEPLISAV SPR is consistently higher than that of Engerix-B. The 2-dose, 1-month regimen has the potential to improve adherence. The combination of the higher immunogenicity and the potential to improve adherence should result in higher seroprotection rates in actual use across all populations at risk for hepatitis B infection. The safety of HEPLISAV has been demonstrated in an integrated analysis of the clinical trials. A comprehensive analysis of autoimmune events showed similar rates in the HEPLISAV and Engerix-B groups. Other AEs occurred at similar rates in both treatment groups.

Although current hepatitis B vaccines have addressed a medical need in infants and adolescents, a hepatitis B vaccine with a comparable safety profile that could offer noninferior serpprotection

after a 2-dose regimen over 1 month would significantly impact the health and welfare of key at-risk adult populations.

HEPLISAV, compared with Engerix-B, has a similar safety profile, induces significantly higher levels of seroprotection in a greater number of individuals at risk, has fewer required doses over a shorter period of time, induces high levels of seroprotection in hyporesponsive populations and responsive populations, and provides earlier seroprotection for those who may be at imminent risk of exposure. HEPLISAV has the potential to meet the currently unmet medical need to reduce the risk of HBV infection and its associated morbidity and mortality in individuals at high or imminent risk of infection.

1.7 Conclusion

Hepatitis B remains a public health problem in adults in the United States. Current vaccines work well in the pediatric population but less well in adults, particularly in some subgroups at high risk for infection. Adherence to a 3-dose, 6-month schedule challenges many in some of the highest risk groups. The delayed time to achieve seroprotective levels of antibody leaves some persons without seroprotection and at unnecessarily prolonged risk for infection. Clinicians need another option to overcome these limitations.

HEPLISAV stimulates a pathway in the innate immune system that is an element of the natural response to an infection. HEPLISAV, compared with Engerix-B, met the primary endpoint of noninferiority, induced significantly higher rates of seroprotection, induced high rates of seroprotection in populations hyporesponsive to currently available vaccines and in populations with good responses, and provided earlier seroprotection that could be beneficial to certain high risk persons in need of rapid protection. In addition, administration of HEPLISAV should increase adherence by virtue of its shorter 2-dose schedule over 1 month.

The safety profile of HEPLISAV was similar to Engerix-B. With enhanced safety surveillance, there were similar rates of local and systemic post-injection reactions, AEs, SAEs, new onset autoimmune disease, exacerbation of pre-existing autoimmune disease, or induction of autoantibodies in HEPLISAV recipients and Engerix-B recipients.

Based on these considerations, the approval of HEPLISAV would benefit adults 18 through 70 years old who are at risk for HBV infection.

2.0 INTRODUCTION

This briefing document presents information on HEPLISAV, a hepatitis B vaccine developed by Dynavax Technologies Corporation. Each dose of HEPLISAV consists of 20 mcg of yeast-derived recombinant hepatitis B surface antigen (rHBsAg) and 3000 mcg of 1018 ISS Adjuvant, a Toll-like receptor 9 (TLR9) agonist for IM administration in a 2-dose regimen at 0 and 1 month (Refer to Table 1 for details regarding the composition and manufacture of HEPLISAV). The proposed indication is immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 through 70 years old.

The HEPLISAV clinical development program for this indication comprises 9 completed clinical trials of HEPLISAV including 7 supportive trials and 2 phase 3 pivotal trials (Refer to Appendix 2 for trial details and formulations of HEPLISAV used in the clinical development program). These trials enrolled 5845 subjects, including 4425 subjects who received HEPLISAV and 1420 subjects who received the comparator vaccine, Engerix-B manufactured by GlaxoSmithKline (Appendix 2, Table 33).

Of 4425 subjects (Safety Population) receiving HEPLISAV during the clinical development program, 3777 or 85.4% were in the 2 pivotal phase 3 trials (Table 1).

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

Trials	HEPLISAV N (%)	Engerix-B N (%)	Total N (%)
Supportive[a]	648 (14.6)	333 (33.5)	981 (16.7)
Pivotal[b]	3777 (85.4)	1087 (76.5)	4864 (83.2)
Total	4425 (100)	1420 (100)	5845 (100)

[a] Supportive trials: HBV0001, DV2-HBV-02, DV2-HBV-03, DV2-HBV-04, DV2-HBV-05, DV2-HBV-08, DV2-HBV-14.
[b] Pivotal trials: DV2-HBV-10, DV2-HBV-16.

The dose, schedule, and number of injections of HEPLISAV in the pivotal trials were based on the results of the phase 1 and 2 supportive trials. The dose of HEPLISAV was first established in HBV0001 which was a phase 1 randomized dose escalation study of the 1018 ISS Adjuvant in healthy subjects in Canada evaluating 300, 650, 1000, or 3000 mcg of 1018 ISS alone or in combination with 20 mcg of HBsAg in a schedule of 0 and 2 months. This trial demonstrated 3000 mcg 1018 ISS as the effective dose to induce antibodies to HBsAg. Clinical trials DV2-HBV-03, DV2-HBV-05, and DV2-HBV-14 provided additional confirmatory immunogenicity data, showing that this dose of 1018 ISS Adjuvant induced protective levels of HBsAg

antibodies. The number of doses was further evaluated in DV2-HBV-04 which evaluated the 20 mcg HBsAg/3000 mcg 1018 ISS dose 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 injections of HEPLISAV at a dose of 20 mcg HBsAg/3000 mcg 1018 ISS given at 0 and 1 month achieved the desired immunogenicity results in persons 40 years of age and older. The timing of injections was evaluated in DV2-HBV-08 which was a phase 2 randomized trial in adults 18 to 39 years of age in Canada evaluating the 20 mcg HBsAg/3000 mcg 1018 ISS dose of HEPLISAV in a 0, 1 vs. 0, 2 month schedule. This study demonstrated that the 0, 1 month regimen had a similar SPR compared to the 0, 2 month schedule. As the 0, 1 month schedule was thought to promote better adherence, this schedule was used for all subsequent trials.

In these supportive trials, HEPLISAV 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. These findings were indicative of transient, local and specific TLR9 stimulation by 1018 ISS, without indication of systemic inflammation, non-specific antibody induction, or an increased incidence of autoimmune disease.

Following establishment of the dose, and regimen of HEPLISAV in the supportive trials, and a safety profile similar to Engerix-B, a large scale phase 3 trial (DV2-HBV-10) was conducted with the proposed commercial formulation. DV2-HBV-10 was a randomized, active-controlled, observer-blinded, multicenter trial conducted in Canada and Germany in 2415 subjects 18 to 55 years old (1809 subjects randomized to HEPLISAV and 606 to Engerix-B). The primary objective of DV2-HBV-10 was to determine the noninferiority of HEPLISAV given as a 2-dose regimen at 0 and 1 month compared to the licensed comparator vaccine, Engerix-B, given at the approved regimen of 3 doses at 0, 1, and 6 months.

Near the end of DV2-HBV-10, a rare autoimmune event of Wegener's granulomatosis (also known as granulomatosis with polyangiitis) was reported as an SAE possibly related to study medication, which led to the placement of a clinical hold on the HEPLISAV development program. Details of this case and the clinical hold are discussed in detail later in this Briefing Document (Section 6 - SAFETY/Autoimmune considerations; Appendix 6). During this period, the clinical development of HEPLISAV was suspended globally and a complete reassessment of the HEPLISAV safety results was conducted including autoantibody evaluation, clinical lab evaluation, AIAEs, and other AEs that might have been autoimmune. After a thorough assessment, and proposed additional surveillance and evaluation of safety in the next pivotal trial protocol, the clinical hold was lifted by the FDA and the second phase 3 pivotal trial (DV2-HBV-16) was conducted.

DV2-HBV-16 used a similar noninferiority design and randomized 2452 subjects (1969 subjects randomized to HEPLISAV and 483 subjects to Engerix-B) 40 to 70 years of age in the United States and Canada. In this trial, additional intensive prospective surveillance for autoimmune disorders was put in place including an autoimmune signs and symptoms questionnaire administered to every subject at each clinic visit, testing for autoantibodies, expert independent evaluation of any suspected autoimmune event, establishment of an independent SEAC for confirmation of each possible autoimmune event, and an independent DSMB for evaluation of safety. Evaluation of the findings of these intensive prospectively establish safety assessments demonstrated that HEPLISAV and Engerix-B have a similar safety profiles and rate of autoimmune events.

The immunogenicity results presented in this Briefing Document are from the pivotal trials DV2-HBV-10 and DV2-HBV-16. The safety results are reported for the 2 pivotal trials and all the supportive clinical trials. In both pivotal trials, HEPLISAV demonstrated noninferiority to Engerix-B at the primary endpoints. In addition, HEPLISAV provided higher peak seroprotection with fewer doses, higher seroprotection in all subpopulations analyzed, including higher seroprotection in populations known to be hyporesponsive to currently licensed hepatitis B vaccines (older adults, men, diabetes, obese individuals, and smokers), and earlier seroprotection compared to Engerix-B.

3.0 MEDICAL NEED

HBV infection is a serious infectious disease which can result in significant morbidity and mortality. Every year in the United States, an estimated 38000 persons are newly infected and 3000 individuals die from chronic liver disease due to HBV (Daniels, Grytdal et al. 2009; Centers for Disease Control and Prevention 2011; Ioannou 2011; Kowdley, Wang et al. 2012). Currently, up to 2.2 million persons are estimated to be living with HBV infection in the United States (Centers for Disease Control and Prevention 2011) and are the source of transmission to others. Over 90% of current HBV infections occur in adults and approximately 50% of all new HBV infections occur in adults over 40 years of age. Once persons over 40 years old become infected, those with symptomatic, acute HBV infection experience higher mortality than younger persons with a case fatality rate of 1.6% to 4.4% compared with 0.8% in persons 18 to 39 years old (Daniels, Grytdal et al. 2009). In older adults, 45% to 59% of those infected with HBV are at risk of developing chronic hepatitis B infection (Polish, Shapiro et al. 1992; Kondo, Tsukada et al. 1993) and up to 40% of chronically infected individuals will develop cirrhosis, liver failure, or hepatocellular carcinoma. Individuals with diabetes who contract HBV also have a higher rate of symptomatic acute hepatitis, chronic HBV infection, and death compared with individuals without diabetes (Reilly 2011; Sawyer and Hoerger 2011). The case fatality rate among diabetics with symptomatic acute HBV infection can be as high as 5% to 18% (Murphy 2011; Sawyer, 2011).

Since 1982, safe and effective hepatitis B vaccines have been recommended for persons with risk factors for exposure to HBV (Centers for Disease Control and Prevention 1982; Sawyer and Hoerger 2011; Centers for Disease Control and Prevention 2012) Table 2. Recently in 2011, these recommendations added adults with diabetes mellitus to those individuals at risk for infection.

Table 2: Individuals With Risk Factors for Hepatitis B Infection

Risk Factors for Hepatitis B Infection
Individuals at risk for infection by sexual exposure
• Sex partners of HBsAg-positive individuals
• Individuals with more than 1 sex partner in the previous 6 months
• Men who have sex with men
• Individuals with a sexually transmitted disease
Individuals at risk for infection by percutaneous or mucosal exposure to blood
• Household contacts of HBsAg-positive individuals
• Injection-drug users
• Individuals with diabetes 19 through 59 years of age and individuals with diabetes ≥ 60 years of age at the discretion of their physician
• 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: (Centers for Disease Control and Prevention 1982; Sawyer and Hoerger 2011; Centers for Disease Control and Prevention 2012).
HBV = hepatitis B virus; HIV = human immunodeficiency virus.

During the decade after the first hepatitis B vaccine was approved, hepatitis B vaccination had little impact on HBV incidence in adults. Vaccinating individuals at high risk for HBV infection, such as injection-drug users and MSM, before they became infected was not generally feasible due to lack of access to these high risk populations. In addition, even when access to high risk population is possible, adherence to the 3-dose vaccine schedule over 6 months was poor in some groups at high risk for HBV (Kane, Alter et al. 1989; Centers for Disease Control and Prevention 1991).

Recognizing the difficulties of immunizing adults, in 1991 the ACIP recommended including hepatitis B vaccine in universal vaccinations for infants, catch-up use in adolescents, and reiterated the need for hepatitis B vaccination for adults with risk factors for HBV infection (Centers for Disease Control and Prevention 1991). The incidence of HBV infection in the United States decreased 82% from 1990 through 2007, but the incidence of infection in older

adults declined much less than in children and young adults (Mast, Margolis et al. 2005; Daniels, Grytdal et al. 2009).

The universal childhood hepatitis B immunization program has been very successful due to a well-established immunization infrastructure and the fact that over 90% of infants and adolescents have a strong antibody response to hepatitis B vaccine. However, HBV infection continues to be a significant public health problem in adults, in whom most HBV infections occur each year (Daniels, Grytdal et al. 2009; Centers for Disease Control and Prevention 2011; Centers for Disease Control and Prevention 2012). The major modes of transmission of HBV in adults are sexual exposure, particularly among heterosexuals with multiple sex partners and MSM, and parenteral exposure in injection-drug users. Using CDC estimates the annual incidence of HBV infection is highest in men 30 to 45 years old (38.9 per 100000 population), and among racial groups it is highest in blacks (17.6 per 100000 population) (Daniels, Grytdal et al. 2009; Centers for Disease Control and Prevention 2011). The incidence in persons with diabetes is also high (18.9 per 100000).

Most adults today did not receive routine hepatitis B vaccination as an infant or adolescent. The challenge of vaccinating adults against HBV is multifactorial and 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. Second, the individual must then accept and adhere to the 3 dose, 6-month hepatitis B vaccine schedule. And finally, the vaccine must provide seroprotection. The first obstacle continues to be a challenge to healthcare providers and public health authorities. The last 2 obstacles can be overcome with an improved hepatitis B vaccine. The currently approved hepatitis B vaccines (Engerix-B and Recombivax) have provided significant benefits, but they have the following limitations that reduce their effectiveness in adults, both in terms of their immunogenicity and administration (Daley, Hennessey et al. 2009; Ladak, Gjelsvik et al. 2012):

- Reduced immunologic responsiveness to a complete vaccine regimen in certain hyporesponsive populations including older adults, men, persons with diabetes mellitus, obese persons, and smokers (Weber, Rutala et al. 1985; Westmoreland, Player et al. 1990; Wismans, van Hattum et al. 1991; Roome, Walsh et al. 1993; Wood, MacDonald et al. 1993; Bock, Kruppenbacher et al. 1996; Douvin, Simon et al. 1997; Averhoff, Mahoney et al. 1998; Rendi-Wagner, Kundi et al. 2001; Fisman, Agrawal et al. 2002; Wolters, Junge et al. 2003; Van der Wielen, Van Damme et al. 2006; Tohme, Awosika-Olumo et al. 2011);

- Requirement for adherence to a complete 3-dose vaccination schedule over 6 months;

- Prolonged time (> 6 months) before development of seroprotection because only 20% to 30% of individuals are protected after receiving 2 doses (Kane, Alter et al. 1989; Mast, Weinbaum et al. 2006).

3.1 Hyporesponsive Populations

One of the potential reasons for ongoing HBV transmission in adults is that some groups of adults do not respond as well as others to the currently licensed HBV vaccines. Among individuals 40 years of age and older, the proportion who achieve seroprotection after a 3-dose regimen of the currently licensed hepatitis B vaccines declines below 90%, and by age 60 years seroprotection develops in less than 75% of those vaccinated (Averhoff, Mahoney et al. 1998).

Men have reduced immune responses to the currently licensed hepatitis B vaccines compared to women, and men have a higher incidence of HBV infection (Westmoreland, Player et al. 1990; Roome, Walsh et al. 1993; Wood, MacDonald et al. 1993; Bock, Kruppenbacher et al. 1996; Centers for Disease Control and Prevention 2011). The higher incidence is largely due to behaviors that put men at risk for infection such as multiple heterosexual sex partners, MSM, and injecting drugs.

Persons with diabetes mellitus have reduced immune responses to current hepatitis B vaccines and a high incidence of HBV infection. The CDC estimates that 4000 cases of hepatitis B infection occur in individuals with diabetes each year in the United States, which is more than 10% of all reported cases of hepatitis B infections (Murphy 2010; Reilly 2011). Outbreaks of acute hepatitis B in long-term care facilities led to the recent recognition that persons with diabetes are at increased risk of HBV infection due to improper use of devices that monitor blood glucose. Because of the increased incidence of HBV infection in individuals with diabetes and outbreaks of hepatitis B infection in individuals with diabetes in long-term care facilities, the ACIP recently released new recommendations for adults with diabetes: (1) hepatitis B vaccine should be routinely administered to all unvaccinated adults with diabetes 19 to 59 years of age; and (2) hepatitis B vaccine may be administered at the discretion of the treating clinician to unvaccinated adults with diabetes who are 60 years of age and older (Sawyer and Hoerger 2011).

However, in the United States an estimated 77.2% of 14 million individuals with diabetes less than 60 years old (10.8 million individuals) have not received 3 or more doses of HBV vaccine (Centers for Disease Control and Prevention 2012).

3.2 Adherence to Current Dosing Schedules

Generally, older adults are more likely to adhere to the vaccination schedule but have a lower immune response to currently licensed vaccines while younger adults have a good immune response to vaccine but are less likely to adhere to the schedule (Averhoff, Mahoney et al. 1998;

Nelson, Bittner et al. 2009). In actual use, not all individuals receive the complete 3-dose vaccine regimen, leaving them susceptible to HBV infection. In a large retrospective VSD Study of 88711 hepatitis B vaccine recipients ≥ 18 years old, 81% received 2 or more doses and only 64% of those vaccinated received all 3 doses of vaccine during an 8-year study period (Nelson, Bittner et al. 2009) (Appendix 3). In a study of an STD clinic population of 3538 MSM who were given hepatitis B vaccination using an accelerated 0, 1, 4-month schedule, 64% of the men received 2 or more doses and only 43% of the men received all 3 doses of a vaccine during a 5-year study period (Gunn, Lee et al. 2007).

3.3 Populations Needing Rapid Protection

For the currently licensed vaccines, the third dose of vaccine, which is administered 6 months after the initial dose, is required for the majority of individuals to achieve seroprotection. Before the third dose at 6 months, only 20% to 30% of older adults vaccinated have antibody levels of 10 mIU/mL or higher. The long time needed to achieve seroprotection may be an issue for individuals at risk of imminent exposure to HBV, including healthcare workers and emergency first-responders, older adults with diabetes who are entering long-term care facilities, travelers to countries with a high prevalence of chronic hepatitis B, and those with behavioral risk factors for infection including heterosexuals with multiple sex partners, MSM, and injection-drug users.

4.0 SCIENTIFIC RATIONALE

HEPLISAV is composed of rHBsAg and 1018 ISS Adjuvant. The rHBsAg in HEPLISAV 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 and is similar to the rHBsAg in several currently licensed hepatitis B vaccines, including Engerix-B and Recombivax. The desired biological activity of rHBsAg is to generate protective antibodies to the 'a' determinant of the S protein. The 1018 ISS Adjuvant is a synthetic oligonucleotide with immunostimulatory cytosine phosphoguanosine (CpG) motif and is a TLR9 agonist. The desired biological activity of 1018 ISS Adjuvant is to enhance generation of antibodies to rHBsAg by activating the innate immune system through stimulation of TLR9.

4.1 Background

Great effort is directed at the identification, isolation, and manufacture of specific antigens that are used in vaccines. Recombinant hepatitis B vaccines were the first examples of this approach, and the development and licensure of these vaccines represented an important milestone in vaccinology. As the first vaccines manufactured with recombinant DNA technology, they represented a new degree of purity, using a single protein in a vaccine.

Modern molecular biology enables the production of these proteins with high purity, but without effective adjuvants, they may not induce an immune response. The most commonly used adjuvant is alum. Alum has a good safety record but has immunologic limitations.

Nucleic acids have a long history as potential adjuvants, starting with poly I:C and poly A:U in the 1960s and continuing with the DNA fraction of BCG and oligodeoxynucleotide (ODN) sequences in the 1980s. The discovery of the ability of bacterial plasmid DNA to increase antibody response and polarize the response toward Th1 and away from Th2 led to the founding of Dynavax Technologies and to the eventual development of 1018 ISS. It is now known that the potent adjuvant activity of 1018 ISS is mediated by a pattern recognition receptor, TLR9 (Higgins, Marshall et al. 2007).

When a host encounters a viral or bacterial pathogen, recognition is achieved primarily through early sentinels called pattern recognition receptors (PRRs), molecules that bind with high avidity to pathogen-associated molecular patterns, including lipid, carbohydrate, peptide, and nucleic acid structures. One of the best-studied PRR families is the TLR family, transmembrane signaling molecules that play a key role in the initiation of innate immune responses and also influence the later and more antigen-specific adaptive immune response (Trinchieri and Sher 2007). Most TLRs are expressed on the cell surface, but a subset of TLRs is expressed in the

endosomal compartment of the cell, into which foreign pathogens can be endocytosed and enzymatically degraded. Short RNA or DNA segments from these pathogens can be presented as ligands for this TLR subset.

The most prominent and well-characterized TLR within this subset is TLR9. In rats and mice, TLR9 is widely expressed on nearly all antigen-presenting cells (APCs) as well as T cells (Boonstra, Rajsbaum et al. 2006). In humans and other primates, TLR9 distribution is primarily limited to plasmacytoid dendritic cells (PDCs) and memory B cells (Hornung, Rothenfusser et al. 2002; Kadowaki, 2001). TLR9 recognizes unmethylated CpG-containing DNA (Latz, Schoenemeyer et al. 2004). A CpG dinucleotide is an absolute requirement for TLR9 activation. Compared with mammalian DNA, bacterial and viral DNA contain a high frequency of unmethylated CpG sequences. Therefore, TLR9 can be activated by DNA viruses, such as herpes simplex virus 1 and 2 (Lund, Sato et al. 2003)and murine cytomegalovirus (Krug, French et al. 2004); bacterial DNA from microbes, such as *Streptococcus pneumoniae* (Mogensen, Paludan et al. 2006), *Propionibacterium acnes* (Kalis, Gumenscheimer et al. 2005), and *Mycobacterium tuberculosis* (von Meyenn, Schaefer et al. 2006); and live attenuated viral or bacterial vaccines. Based on the observation that bacterial plasmid DNA alone can also stimulate TLR9, bacterial DNA or short, synthetic ODN sequences engineered with 1 or more CpG motifs (Zelenay, Elias et al. 2003)can also be used as TLR9 agonists. CpG-containing ODNs are referred to as CpG-ODNs or immunostimulatory sequence (ISS). The ISS is captured in a non-specific manner by DNA receptors and transferred into the endosomal compartment. The potent Th1 immune response produced by CpG activation of the innate immune system supported the potential of ISS as vaccine adjuvants as well as potential immunomodulators in broad therapeutic applications against cancer, infectious diseases, asthma, and allergies.

4.2 TLR9 Stimulation: Mechanism of Action and Therapeutic Rationale

TLR9 stimulation by either foreign DNA or ISS induces maturation of pDCs into efficient antigen-presenting cells, increasing their expression of CD40, CD86, MHC-I, and MHC-II (Hartmann, Weiner et al. 1999) and is also a potent inducer of type I interferons (IFNs, specifically IFN-alpha) and interleukin (IL)-12, pro-inflammatory cytokines important for the differentiation of naïve T-cells into Th1 cells (Duramad, Fearon et al. 2003; Ashkar, 2002). TLR9 agonists co-administered with antigen can induce antigen-specific antibody production and increased Th1 immune responses through TLR9-mediated pDC activation (Raz, Tighe et al. 1996).

Several groups have evaluated the immune response to CpG-ODNs admixed with or conjugated to recombinant antigens (Tighe, Takabayashi et al. 2000; Alcon, Baca-Estrada et al. 2005; Heit, Schmitz et al. 2005; Hayashi, 2005; Jerome, Graser et al. 2006; Standley, Mende et al. 2007). The CpG-ODN CPG7909 has been shown to enhance antibody responses to the recombinant

hepatitis B vaccine Engerix-B (Cooper, Davis et al. 2004; Cooper, Davis et al. 2005) as well as to malaria, pneumococcus, and anthrax antigens (Ellis, Mullen et al. 2009;Sogaard, 2010; Rynkiewicz, Rathkopf et al. 2011). 1018 ISS, the ISS and TLR9 agonist used as the adjuvant in HEPLISAV, has been evaluated in several other clinical settings, as a cancer immunotherapeutic by the subcutaneous route, as an asthma immunotherapeutic by the aerosol route, as an allergy immunotherapeutic conjugated to ragweed, and as a vaccine adjuvant in HEPLISAV. These other 1018 ISS development programs provided important information for the HEPLISAV program. In these programs, 1263 subjects received 1018 ISS, including 149 in the cancer and asthma programs who received higher doses and more intensive regimens of 1018 ISS, and 127 pediatric patients in the ragweed immunotherapy program. No safety concerns were observed in these development programs.

In the ragweed immunotherapy program, the largest of the non-HEPLISAV programs, 1018 ISS was conjugated to Amb a 1, the major allergen of ragweed. The resulting Amb a 1-immunostimulatory phosphorothioate oligodeoxyribonucleotide conjugate (AIC) induced a shift of ragweed-specific responses from Th2 toward Th1, with a decrease in eosinophilia and nasal inflammatory response. Systemic adverse effects were not observed, and no increase in the titer of ANA, or anti-dsDNA or anti-ssDNA was detected (Simons, Shikishima et al. 2004; Tulic, Fiset et al. 2004; Creticos, Schroeder et al. 2006).

In the non-Hodgkin's lymphoma program, which used 1018 ISS alone at doses approximately 12 times the dose of 1018 ISS in HEPLISAV, 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, with no systemic toxicity (Friedberg, Kim et al. 2005).

The selection of 1018 ISS as a vaccine adjuvant was based on its specific pattern of immunostimulatory activity. 1018 ISS is a "B-class" ISS, which is effective at inducing PDC maturation, but induces relatively lower levels of proinflammatory cytokines than other classes of ISS (Higgins, Marshall et al. 2007).

The selection of HBsAg as the vaccine antigen to combine with 1018 ISS was based on several criteria. A vaccine given to antigen-naïve individuals, as in the case of hepatitis B vaccine, rather than individuals with immunologic memory, as in the case of seasonal influenza vaccine, would allow for better evaluation of the effect of 1018 ISS on the immune response. Evaluation in adults was preferred over pediatric subjects. A known protective antigen was preferred over an antigen not known to be protective. A recombinant subunit antigen, lacking innate immune ligands, was preferred to an inactivated pathogen. A known correlate of protection was preferred over an unknown correlate. A vaccine that could be improved was preferred to one that was highly immunogenic. A vaccine with an excellent safety record as the comparator would allow for optimal safety signal detection. Finally, a vaccine recommended for at-risk persons, rather

than universal immunization, would allow for gradual expansion of the safety database post-approval and careful pharmacovigilance evaluation. Hepatitis B vaccine satisfied all these considerations and was selected as the model to evaluate 1018 ISS as an adjuvant.

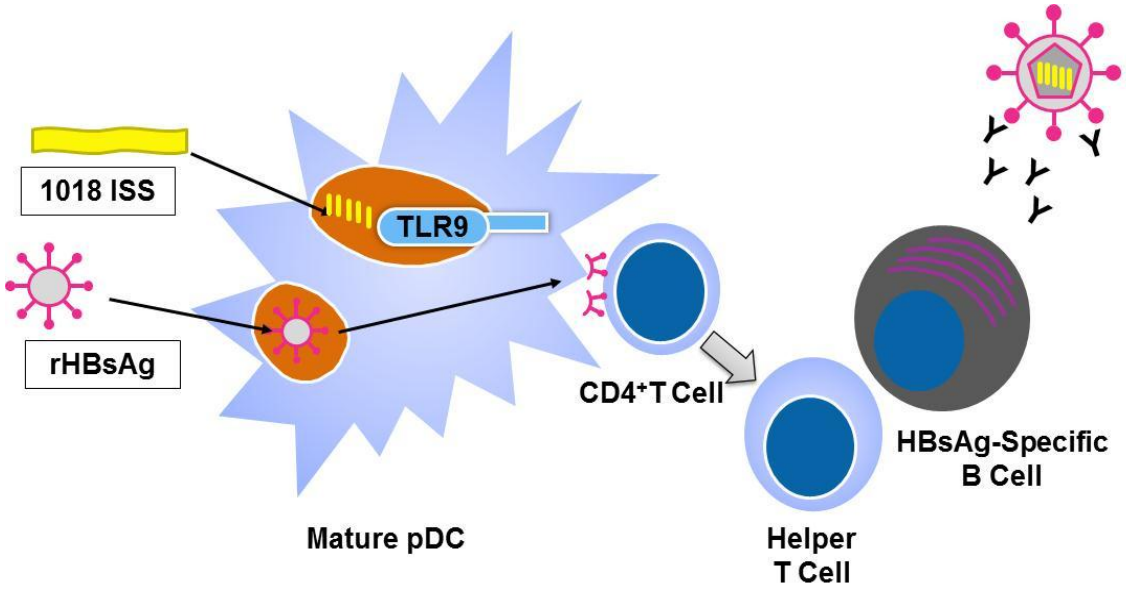
In preclinical studies, the ability of 1018 ISS to induce strong humoral immune responses to HBsAg was consistently demonstrated in mice, rats, and baboons. In addition, the 1018 ISS-induced immune response in mice was characterized by the preferential induction of IgG2a antibodies, indicative of a Th1 response.

As the adjuvant in HEPLISAV, 1018 ISS is thought to have the following actions:

- Stimulating TLR9 in pDCs that have taken up rHBsAg
- Converting pDCs into activated dendritic cells that present HBsAg epitopes to CD4+ T cells
- Promotes differentiation of CD4+ T cells to helper T cells through IFN-alpha and IL-12, leading to proliferation and antibody secretion by HBsAg-specific B cells.

Figure 1 presents this proposed mechanism of action for 1018 ISS Adjuvant.

Figure 1: Mechanism of Action for 1018 ISS Adjuvant



1018 ISS thus targets a single, well-defined, pattern-recognition receptor of the innate immune system. The response to 1018 ISS mimics a component of the regularly occurring immune response to viral and bacterial pathogens and live attenuated viral vaccines.

5.0 IMMUNOGENICITY

The goal of effective HBV vaccines is to induce anti-HBs. Based on results from the early HBV vaccine efficacy trials, achieving a post-vaccination anti-HBs concentration of ≥ 10 mIU/mL has been shown to correlate with protection against HBV infection (Centers for Disease Control and Prevention 1982; Francis, 1982; Szmuness, Stevens et al. 1982; Centers for Disease Control and Prevention 1993; Jack, Hall et al. 1999). Thus, the HEPLISAV clinical development program, like other clinical development programs for hepatitis B vaccines (Merck & Co. 1987;SmithKline Biologicals, 1989), has used the seroprotection rate or SPR, the proportion of individuals achieving an anti-HBs level ≥10 mIU/mL after vaccination, as the immune correlate of protection

Healthy individuals who develop anti-HBs concentrations ≥ 10 mIU/mL after vaccination also develop long-term protection even if their antibody levels subsequently decline to < 10 mIU/mL (Mast and Ward 2008; Leuridan and Van Damme 2011). An important indicator of the long-term effectiveness of a hepatitis B vaccine in a healthy population is the peak SPR after vaccination. For individuals who are at immediate risk of HBV exposure, the shortest time to seroprotection is desirable. In view of these considerations, this document presents the SPR at the primary endpoint, the peak SPR, and the SPR at early time points after vaccination.

The immunogenicity achieved with HEPLISAV has been established in the 2 pivotal trials, DV2-HBV-10 and DV2-HBV-16. Compared to subjects vaccinated with 3 doses of Engerix-B over 6 months, subjects vaccinated with 2 doses of HEPLISAV administered over 1 month achieved:

- Noninferiority of the seroprotection rate at the primary endpoint
- Significantly higher seroprotection
- Higher seroprotection in all subpopulations analyzed
- Significantly higher seroprotection in populations hyporesponsive to currently licensed HBV vaccines (older adults, men, persons with diabetes, obese persons, and smokers)
- Earlier seroprotection

5.1 Study Designs and Baseline Information for the Pivotal Trials

The demonstration of seroprotection in the 2 pivotal trials relies on head-to-head comparisons between HEPLISAV and Engerix-B. Both trials employed a noninferiority trial design and were

powered to demonstrate the noninferiority of HEPLISAV compared to Engerix-B (HEPLISAV SPR minus Engerix-B SPR) with a noninferiority margin of -10%.

5.1.1 Features Common to the Two Pivotal Trials

Pivotal trials DV2-HBV-10 and DV2-HBV-16 were both randomized, subject- and observer-blinded, active-controlled, parallel-group, multicenter trials to compare immune responses following injection with 2 doses of HEPLISAV and 1 dose of placebo to 3 doses of Engerix-B. In these trials, HEPLISAV was administered at 0 and 4 weeks and a dose of placebo was administered at 24 weeks. Engerix-B was administered at 0, 4, and 24 weeks. Engerix-B was chosen as the licensed comparator vaccine for these trials because it is approved by the regulatory authorities in the countries where the trials were to be conducted, and is the hepatitis B vaccine used most frequently by clinicians in the United States, Canada, and Europe. Levels of anti-HBs were determined using a validated commercial assay.

Eligible subjects in both trials were generally healthy volunteers (no clinically debilitating acute or chronic illnesses) who were serum negative for HBsAg, anti-HBs, and anti-HBc; had no history of HBV infection or had no prior immunization with any hepatitis B vaccine.

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. In addition, an unblinded study monitor with no other study responsibilities confirmed drug accountability. In both trials, the designated unblinded staff was not involved in assessing safety and was instructed not to communicate treatment assignments to the personnel responsible such assessments.

5.1.2 DV2-HBV-10

The primary immunogenicity objective for DV2-HBV-10 was to demonstrate noninferiority of the SPR at Week 12 following injection with HEPLISAV at Weeks 0 and 4 (placebo at Week 24) to the SPR at Week 28 following injection with Engerix-B at Weeks 0, 4, and 24.

Eligible subjects were adults 18 through 55 years old. Subjects were randomized in a 3:1 ratio to receive HEPLISAV or Engerix-B. 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 2910 individuals were screened, 2415 subjects were randomized (1809 to HEPLISAV and 606 to Engerix-B), and 2334 subjects completed all visits.

5.1.3 DV2-HBV-16

The primary immunogenicity objective for DV2-HBV-16 was to demonstrate the noninferiority of the immune response to HEPLISAV vaccination as measured by 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).

Eligible subjects were adults 40 through 70 years old. Subjects were randomized in a 4:1 ratio to receive HEPLISAV or Engerix-B stratified by age group: 40 to 49 years, 50 to 59 years, or 60 to 70 years and by site. Subjects were followed for 52 weeks after the first injection and returned to the clinical 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 3793 individuals were screened, 2452 subjects were randomized (1969 to HEPLISAV and 483 to Engerix-B), and 2269 subjects (92.5%) completed all visits.

5.1.4 Analysis Populations in Both Trials

In the comparison of the 2-dose regimen of HEPLISAV with the 3-dose regimen of Engerix-B, the PP population was chosen for the primary endpoint analyses. The PP population was defined prior to unblinding to comprise those subjects who received study treatment within the protocol-defined windows, received all study injections as randomized, had no major protocol deviations, and had anti-HBs levels obtained within visit windows at baseline and at the visits for the primary endpoints. The PP population consisted of 1557 HEPLISAV subjects and 533 Engerix-B subjects for DV2-HBV-10, and 1513 HEPLISAV subjects and 359 Engerix-B subjects for DV2-HBV-16 (Table 3).

The modified intent-to-treat (mITT) population was defined as all subjects who received at least 1 study injection and had at least 1 post-injection immunogenicity evaluation. The mITT population consisted of 1789 HEPLISAV subjects and 603 Engerix-B subjects for DV2-HBV-10, and 1947 HEPLISAV subjects and 476 Engerix-B subjects for DV2-HBV-16. In the pooled mITT population there were 3736 HEPLISAV subjects and 1079 Engerix-B subjects (Table 3). The PP population was chosen for the evaluations of the primary objective because the complete, 3-dose regimen of Engerix-B is necessary to induce seroprotection in most subjects. Those who did not receive the third dose of Engerix-B at Week 24 would be much less likely to achieve seroprotection than subjects in the HEPLISAV group who received 2 doses of HEPLISAV and missed the placebo injection at Week 24. To be included in the PP population, subjects had to receive their third study injection regardless of treatment group. Non-adherence with the third dose would affect the SPR of Engerix-B but not HEPLISAV, with results likely favoring

HEPLISAV if the mITT population was used for the primary endpoint. Therefore, the most conservative analysis of the comparative seroprotection of HEPLISAV and Engerix-B uses the PP population.

For analyses of subpopulations, the mITT populations of DV2-HBV-10 and DV2-HBV-16 were pooled to provide a larger sample size to assess seroprotection results, particularly in those subpopulations that are known to have reduced responses to currently licensed hepatitis B vaccines (eg, older adults, men, persons with diabetes, obese persons, smokers). The pooling of the mITT populations across the 2 trials for these analyses is supported by the following:

- In each trial, the results for the mITT population were consistent with the results for the PP population.
- The SPRs in the 40 to 55-year-olds in the mITT populations — the age group enrolled in both trials — were similar across the trials.

5.1.5 Subject Disposition

In DV2-HBV-10 and DV2-HBV-16, discontinuation rates were low and were comparable for subjects randomized to receive HEPLISAV or Engerix-B. In DV2-HBV-10, 3.5% of HEPLISAV subjects and 3.0% of Engerix-B subjects discontinued from the trial. In the longer DV2-HBV-16 trial, 7.7% of HEPLISAV subjects and 6.6% of Engerix-B subjects discontinued from the trial. The most frequent reason for discontinuation from both trials was loss to follow-up (1.7% in each treatment group in DV2-HBV-10; and 4.1% of HEPLISAV subjects and 2.7% of Engerix-B subjects in DV2-HBV-16). The second most frequent reason for discontinuation from both trials was consent withdrawn (1.0% of HEPLISAV subjects and 0.3% of Engerix-B subjects in DV2-HBV-10; and 2.3% of HEPLISAV subjects and 2.5% of Engerix-B subjects in DV2-HBV-16). Across both trials, 94.3% of HEPLISAV and 95.4% of Engerix-B subjects completed treatment (Table 3).

Table 3: Subject Disposition in DV2-HBV-10 and DV2-HBV-16

Study	DV2-HBV-10		DV2-HBV-16		Total	Total
Disposition	**HEPLISAV n (%)**	**Engerix-B n (%)**	**HEPLISAV n (%)**	**Engerix-B n (%)**	**HEPLISAV n (%)**	**Engerix-B n (%)**
Randomized	1809 (100)	606 (100)	1969 (100)	483 (100)	3778 (100)	1089 (100)
Completed	1746 (96.5)	588 (97.0)	1818 (92.3)	451 (93.4)	3564 (94.3)	1039 (95.4)
Discontinued	63 (3.5)	18 (3.0)	151 (7.7)	32 (6.6)	214 (5.7)	50 (4.6)
Adverse Event	2 (0.1)	2 (0.3)	1 (< 0.1)	0	3 (< 0.1)	2 (0.2)
Subject noncompliance	3 (0.2)	2 (0.3)	6 (0.3)	3 (0.6)	9 (0.2)	5 (0.5)
Consent withdrawn	18 (1.0)	2 (0.3)	45 (2.3)	12 (2.5)	63 (1.7)	14 (1.3)
Lost to follow-up	30 (1.7)	10 (1.7)	81 (4.1)	13 (2.7)	111 (2.9)	23 (2.1)
Death	0	0	1 (0.1)	1 (0.2)	1 (< 0.1)	1 (0.1)
Protocol violation	2 (0.1)	0	3 (0.2)	1 (0.2)	5 (0.1)	1 (0.1)
Other	8 (0.4)	2 (0.3)	14 (0.7)	2 (0.4)	22 (0.6)	4 (0.4)
PP Population	1557 (86.1)	533 (88.0)	1513 (76.8)	359 (74.3)	3070 (81.3)	892 (81.9)
mITT Population	1789 (98.9)	603 (99.5)	1947 (98.9)	476 (98.6)	3736 (98.9)	1079 (99.1)
Safety Population	1809 (100)	606 (100)	1968 (99.9)	481 (99.6)	3777 (99.9)	1087 (99.8)

Data Source: ISE Table 2.7.3-4.
mITT = modified intent-to-treat; n = number of subjects in the group; PP = per-protocol.

5.1.6 Demographic and Baseline Characteristics

The demographic and baseline characteristics, including those most likely to affect seroprotection (age, male sex, body mass index [BMI] $\geq$ 30 kg/m^2, diabetes, smoking history), were balanced between the HEPLISAV and Engerix-B groups in the pivotal trials and were not expected to bias the seroprotection results (Table 4 and Table 5).

In DV2-HBV-10, in the HEPLISAV and Engerix-B groups, respectively: The mean ages were 40.3 years and 40.4 years; 53.8% and 58.3% were women; 94.1% and 92.1% were white; 35.3% and 36.0% were smokers; the mean BMI was 27.3 kg/m^2 and 27.6 kg/m^2; and 2.9% and 3.2% of subjects had type 2 diabetes mellitus.

In DV2-HBV-16, in the HEPLISAV and Engerix-B groups, respectively: The mean ages were 53.8 years and 54.2 years; 52.2% and 50.4% were women; 83.0% and 84.4% were white; 20.4% and 21.2% were smokers; and 8.8% and 8.4% of subjects had type 2 diabetes mellitus. The mean BMI was 29.9 kg/m^2 in both treatment groups.

Table 4: Demographic and Baseline Characteristics in DV2-HBV-10 and DV2-HBV-16 (PP Population and Pooled)

Study	DV2-HBV-10		DV2-HBV-16		Total	Total
	HEPLISAV (N = 1557)	Engerix-B (N = 533)	HEPLISAV (N = 1123)	Engerix-B (N = 359)	HEPLISAV (N = 2680)	Engerix-B (N = 892)
Age (years) n (%)						
18 – 39	676 (43.4)	226 (42.4)	0	0	676 (25.2)	226 (25.3)
40 – 70	881 (56.6)	307 (57.6)	1123 (100)	359 (100)	2004 (74.8)	666 (74.7)
Mean (SD)	40.3 (9.25)	40.4 (8.88)	53.8 (7.78)	54.2 (7.84)	45.9 (10.95)	46.0 (10.85)
Range (years)	18, 55	18, 55	40, 70	40, 70	18, 70	18, 70
Sex, n (%)						
Women	837 (53.8)	311 (58.3)	586 (52.2)	181 (50.4)	1423 (53.1)	492 (55.2)
Men	720 (46.2)	222 (41.7)	537 (47.8)	178 (49.6)	1257 (46.9)	400 (44.8)
Race, n (%)						
White	1465 (94.1)	491 (92.1)	932 (83.0)	303 (84.4)	2397 (89.4)	794 (89.0)
Black	29 (1.9)	17 (3.2)	165 (14.7)	48 (13.4)	194 (7.2)	65 (7.3)
Asian	35 (2.2)	18 (3.4)	12 (1.1)	2 (0.6)	47 (1.8)	20 (2.2)
Other[a]	28 (1.8)	7 (1.3)	14 (1.2)	6 (1.7)	42 (1.6)	13 (1.5)
Ethnicity, n (%)						
Hispanic	36 (2.3)	22 (4.1)	64 (5.7)	22 (6.1)	100 (3.7)	44 (4.9)
Non-Hispanic or Non-Latino	1521 (97.7)	511 (95.9)	1058 (94.2)	337 (93.9)	2579 (96.2)	848 (95.1)
Missing	0	0	1 (0.1)	0	1 (< 0.1)	0
Medical History, n (%)						
Diabetes mellitus	45 (2.9)	17 (3.2)	99 (8.8)	30 (8.4)	144 (5.4)	47 (5.3)
BMI (kg/m^2)						
N	1555	532	1121	359	2676	891
Mean (SD)	27.3 (5.71)	27.6 (6.15)	29.9 (6.37)	29.9 (6.53)	28.4 (6.14)	28.6 (6.41)
Range	15, 58	16, 63	14, 56	19, 61	14, 58	16, 63
BMI Stratum, n (%)						
< 30 kg/m^2	1171 (75.2)	386 (72.4)	627 (55.8)	205 (57.1)	1798 (67.1)	591 (66.3)
≥30 kg/m^2	384 (24.7)	146 (27.4)	494 (44.0)	154 (42.9)	878 (32.8)	300 (33.6)
Smoker, n (%)[b]						
Yes	550 (35.3)	192 (36.0)	229 (20.4)	76 (21.2)	779 (29.1)	268 (30.0)
No	1007 (64.7)	341 (64.0)	894 (79.6)	283 (78.8)	1901 (70.9)	624 (70.0)

Data Source: ISE Table 2.7.3-6.
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] Includes American Indian/Alaska Native, Native Hawaiian or other Pacific Islander, and Other race.
[b] Implies regular smoking within 1 year before enrollment in the study.

The demographics of subjects in the pooled mITT population were similar to those in the PP population (Table 5) and were balanced between the 2 treatment groups. For HEPLISAV and Engerix-B, respectively: Mean ages were 47.2 years and 46.0 years; 52.5% and 54.1% were women; 87.8% and 88.1% were white; 28.6% and 31.1% were smokers; the mean BMI was 28.8 kg/m^2 and 28.6 kg/m^2; and 6.3% and 5.4% had type 2 diabetes mellitus.

Table 5: Demographic and Baseline Characteristics in DV2-HBV-10 and DV2-HBV-16 (Pooled mITT Analysis Population)

	HEPLISAV n (%) (N = 3736)	**Engerix-B n (%) (N = 1079)**
Age (years)		
18 – 39	812 (21.7)	274 (25.4)
40 – 70	2924 (78.3)	805 (74.6)
Mean (SD)	47.2 (11.17)	46.0 (11.01)
Range	18, 70	18, 70
Sex, n (%)		
Women	1961 (52.5)	584 (54.1)
Men	1755 (47.5)	495 (45.9)
Race, n (%)		
White	3282 (87.8)	951 (88.1)
Black	327 (8.8)	86 (8.0)
Asian	66 (1.8)	26 (2.4)
Other[a]	61 (1.6)	16 (1.5)
Ethnicity, n (%)		
Hispanic	162 (4.3)	56 (5.2)
Non-Hispanic or Non-Latino	3572 (95.6)	1023 (94.8)
Missing	2 (0.1)	0
Medical History, n (%)		
Diabetes mellitus	235 (6.3)	58 (5.4)
BMI (kg/m^2)		
N	3731	1077
Mean (SD)	28.8 (6.20)	28.6 (6.39)
Range	14, 67	16, 63
BMI Stratum, n (%)		
< 30 kg/m^2	2420 (64.8)	707 (65.5)
≥ 30 kg/m^2	1311 (35.1)	370 (34.3)
Smoker, n (%)[b]		
Yes	1067 (28.6)	336 (31.1)
No	2669 (71.4)	743 (68.9)

Data Source: ISE Table 50, ISS Table 2.1.7 and post-hoc analysis.
BMI = body mass index; mITT= modified intent-to-treat; n = number of subjects with characteristic; N = number of subjects in the population in the treatment group; SD = standard deviation.
[a] Other race includes American Indian/Alaska Native, Native Hawaiian or other Pacific Islander, and other race.
[b] Implies regular smoking within 1 year before enrollment in the study.

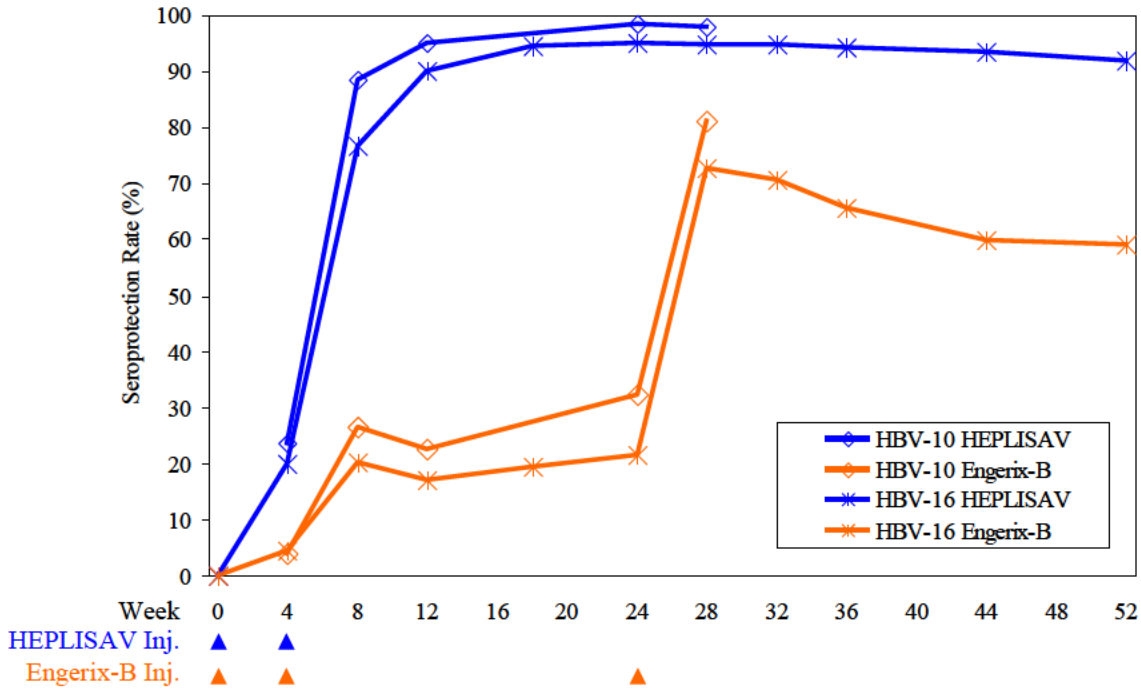
5.2 Immunogenicity Results

5.2.1 Overview of SPR Results in the PP Population

In both trials HEPLISAV demonstrated noninferiority to Engerix-B as measured by the SPRs at the primary endpoints. In addition, the peak SPR and the SPR at each visit were statistically significantly higher in the HEPLISAV group than in the Engerix-B group in each trial.

Figure 2 presents comparisons of the SPRs by visit in DV2-HBV-10 and DV2-HBV-16.

Figure 2: Seroprotection Rates by Visit in DV2-HBV-10 and DV2-HBV-16 (PP Population)



Data Source: ISE Figure 2.7.3-2.
Inj = injection; PP = per-protocol.
Subjects were followed for 28 weeks after the first injection in DV2-HBV-10 and for 52 weeks in DV2-HBV-16.

5.2.2 Primary Endpoint Result

In the pivotal phase 3 trials, 2 doses of HEPLISAV administered over 4 weeks induced a SPR that was noninferior than that induced by 3 doses of Engerix-B administered over 24 weeks.

In DV2-HBV-10, the SPR in the HEPLISAV group at Week 12 was 95.0% and the SPR in the Engerix-B group at Week 28 was 81.1%. The difference between SPRs (HEPLISAV minus Engerix-B) was 13.9% (95% CI: 10.6%, 17.6%), which met the prospectively-defined criterion for the primary endpoint of noninferiority (lower limit of the 95% CI > -10%) (Table 6).

Table 6: Seroprotection Rates at the Primary Endpoint in DV2-HBV-10 (PP Population)

Study	DV2-HBV-10		
	HEPLISAV[a]	Engerix-B[a]	
	SPR (%) (95% CI)[b] (N = 1557)	SPR (%) (95% CI)[b] (N = 533)	Difference in SPRs (%) (HEPLISAV-Engerix-B) (95% CI)[c]
Primary endpoint[d]	95.0 (94.0, 96.1)	81.1 (77.7, 84.4)	13.9 (10.6, 17.6)

Data Source: Clinical Study Report for DV2-HBV-10, Section 14.1.2, Table 26.1B.
CI = confidence interval; N = number of subjects in the analysis population in the group; PP = per protocol; SPR = seroprotection rate.
[a] Study injections of HEPLISAV were given at Weeks 0, 4, and 24 (placebo); of Engerix-B at Weeks 0, 4, and 24.
[b] 95% CIs were calculated using the Clopper-Pearson method.
[c] Estimated difference and associated CI is based on a statistical analysis model adjusting for age groups (18 through 39 years versus 40 through 55 years). The stratified Miettinen and Nurminen method was used to calculate the 95% CIs.
[d] Primary endpoint in DV2-HBV-10 was seroprotection rate at Week 12 for HEPLISAV and Week 28 for Engerix-B.

In DV2-HBV-16, the SPR in the HEPLISAV group at Week 12 was 90.0% and the SPR in the Engerix-B group at Week 32 was 70.5%. The difference between SPRs (HEPLISAV minus Engerix-B) was 19.6% (95% CI: 14.7%, 24.7%), which met the prospectively-defined criterion for the primary endpoint of noninferiority (lower limit of the 95% CI > -10%) (Table 7).

Table 7: Seroprotection Rates at the Primary Endpoint in DV2-HBV-16 (PP Population)

Study	DV2-HBV-16		
	HEPLISAV[a]	Engerix-B[a]	
	SPR (%) (95% CI)[b] (N = 1123)	SPR (%) (95% CI)[b] (N = 359)	Difference in SPRs (%) (HEPLISAV-Engerix-B) (95% CI)[c]
Primary endpoint[d]	90.0 (88.1, 91.7)	70.5 (65.5, 75.1)	19.6 (14.7, 24.7)

Data Source: Clinical Study Report for DV2-HBV-16, Section 14.2.
CI = confidence interval; N = number of subjects in the analysis population in the group; PP = per protocol; SPR = seroprotection rate.
The PP Population for the HEPLISAV group in DV2-HBV-16 is the Noninferiority PP Population excluding subjects who received Lot TDG006.
[a] Study injections of HEPLISAV were given at Weeks 0, 4, and 24 (placebo); of Engerix-B at Weeks 0, 4, and 24.
[b] 95% CIs were calculated using the Clopper-Pearson method.
[c] Two-sided 95% CIs of the difference in seroprotection rates between the HEPLISAV group at 12 weeks and the Engerix-B group at 32 weeks were calculated using the Newcombe score method with continuity correction.
[d] Primary endpoint in DV2-HBV-16, the primary endpoint was Week 12 for HEPLISAV and Week 32 for Engerix-B.

5.2.3 Seroprotection Rate by Visit

In both pivotal trials, the peak SPR in the HEPLISAV group occurred at Week 24, 20 weeks after the last dose of HEPLISAV and was significantly higher than the peak SPR in the Engerix-B group, which occurred at Week 28, 4 weeks after the last dose of Engerix-B. In addition, at each trial visit, the SPR in the HEPLISAV group was significantly higher than in the Engerix-B group (Table 8).

In the DV2-HBV-10 PP population, the peak SPR induced by HEPLISAV was 98.3% and the peak SPR induced by Engerix-B was 81.1%. The difference in SPRs was 17.2% (95% CI: 14.0%, 20.8%). Over the course of the DV2-HBV-10 study, the SPR in the HEPLISAV group remained significantly higher than the SPR in the Engerix-B group (Table 8). In the DV2-HBV-16 PP population, the peak SPR induced by HEPLISAV was 95.1% and the peak SPR induced by Engerix-B was 72.8%. The difference in SPRs was 22.3% (95% CI: 17.7%, 27.2%). Over the course of the DV2-HBV-16 study, the SPR in the HEPLISAV group remained significantly higher than the SPR in the Engerix-B group (Table 8).

HEPLISAV also provided earlier seroprotection. After 2 study injections, at Week 8, in DV2-HBV-10, the SPR in the HEPLISAV group (88.5%) was not only significantly higher than the SPR in the Engerix-B group at Week 8 (26.4%; difference = 62.1%, 95% CI: 58.0%, 66.0%), but

was also higher than the peak SPR in the Engerix-B group at Week 28 (81.1%). At Week 8, in DV2-HBV-16, the SPR in the HEPLISAV group was 76.6% and was not only significantly higher than the SPR in the Engerix-B group at Week 8 (20.3%; difference = 56.2%, 95% CI: 51.1%, 60.7%), but was also higher than the peak SPR in the Engerix-B group at Week 28 (72.8%).

Table 8: Seroprotection Rates by Visit in DV2-HBV-10 and DV2-HBV-16 (PP Population)

Trial	DV2-HBV-10					DV2-HBV-16				
Sub group	18 to 55 Years					40 to 70 Years				
	HEPLISAV[a]		Engerix-B[b]			HEPLISAV[a]		Engerix-B[b]		
Visit	n/N	SPR (%) (95% CI)[c]	n/N	SPR (%) (95% CI)[c]	Difference in SPRs (%) (HEPLISAV-Engerix-B) (95% CI)[d]	n/N	SPR (%) (95% CI)[e]	n/N	SPR (%) (95% CI)[e]	Difference in SPRs (%) (HEPLISAV-Engerix-B) (95% CI)[f]
Peak SPR[g]	1521/1548	98.3 (97.5, 98.8)	432/533	81.1 (77.5, 84.3)	17.2 (14.0, 20.8)	1068/1123	95.1 (93.7, 96.3)	260/357	72.8 (67.9, 77.4)	22.3 (17.7, 27.2)
Week 4	366/1548	23.6 (21.5, 25.8)	21/531	4.0 (2.3, 5.6)	19.7 (16.8, 22.4)	223/1123	19.9 (17.6, 22.3)	16/359	4.5 (2.6, 7.1)	15.4 (11.9, 18.4)
Week 8	1372/1550	88.5 (86.9, 90.1)	140/531	26.4 (22.6, 30.1)	62.1 (58.0, 66.0)	859/1122	76.6 (74.0, 79.0)	73/359	20.3 (16.3, 24.9)	56.2 (51.1, 60.7)
Week 12[h]	1480/1557	95.0 (94.0, 96.1)	120/533	22.5 (19.0, 26.1)	72.5 (68.6, 76.0)	1011/1123	90.0 (88.1, 91.7)	61/359	17.0 (13.3, 21.3)	73.0 (68.4, 76.9)
Week 24	1522/1549	98.3 (97.6, 98.9)	172/531	32.4 (28.4, 36.4)	65.8 (61.6, 69.7)	1068/1123	95.1 (93.7, 96.3)	77/359	21.4 (17.3, 26.1)	73.7 (68.9, 77.7)
Week 28[i]	1525/1557	97.9 (97.2, 98.7)	432/533	81.1 (77.7, 84.4)	16.8 (13.6, 20.4)	1064/1122	94.8 (93.4, 96.1)	260/357	72.8 (67.9, 77.4)	22.0 (17.4, 27.0)
Week 32[j]	—	—	—	—	—	1065/1123	94.8 (93.4, 96.1)	253/359	70.5 (65.5, 75.1)	24.4 (19.7, 29.4)
Week 36	—	—	—	—	—	1048/1111	94.3 (92.8, 95.6)	233/355	65.6 (60.4, 70.6)	28.7 (23.7, 33.9)

Table 8: Seroprotection Rates by Visit in DV2-HBV-10 and DV2-HBV-16 (PP Population) (Cont'd)

Trial	DV2-HBV-10					DV2-HBV-16				
Sub group	18 to 55 Years					40 to 70 Years				
	HEPLISAV[a]		Engerix-B[b]			HEPLISAV[a]		Engerix-B[b]		
Visit	n/N	SPR (%) (95% CI)[c]	n/N	SPR (%) (95% CI)[c]	Difference in SPRs (%) (HEPLISAV-Engerix-B) (95% CI)[d]	n/N	SPR (%) (95% CI)[e]	n/N	SPR (%) (95% CI)[e]	Difference in SPRs (%) (HEPLISAV-Engerix-B) (95% CI)[f]
Week 52	—	—	—	—	—	1012/1101	91.9 (90.1, 93.5)	209/354	59.0 (53.7, 64.2)	32.9 (27.6, 38.3)

Data Source: Clinical study reports for DV2-HBV-10, Section 14.1.2, Tables 25.1B, 28.1B; DV2-HBV-16, Section 14.2, Table 14.1.3-6; ISE Table 1; ISE Table 8.
anti-HBsAg = antibody against hepatitis B surface antigen; CI = confidence interval; n = number of subjects with post-injection anti-HBsAg greater than or equal to 10 mIU/mL; N = number of subjects in the analysis population in the group; PP = per-protocol; 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.
[c] The 95% CIs for the SPR were calculated using the normal approximation to the binomial.
[d] The SPR differences and associated CIs were based on a statistical analysis model adjusting for age categories (less than 40 years vs. greater than or equal to 40 years). The stratified Miettinen and Nurminen method is used to calculate 95% CIs.
[e] 95% CIs of SPRs were calculated using the Clopper-Pearson method.
[f] 95% CIs of the difference in seroprotection rates between the HEPLISAV group and the Engerix-B group were calculated using the Newcombe score method with continuity correction.
[g] In subjects who received HEPLISAV, the peak SPR was at Week 24. In subjects who received Engerix-B, the peak SPR was at Week 28.
[h] Primary endpoint for HEPLISAV in DV2-HBV-10 and DV2-HBV-16.
[i] Primary endpoint for Engerix-B in DV2-HBV-10.
[j] Primary endpoint for Engerix-B in DV2-HBV-16.

5.2.4 Subpopulation Analyses (Pooled mITT Population)

HEPLISAV induced higher peak SPRs in each subpopulation than Engerix-B. These results were consistent across all subpopulations analyzed, including subpopulations known to be hyporesponsive to currently licensed hepatitis B vaccines, ie, older adults, men, persons with diabetes mellitus, obese persons, and smokers, as well as in subpopulations with a good response to licensed vaccines, ie, young adults, women, whites, blacks, non-obese persons, and nonsmokers (Appendix 4, Table 38, Table 39, Table 40, and Table 41). Appendix 4 presents details for the individual subpopulations analyzed.

5.2.4.1 SPR by Age Group

In all age groups, the peak SPR induced by HEPLISAV was significantly higher than that induced by Engerix-B Figure 3 and Table 9. In participants < 30 years old, the peak SPR in the HEPLISAV group was 99.7%; in the Engerix-B group it was 92.7%. Of 306 subjects < 30 years old who received HEPLISAV, only 1 was not seroprotected while 7 of the 96 subjects who received Engerix-B were not seroprotected.

In older subjects, the peak SPRs in the HEPLISAV groups were also significantly higher than in the Engerix-B groups with an increasing difference in SPRs with increasing age. The difference in SPRs (HEPLISAV minus Engerix-B) ranged from 6.8% in subjects < 30 years old, to 12.4% in subjects 30 to 39 years old, to more than 22% in subjects aged 40 years and older.

Engerix-B offers high rates of seroprotection to young adults, but the peak SPR in subjects < 30 years of age who received HEPLISAV was significantly higher than in those young adults who received Engerix-B. In fact, the proportion of those not seroprotected was 24 times higher in the Engerix-B group than in the HEPLISAV group. In addition, the SPR in subjects > 60 years old who received HEPLISAV was similar to the SPR in subjects < 30 years old who received Engerix-B.

Figure 3: Seroprotection Rates by Age Subgroup and Visit in Subjects in DV2-HBV-10 and DV2-HBV-16 (Pooled mITT Analysis Population)

Data Source: ISE Figure 2.7.3-6.
E = Engerix-B; H = HEPLISAV; mITT = modified intent-to-treat; SPR = seroprotection rate.

Table 9: Seroprotection by Age Subgroup and Visit in DV2-HBV-10 and DV2-HBV-16 (Pooled mITT Analysis Population)

Visit Age Category (years)	HEPLISAV[a] n/N	HEPLISAV[a] SPR (%) (95% CI)[c]	Engerix-B[b] n/N	Engerix-B[b] SPR (%) (95% CI)[c]	%Difference in SPRs (HEPLISAV-Engerix-B) (95% CI)[d]
Peak[e]					
18 - 29	305/306	99.7 (98.3, 100.0)	89/96	92.7 (85.6, 97.0)	6.8 (3.0, 13.8)
30 - 39	518/523	99.0 (98.5, 99.9)	145/168	86.3 (80.2, 91.1)	12.4 (7.9, 18.5)
40 - 49	1285/1321	97.3 (96.2, 98.1)	284/382	74.5 (69.7, 78.7)	22.9 (18.7 - 27.6)
50 - 59	1073/1127	95.2 (93.8 - 96.4)	200/276	72.5 (66.8, 77.6)	22.7 (17.6 - 28.4)
60 - 70	481/525	91.6 (88.9, 93.8)	86/127	67.7 (58.8, 75.7)	23.9 (16.0 - 32.7)
Week 4					
18 - 29	109/311	35.0 (29.7, 40.6)	7/100	7.0 (2.9, 13.9)	28.0 (19.5, 34.5)
30 - 39	140/493	28.4 (24.5, 32.6)	8/173	4.6 (2.0, 8.9)	23.8 (18.0, 28.4)
40 - 49	274/1273	21.5 (19.3, 23.9)	13/394	3.3 (1.8, 5.6)	18.2 (15.1, 20.9)
50 - 59	212/1104	19.2 (16.9, 21.7)	13/280	4.6 (2.5, 7.8)	14.6 (10.7, 17.6)
60 - 70	78/542	14.4 (11.5, 17.6)	5/130	3.8 (1.3, 8.7)	10.5 (4.9, 14.3)
Week 8					
18 - 29	302/313	96.5 (93.8, 98.2)	43/98	43.9 (33.9, 54.3)	52.6 (42.4, 62.1)
30 - 39	460/487	94.5 (92.0, 96.3)	48/171	28.1 (21.5, 35.4)	66.4 (58.8, 72.8)
40 - 49	1061/1255	84.5 (82.4, 86.5)	96/389	24.7 (20.5, 29.3)	59.9 (54.9, 64.3)
50 - 59	824/1091	75.5 (72.9, 78.1)	48/279	17.2 (13.0, 22.2)	58.3 (52.8, 63.0)
60 - 70	352/540	65.2 (61.0, 69.2)	18/128	14.1 (8.6, 21.3)	51.1 (42.9, 57.4)
Week 12					
18 - 29	302/304	99.3 (97.6, 99.9)	45/98	45.9 (35.8, 56.3)	53.4 (43.4, 62.9)
30 - 39	478/485	98.6 (97.0, 99.4)	42/171	24.6 (18.3, 31.7)	74.0 (66.8, 79.9)
40 - 49	1166/1245	93.7 (92.2, 94.9)	79/388	20.4 (16.5, 24.7)	73.3 (68.7, 77.2)
50 - 59	980/1090	89.9 (88.0, 91.6)	38/277	13.7 (9.9, 18.3)	76.2 (71.2, 80.1)
60 - 70	440/536	82.1 (78.6, 85.2)	18/127	14.2 (8.6, 21.5)	67.9 (59.9, 73.7)
Week 24					
18 - 29	305/306	99.7 (98.2, 100.0)	55/95	57.9 (47.3, 68.0)	41.8 (32.2, 51.8)
30 - 39	480/482	99.6 (98.5, 99.9)	53/170	31.2 (24.3, 38.7)	68.4 (61.0, 74.9)
40 - 49	1200/1234	97.2 (96.2, 98.1)	99/382	25.9 (21.6, 30.6)	71.3 (66.6, 75.5)
50 - 59	1023/1073	95.3 (93.9, 96.5)	63/277	22.7 (17.9, 28.1)	72.6 (67.1, 77.3)
60 - 70	481/525	91.6 (88.9, 93.8)	25/128	19.5 (13.1, 27.5)	72.1 (63.9, 78.3)
Week 28					
18 - 29	302/304	99.3 (97.6, 99.9)	89/96	92.7 (85.6, 97.0)	6.6 (2.7, 13.8)
30 - 39	473/478	99.0 (97.6, 99.7)	145/168	86.3 (80.2, 91.1)	12.6 (8.1, 18.7)
40 - 49	1192/1227	97.1 (96.1, 98.0)	284/381	74.5 (69.9, 78.8)	22.6 (18.4, 27.3)
50 - 59	1017/1066	95.4 (94.0, 96.6)	200/276	72.5 (66.8, 77.6)	22.9 (17.8, 28.6)
60 - 70	479/526	91.1 (88.3, 93.4)	86/127	67.7 (58.8, 75.7)	23.3 (15.4, 32.2)

Table 9: Seroprotection by Age Subgroup and Visit in DV2-HBV-10 and DV2-HBV-16 (Pooled mITT Analysis Population) (Cont'd, table footnotes)

Data Source: Post-hoc analyses by age.
CI = confidence interval; mITT = modified intent-to-treat; n = number of subjects with post-injection anti-HBsAg ≥ 10 mIU/mL; N = number of subjects in the population in the group; SPR = seroprotection rate.

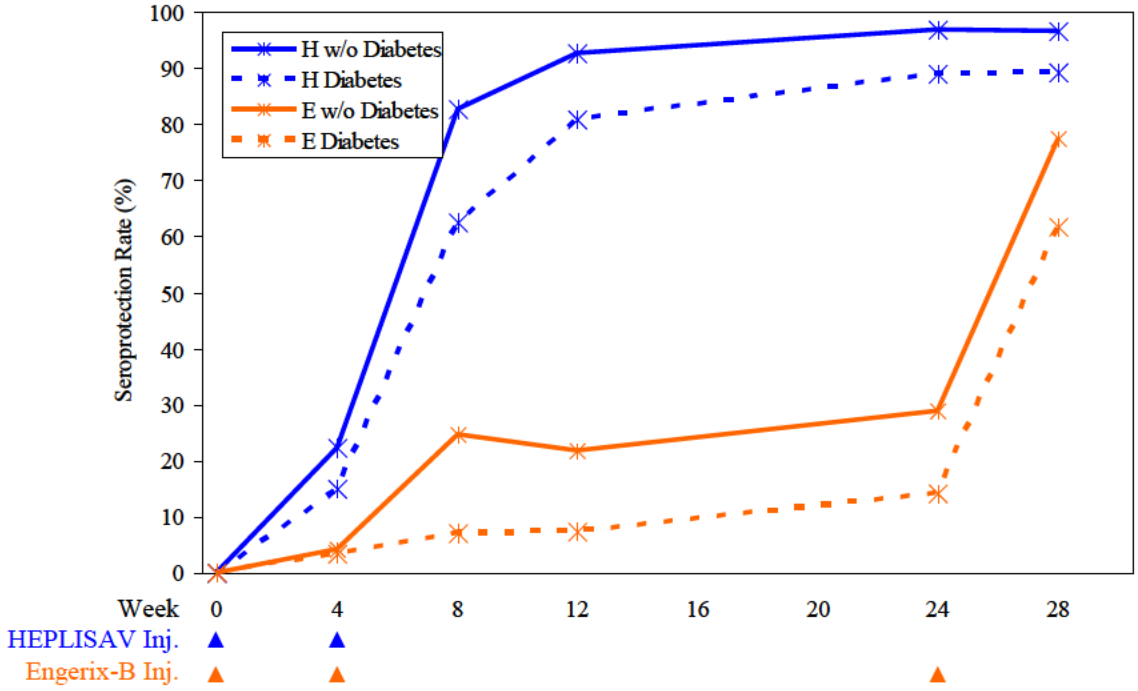
[a] Study injections were given at Weeks 0, 4, and 24 (placebo).
[b] Study injections were given at Weeks 0, 4, and 24.
[c] 95% CIs of seroprotection rates were calculated using the Clopper Pearson method.
[d] 95% CIs of the difference in seroprotection rates between the HEPLISAV group and the Engerix-B group at each visit were computed using the Newcombe score method with continuity correction.
[e] In subjects who received HEPLISAV, the peak SPR occurred at Week 24 in DV2-HBV-10 and DV2-HBV-16. In subjects who received Engerix-B, the peak SPR occurred at Week 28 in DV2-HBV-10 and DV2-HBV-16.

5.2.4.2 SPR in Subjects With Type 2 Diabetes

In subjects with type 2 diabetes, the peak SPR induced by HEPLISAV, which occurred at Week 28, was 89.3% and the peak SPR induced by Engerix-B, which also occurred at Week 28, was 61.8% with a difference in SPRs of 27.5% (95% CI: 15.0%, 41.1%). In subjects without diabetes, the peak SPR induced by HEPLISAV, which occurred at Week 24, was 96.9% and the peak SPR induced by Engerix-B, which occurred at Week 28, was 77.5% with a difference in SPRs of 19.3% (95% CI: 16.8%, 22.1%) (Figure 4, Table 10).

In subjects with type 2 diabetes 18 to 59 years old, in whom hepatitis B vaccine is now recommended, the peak SPR at Week 28 in the 154 subjects who received HEPLISAV was 91.6%, and in the 37 subjects who received Engerix-B was 56.8% with a difference in SPRs of 34.8% (95% CI, 19.4%, 50.9%).

Figure 4: Seroprotection Rates in Subjects With and Without Type 2 Diabetes Mellitus by Visit in DV2-HBV-16 and DV2-HBV-10 (Pooled mITT Analysis Population)



Data Source: ISE Figure 2.7.3-10.
E = Engerix-B; H = HEPLISAV; inj = injection; mITT = modified intent-to-treat; w/o = without.

Table 10: Seroprotection Rates by Diabetes Status and Visit in DV2-HBV-10 and DV2-HBV-16 (Pooled mITT Analysis Population)

Diabetes Status/ Visit	HEPLISAV[a] n/N	HEPLISAV[a] SPR (%) (95% CI)[c]	Engerix-B[b] n/N	Engerix-B[b] SPR (%) (95% CI)[c]	Difference in SPRs (%) (HEPLISAV-Engerix-B) (95% CI)[d]
Peak[e]					
Diabetes	201/225	89.3 (84.5, 93.0)	34/55	61.8 (47.7, 74.6)	27.5 (15.0, 41.1)
W/o Diabetes	3286/3392	96.9 (96.2, 97.4)	770/993	77.5 (74.8, 80.1)	19.3 (16.8, 22.1)
Week 4					
Diabetes	35/234	15.0 (10.6, 20.2)	2/58	3.4 (0.4, 11.9)	11.5 (2.0, 17.0)
W/o Diabetes	778/3489	22.3 (20.9, 23.7)	44/1019	4.3 (3.2, 5.8)	18.0 (16.0, 19.8)
Week 8					
Diabetes	145/232	62.5 (55.9, 68.7)	4/57	7.0 (1.9, 17.0)	55.5 (43.7, 62.6)
W/o Diabetes	2854/3454	82.6 (81.3, 83.9)	249/1008	24.7 (22.1, 27.5)	57.9 (54.9, 60.8)
Week 12					
Diabetes	185/229	80.8 (75.1, 85.7)	4/55	7.3 (2.0, 17.6)	73.5 (61.8, 79.6)
W/o Diabetes	3181/3431	92.7 (91.8, 93.6)	218/1006	21.7 (19.2, 24.3)	71.0 (68.2, 73.6)
Week 24					
Diabetes	203/228	89.0 (84.2, 92.8)	8/56	14.3 (6.4, 26.2)	74.7 (62.2, 82.2)
W/o Diabetes	3286/3392	96.9 (96.2, 97.4)	287/996	28.8 (26.0, 31.7)	68.1 (65.1, 70.8)
Week 28					
Diabetes	201/225	89.3 (84.5, 93.0)	34/55	61.8 (47.7, 74.6)	27.5 (15.0, 41.1)
W/o Diabetes	3262/3376	96.6 (96.0, 97.2)	770/993	77.5 (74.8, 80.1)	19.1 (16.5, 21.8)

Data Source: ISE Table 37.

CI = confidence interval; n = Number of subjects with anti-HBs ≥ 10 mIU/mL in the treatment group; N = Number of subjects in the treatment group; SPR = seroprotection rate (proportion of subjects with anti-HBs ≥ 10 mIU/mL); W/o = without.

[a] Study injections were given at Weeks 0, 4, and 24 (placebo).

[b] Study injections were given at Weeks 0, 4, and 24.

[c] 95% CIs of SPRs were calculated using Clopper-Pearson method.

[d] 95% CI of difference in SPRs was calculated using Newcombe score method with continuity correction.

[e] In persons with diabetes who received HEPLISAV, the peak SPR occurred at Week 28. In persons without diabetes who received HEPLISAV, the peak SPR occurred at Week 24. In both subpopulations, in those who received Engerix-B, the peak SPR occurred at Week 28.

5.2.4.3 Peak SPR by Sex, Race, Body Mass Index, Smoking Status

HEPLISAV induced significantly higher peak SPRs in men, women, whites, blacks, obese subjects, nonobese subjects, smokers, and nonsmokers than Engerix-B (Table 11). These results were also consistent across subpopulations except Asians, where the numbers of subjects in the Engerix-B group were too small for meaningful comparisons. Appendix 4 presents details for the individual subpopulations analyzed.

Table 11: Peak Seroprotection Rates by Subpopulation in DV2-HBV-10 and DV-HBV-16 (Pooled mITT Analysis Population)

	HEPLISAV[a]		Engerix-B[b]		
Visit Subpopulation	n/N	SPR (%) (95% CI)[c]	n/N	SPR (%) (95% CI)[c]	Difference in SPRs (%) (HEPLISAV-Engerix-B) (95% CI)[d]
Peak[e]					
Sex					
Men	1644/1711	96.1 (95.1, 97.0)	356/483	73.7 (69.5, 77.6)	22.4 (18.5, 26.6)
Women	1845/1909	96.6 (95.7, 97.4)	448/565	79.3 (75.7, 82.6)	17.4 (14.1, 21.0)
Race					
White	3078/3196	96.3 (95.6, 96.9)	713/926	77.0 (74.1, 79.7)	19.3 (16.6, 22.2)
Black	296/304	97.4 (94.9, 98.9)	58/80	72.5 (61.4, 81.9)	24.9 (16.0, 35.6)
Asian	61/63	96.8 (89.0, 99.6)	23/26	88.5 (69.8, 97.6)	8.4 (-2.0, 26.3)
Other[f]	54/57	94.7 (85.4, 98.9)	10/16	62.5 (35.4, 84.8)	32.2 (11.8, 55.9)
BMI					
Obese	1205/1265	95.3 (93.9, 96.4)	243/356	68.3 (63.1, 73.1)	27.0 (22.2, 32.1)
Nonobese	2279/2347	97.1 (96.3, 97.7)	560/690	81.2 (78.0, 84.0)	15.9 (13.1, 19.1)
Smoking Status					
Smoker	991/1020	97.2 (95.9, 98.1)	220/319	69.0 (63.6, 74.0)	28.2 (23.2, 33.5)
Nonsmoker	2498/2600	96.1 (95.9, 98.1)	584/729	80.1 (77.0, 82.9)	16.0 (13.1, 19.1)

Data Source: Appendix 4; ad hoc analyses, CSR HBV-10 and CSR HBV-16 mITT Populations.
BMI=body mass index; CI = confidence interval; mITT = modified intent-to-treat; N = number of subjects in the population in the group; n = number of subjects with post-injection anti-HBs ≥10 mIU/mL; SPR = seroprotection rate.
Subjects with a BMI ≥30 kg/m^2 were considered obese.

[a] Study injections were given at Weeks 0, 4, and 24 (placebo).
[b] Study injections were given at Weeks 0, 4, and 24.
[c] 95% CIs of seroprotection rates were calculated using the Clopper-Pearson method.
[d] 95% CIs of the difference in seroprotection rates between the HEPLISAV group and the Engerix-B group were calculated using the Newcombe score method with continuity correction.
[e] In men, women, white and black subjects, nonobese subjects, smokers, and nonsmokers who received HEPLISAV, the peak SPR occurred at Week 24. In Asian, subjects of Other races, and obese subjects who received HEPLISAV, the peak SPR occurred at Week 28. In all subpopulations, in those who received Engerix-B, the peak SPR occurred at Week 28.
[f] "Other" race includes American Indian/Alaska Native, Native Hawaiian or other Pacific Islander, and other race.

5.3 Immunogenicity Conclusions

Both pivotal trials met their primary endpoints, demonstrating noninferiority of HEPLISAV seroprotection compared to Engerix-B. In addition, vaccination with 2 doses of HEPLISAV

over 1 month achieved significantly higher peak SPRs, and earlier seroprotection than 3 doses of Engerix-B administered over 6 months. These results were consistent at all clinic visits and across all subpopulations analyzed including populations typically hyporesponsive to licensed HBV vaccines: Older adults, men, persons with diabetes, obese persons, and smokers.

6.0 SAFETY

6.1 Overview of Safety

The HEPLISAV clinical program included standard vaccine safety assessments and 2 areas of special assessment. Since 1018 ISS is an ODN, early trials included assessments of ODN class-related AEs, including potential changes in chemistry, hematology, coagulation, and complement parameters. As expected, since the 1018 ISS dose in HEPLISAV is far below the ODN concentrations associated with these class-related AEs, such events were not seen in the early trials and were not monitored in the later trials. Since 1018 ISS is a vaccine adjuvant, special attention was also given to laboratory and clinical assessments for autoimmune events.

The program evaluated safety in 5845 subjects, 4425 HEPLISAV recipients and 1420 Engerix-B recipients. The pooled phase 3 Safety Population from DV2-HBV-10 and DV2-HBV-16 included a total of 4864 subjects: 3777 HEPLISAV recipients and 1087 Engerix-B recipients. Unless otherwise noted, the analyses below were performed in the pooled phase 3 Safety Population. Note: Throughout the safety sections HEPLISAV refers to subjects who received the commercial formulation in the pivotal phase 3 trials and HEPLISAV (ALL) refers to subjects who received any formulation of HEPLISAV, including those in the supportive trials.

The safety and tolerability of HEPLISAV was similar to that of Engerix-B. The majority of AEs were mild to moderate, self-limited, and did not lead to discontinuation.

HEPLISAV and Engerix-B had similar rates of post-injection reactions (HEPLISAV: 55.1%; Engerix-B: 57.1%) as well as local post-injection reactions (HEPLISAV: 42.8%; Engerix-B: 41.1%) and systemic post-injection reactions (HEPLISAV: 32.3%; Engerix-B: 25.1%). The most frequent local post-injection reaction in both treatment groups was injection-site pain (HEPLISAV: 41.7%; Engerix-B: 40.5%). The 2 most frequent systemic post-injection reactions in both treatment groups were headache (HEPLISAV: 20.1%; Engerix-B: 25.3%) and fatigue (HEPLISAV: 21.4%; Engerix-B: 25.1%). Most injection reactions were self-limited and mild or moderate in severity.

AEs occurred at similar rates in both treatment groups (HEPLISAV: 55.3%; Engerix-B: 58.0%). The large majority of AEs in both groups were mild or moderate in severity. Severe AEs were reported by 7.6% of HEPLISAV recipients and 10.4% of Engerix-B recipients. The 3 most frequently reported AEs in each treatment group were the same: Nasopharyngitis (HEPLISAV: 10.1%; Engerix-B: 11.5%); headache (HEPLISAV: 6.9%; Engerix-B: 7.0%); and, back pain (HEPLISAV: 3.4%; Engerix-B: 3.5%). Syncope occurred at a low frequency and at similar rates in both treatment groups (HEPLISAV: 0.1%; Engerix-B: 0.1%). Withdrawals due to AEs were infrequent and were similar between treatment groups

(HEPLISAV: 0.08%; Engerix-B: 0.18%). Three HEPLISAV recipients withdrew due to unrelated AEs; 2 Engerix-B recipients withdrew due to AEs, one of which — moderate arthritis 8 days after the last active dose – was considered by the investigator to be related to treatment.

SAEs were reported at similar rates for both HEPLISAV and Engerix-B recipients (HEPLISAV: 2.8%; Engerix-B: 3.3%). In each group, 1 SAE occurred which the investigator considered to be related to study treatment.

SAE rates were also determined across all trials. The frequencies of SAEs were similar in both treatment groups [HEPLISAV (ALL): 2.7%; Engerix-B: 3.7%]. The RR of an SAE in the HEPLISAV (ALL) group compared with the Engerix-B group was 0.74 (95% CI: 0.54, 1.03).

There were no deaths in the phase 1 or 2 supportive trials or in DV2-HBV-10. In DV2-HBV-16, 2 deaths occurred: 1 (pulmonary embolism) in the HEPLISAV group and 1 (myocardial infarction) in the Engerix-B group. Both deaths were considered by the investigator to be unrelated to vaccination.

AESIs, defined in Section 6.5.2, were infrequent (HEPLISAV: 0.21%; Engerix-B: 0.37%). The RR of AESIs was 0.57 (95% CI: 0.17, 1.91). Among subjects with pre-existing events of special interest, HEPLISAV and Engerix-B were associated with similar rates of exacerbations of these pre-existing events (HEPLISAV: 2.3%; Engerix-B: 4.3%).

In DV2-HBV-16, 2 additional events were confirmed by the SEAC as autoimmune that were not already included as AESIs. Both events occurred in the HEPLISAV group. Adding these events to the predefined AESIs, the RR of autoimmune events was 0.72 (95% CI: 0.23, 2.29).

Rates of development of autoantibodies were similar between recipients of HEPLISAV and recipients of Engerix-B, including ANA (HEPLISAV: 5.5%; Engerix-B: 5.1%), and anti-dsDNA (HEPLISAV: 1.2%; Engerix-B: 1.0%). Retrospective testing for ANCA revealed no additional subjects with ANCA-positive results in either treatment group beyond those subjects identified with ANCA-associated vasculitis in DV2-HBV-10.

6.2 Autoimmune Considerations

Prior to the first pivotal phase 3 trial, DV2-HBV-10, no unusual autoimmune events were reported by the approximately 700 subjects who received HEPLISAV and 350 who subjects received Engerix-B in the clinical development program. In DV2-HBV-10, however, 2 rare, serious AIAEs were reported.

Two cases of ANCA- associated vasculitis occurred: 1 case of c-ANCA vasculitis, or granulomatosis with polyangiitis (GPA – formerly known as Wegener's granulomatosis) in a

HEPLISAV recipient; and, 1 case of p-ANCA vasculitis or microscopic polyangiitis in an Engerix-B recipient. Both cases occurred in older women, in whom the incidence of ANCA-associated vasculitis is highest.

The case of p-ANCA vasculitis occurred 3 months after the second dose of Engerix-B and was considered not related to study treatment by the investigator. The case of c-ANCA vasculitis occurred 5 months after the second dose of HEPLISAV and 1 month after the third (placebo) injection and was considered possibly related to study treatment by the site investigator. In light of the serious nature of this AE, the theoretical risk of autoimmunity with adjuvanted vaccines, and the low incidence of ANCA-associated vasculitis in the general population, the HEPLISAV development program was placed on clinical hold while the safety of HEPLISAV was evaluated.

The investigation of ANCA-associated vasculitis in a HEPLISAV recipient and a broader assessment of the possibility of an increased risk of AIAEs with HELPISAV focused on 4 major questions:

1) Was there evidence for an increased incidence of ANCA in HEPLISAV recipients compared with Engerix-B recipients?

2) Was there evidence for an increased incidence of other autoimmune antibodies in HEPLISAV recipients compared with Engerix-B recipients?

3) Was there evidence for an increased incidence of ANCA-associated vasculitis in HEPLISAV subjects compared with Engerix-B subjects?

4) Was there evidence for an increased incidence in AIAEs in HEPLISAV recipients compared with Engerix-B recipients?

First, available serum specimens from baseline, Month 3 (2 months after the last HEPLISAV dose) and Month 7 (1 month after the last Engerix dose) from 2024 subjects in DV2-HBV-10 and 2 prior trials were tested for ANCA. The testing algorithm used enzyme-linked immunosorbent assay (ELISA) for myeloperoxidase, the target for p-ANCA antibodies, and proteinase-3 (PR3), the target for c-ANCA antibodies. Specimens that were ELISA-positive were then tested by an IFA for confirmation. There were no specimens that were c-ANCA or p-ANCA positive by IFA in any of the subjects tested, other than the 2 initially reported. Dynavax concluded that the risk of development of ANCA was similar between HEPLISAV recipients and Engerix-B recipients.

Second, Dynavax has considered ANA and anti-dsDNA to be important safety biomarkers during the development program. ANA is a sensitive but relatively non-specific marker of autoimmune disease. In a pooled analysis of available data from supporting trials and DV2-

HBV-10, the number of subjects who went from ANA-negative to ANA-positive was 52 of 2145 (2.4%) subjects in the HEPLISAV group and 22 of 684 (3.2%) subjects in the Engerix-B group. Anti-dsDNA, development of which is correlated with SLE, is also of theoretical concern with oligonucleotides such as 1018 ISS that are structurally similar to DNA and could potentially induce cross reactive antibodies to dsDNA. In DV2-HBV-10, the number of subjects who went from anti-dsDNA negative to positive was 9 of 1725 (0.52%) subjects in the HEPLISAV group and 3 of 576 (0.52%) subjects in the Engerix-B group. In a pooled analysis of available data from supporting trials and DV2-HBV-10, the rates were 10 of 2077 (0.48%) subjects and 4 of 681 (0.59%) subjects, respectively.

Based on the observed cases of GPA and microscopic polyangiitis, the rate of ANCA-associated vasculitis in DV2-HBV-10 was 1 of 1809 (0.06%) subjects for HEPLISAV recipients and 1 of 606 (0.17%) subjects for Engerix-B recipients. AEs from all subjects from the entire clinical development program to date were reviewed for other cases that might represent ANCA-associated vasculitis. Cases of possible vasculitis or associated conditions were investigated, but no additional cases of ANCA-associated vasculitis were identified in the supporting trials. In the entire HEPLISAV program, the rate was 1 of 2500 (0.04%) subjects for HEPLISAV recipients and 1 of 930 (0.11%) subjects for Engerix-B recipients.

There is no known association between the humoral response to HBsAg and any particular autoimmune disease. However, there remains a theoretical concern that adjuvanted vaccines might increase the risk of autoimmune disease without preference for a specific disease. To explore this possibility, Dynavax reviewed all AEs of autoimmune disease in DV2-HBV-10, and in the entire HEPLISAV development program to date. In DV2-HBV-10, the rates of AIAEs were 5 of 1809 (0.28%) subjects in HEPLISAV recipients and 3 of 606 (0.50%) subjects in Engerix-B recipients. In the supporting trials, 3 additional events were identified: 2 in HEPLISAV recipients and 1 in Engerix-B recipients. In the clinical development program to date, the rates of autoimmune adverse events were 7 of 2500 (0.28%) subjects in HEPLISAV recipients and 4 of 930 (0.43%) subjects in Engerix-B recipients (RR: 0.65; 95% CI: 0.19, 2.22).

These findings demonstrated that, while the events of ANCA-associated vasculitis in both treatment groups were unexpected, the rates of ANCA antibody, autoantibody formation, ANCA-associated vasculitis, and autoimmune disease were similar in HEPLISAV recipients and Engerix-B recipients. Based on these assessments and the plan to conduct enhanced surveillance for autoimmune diseases in future trials, FDA allowed resumption of the HEPLISAV clinical development program.

A review of best practices for the identification and evaluation of rare AEs in vaccine clinical trials was conducted. Methods employed by Merck to monitor for events of intussusception in

the pivotal phase 3 trials of rotavirus vaccine were considered to be the best and most applicable. These methods included increased surveillance for the events of interest, independent adjudication of all potential events blind to treatment group, and DSMB review of all events with the ability to unblind treatment assignments. These methods also had the benefit of previous review by the Vaccines and Related Biologic Products Advisory Committee (VRBPAC), including a discussion of the acceptable RR and upper bound of the 95% confidence interval for the rare event in question. A RR of 2.0 and upper bound of 10.0 were established as the criteria for intussusception in infants.

These methods were adapted for the HEPLISAV clinical program. To increase surveillance for autoimmune disease, a questionnaire to elicit signs and symptoms of potential autoimmune disease was used at every trial visit. To increase the quality of the evaluation of potential autoimmune disease, subjects who reported symptoms on the questionnaire consistent with a potential diagnosis of autoimmune disease were evaluated by a local independent medical expert. To increase the consistency of the evaluation of expert confirmed cases, an independent expert committee, the Safety Evaluation and Adjudication Committee or SEAC, adjudicated whether events were autoimmune and whether they were related to study treatment.

While a case of a rare, serious autoimmune disease occurred in a subject who received HEPLISAV in DV2-HBV-10, comprehensive assessment of autoimmune events in the HEPLISAV clinical development to that time, and following enhanced surveillance in DV2-HBV-16, revealed a similar rate of autoimmune events in subjects who received HEPLISAV compared with subjects who received Engerix-B.

6.3 Safety Evaluation Plan

The safety of HEPLISAV was assessed in a total safety database of 5845 subjects 18 and older, which includes 4425 HEPLISAV recipients and 1420 Engerix-B recipients. The pooled Safety Population of 2 pivotal phase 3 trials DV2-HBV-10 and DV2-HBV-16, which compared the safety of proposed commercial formulation of HEPLISAV to Engerix-B, includes 3777 HEPLISAV recipients and 1087 Engerix-B recipients.

The safety assessment in the clinical program included:

- Solicited post-injection reactions (PIRs);
- AEs, SAEs, and deaths;
- Safety data related to autoimmunity:
    - AESIs identified from the clinical databases

- Solicited AEs possibly related to autoimmunity, adjudicated by an independent SEAC in study DV2-HBV-16

- Laboratory assessments of autoantibodies.

Clinical evaluation of the safety of HEPLISAV in healthy adults integrated standard clinical study safety data collection with assessments for potential AIAEs. The safety events of HEPLISAV were compared to those occurring in recipients of Engerix-B. Details of study designs for DV2-HBV-10 and DV2-HBV-16 were provided earlier in Section 5.1.

In DV2-HBV-10, the following safety assessments were conducted beginning after the first injection:

- Incidence and severity of solicited post-injection local and systemic reactions (7 days following each injection)

- Incidence, severity, and relationship to study treatment of AEs and SAEs for 28 weeks

- Mean values and change from baseline in vital signs; and incidence of concomitant medication and vaccination use

- ANCA testing was performed retrospectively on banked specimens

- AESIs were collected through a programmatic search of the clinical database.

- Change from baseline to Week 28 in ANA and anti-dsDNA

In DV2-HBV-16 the following safety assessments were conducted beginning after the first injection:

- Incidence and severity of solicited post-injection local and systemic reactions (7 days following each injection)

- Incidence, severity, and relationship to study treatment of AEs (28 weeks) and SAEs/possible autoimmune events (52 weeks)

- Mean values and change from baseline to Week 52 in vital signs; and incidence of concomitant medication and clinical laboratory tests (serum chemistry, hematology)

- Pre-defined AESIs were collected through a programmatic search of the clinical database.

- Change from baseline to Week 52 in ANA and anti-dsDNA

- AEs that were possibly autoimmune in origin were assessed by independent experts in a prospective manner in Study DV2-HBV-16 and referred for adjudication to SEAC.

Safety findings related to autoimmune events were analyzed extensively on an individual basis and by treatment group.

Appendix 2 provides study design details of supportive clinical trials; data from those trials are included in HEPLISAV (ALL) data.

6.3.1 Safety Analysis Population

The Safety Population is composed of enrolled subjects who received at least 1 study injection and had any post-baseline safety data. For the analysis of safety data, subjects were included in the treatment group corresponding to the study treatment they actually received. Table 12 presents a summary of the adult Safety Population for pivotal trials DV2-HBV-10 and DV2-HBV-16, for the supporting trials, and for all trials.

Table 12: Safety Populations

	Treatment Group		
Population	**HEPLISAV**	**Engerix-B**	**Total**
DV2-HBV-10 Safety Population	1809	606	2415
DV2-HBV-16 Safety Population	1968	481	2449
Phase 3 Safety Population	3777	1087	4864
Supporting Trials	648	333	981
All trials Safety Population	4425	1420	5845

Data Source: ISS Figure 2.7.4-1 and ISS Tables 2.7.4-4, 2.7.4-5, and 2.7.4-6.

Analyses of safety data for the phase 3 Safety Population are presented. Detailed demographic characteristics of this population are presented in Section 6.3.3.

6.3.2 Extent of Exposure

Table 13 presents the extent of exposure to HEPLISAV and Engerix-B by treatment group for the safety analysis population in pivotal trials DV2-HBV-10 and DV2-HBV-16.

In these 2 trials, 3777 HEPLISAV subjects and 1087 Engerix-B subjects ≥ 18 years old received at least 1 dose of vaccine; 3712 (98.3%) subjects completed the 2-dose regimen of HEPLISAV, and 1046 (96.2%) subjects completed the 3-dose regimen of Engerix-B.

Table 13: Extent of Exposure by Treatment Group (Phase 3 Safety Population)

	Treatment Group	
Dose	**HEPLISAV (N = 3777)**	**Engerix-B (N = 1087)**
Dose 1 only	(1.7)	(1.4)
Doses 1 and 2 only	(98.3)	(2.4)
Doses 1, 2, and 3	NA	(96.2)
Total Subjects	(100)	(100)

Data Source: ISS Table 1.1.7, Table 1.1.8, and Table 1.1.9.
NA = not applicable.

6.3.3 Demographic and Baseline Characteristics

Overall, the treatment groups were similar for demographic and baseline characteristics, as shown in Table 14. Demographic and baseline characteristics were similar between treatment groups with respect to gender, mean age in years, percentage of subjects with a BMI > 30 kg/m^2, race, ethnicity, and smoking status (Appendix 4).

Table 14: Demographic and Baseline Characteristics by Treatment Group (Phase 3 Safety Population)

	Treatment Group	
	HEPLISAV (N = 3777)	**Engerix-B (N = 1087)**
Sex (%)		
Men	(47.5)	(45.8)
Women	(52.5)	(54.2)
Age Subgroup (%)		
18-39 Years	(21.7)	(25.3)
40-55 Years	(56.0)	(56.5)
56-70 Years	(22.3)	(18.2)
Age (years)		
N	3777	1087
Mean (SD)	47.3 (11.15)	46.0 (10.98)
Median	48.00	46.00
Range	18-70	18-70
BMI Stratum (%)		
< 30 kg/m^2	(64.7)	(65.6)
≥ 30 kg/m^2	(35.1)	(34.2)
Race (%)		
White	(87.6)	(87.9)
Black or AA	(8.9)	(8.2)
Asian	(1.8)	(2.4)
Other[a]	(1.7)	(1.6)
Ethnicity (%)		
Hispanic	(4.3)	(5.2)
Non-Hispanic	(95.6)	(94.8)
Smoking Status (%)		
Yes[b]	(28.7)	(31.5)
No	(71.3)	(68.5)
Type 2 Diabetes (%)		
With disease	(6.3)	(5.2)
Without disease	(93.7)	(94.8)

Data Source: ISS Table 2.7.4-2, ISS Tables 2.1.7, 2.1.8, and 2.1.9, and post-hoc analysis (diabetes data).
AA = African American, BMI = body mass index, NA = not applicable; SD = standard deviation.
[a] Other = Combined American Indian, Alaska Native, Native Hawaiian or other Pacific Islander, or other race.
[b] History of smoking within 1 year prior to enrollment in the study.

6.4 Standard Safety Assessments

Table 15 presents a summary of major categories of safety events by treatment group for the phase 3 Safety Population.

Table 15: Percent of Subjects With Safety Events by Treatment Group (Phase 3 Safety Population)

	Treatment Group	
Type of event	**HEPLISAV (N = 3777)**	**Engerix-B (N = 1087)**
Any PIR	(55.1)	(57.1)
Local PIRs	(42.8)	(41.1)
Systemic PIRs	(32.3)	(37.4)
Any AE	(55.3)	(58.0)
Any SAE	(2.8)	(3.3)
Discontinuation of treatment due to AE	(0.5)	(0.4)
Death	(< 0.1%)	(0.1)

Data Source: ISS Table 2.7.4-4.
AE = adverse event; PIR = post-injection reaction; SAE = serious adverse event.

6.4.1 Post-injection Reactions

HEPLISAV and Engerix-B had similar rates of overall post-injection reactions (HEPLISAV: 55.1%; Engerix-B: 57.1%).

Table 16 presents an overview of subjects with post-injection reactions by treatment group.

Table 16: Percent of Subjects With Post-injection Reactions by Treatment Group (Phase 3 Safety Population)

	Treatment Group	
	HEPLISAV (N = 3777)	**Engerix-B (N = 1087)**
Phase 3 Safety Population N	3762	1084
Any PIR		
Subjects with Reactions	(55.1)	(57.1)
Subjects with Severe Reactions	(3.2)	(5.1)
Local PIR		
Subjects with Reactions	(42.8)	(41.1)
Subjects with Severe Reactions	(0.6)	(0.4)
Systemic PIR		
Subjects with Reactions	(32.3)	(37.4)
Subjects with Severe Reactions	(2.8)	(4.9)

Data Source: ISS Table 2.7.4-12.
PIR = post-injection reaction.

6.4.1.1 Local Post-injection Reactions

The frequency of local post-injection reactions was similar in HEPLISAV subjects (55.1%) and Engerix-B subjects (57.1%). Table 17 presents frequencies of redness, swelling, and pain by treatment group and severity. Injection site pain was the most frequent local reaction in both groups (HEPLISAV; 41.7%; Engerix-B 40.5%). Severe pain was infrequent and similar between treatment groups (HEPLISAV: 0.5%; Engerix-B: 0.4%).

Table 17: Percent of Subjects With Local Post-injection Reactions by Treatment Group, DV2-HBV-10 and DV2-HBV-16 (Pooled Safety Population)

	Treatment Group	
	HEPLISAV (N = 3777)	**Engerix-B (N = 1087)**
Pooled Safety Population N	3762	1084
Subjects with local reactions	(42.8)	(41.1)
Injection-Site Redness[a]		
Subjects with Redness	(3.7)	(1.1)
Severe	(0.0)	0.0
Injection-Site Swelling[a]		
Subjects with Swelling	(2.4)	(1.3)
Severe	(0.0)	0
Injection-Site Pain		
Subjects with Pain	(41.7)	(40.5)
Severe	(0.5)	(0.4)

Data Source: ISS Table 2.7.4-13.
[a] Redness/Swelling: Severe = greater than 100 mm.

6.4.1.2 Systemic Post-injection Reactions

The frequency of systemic post-injection reactions was similar between HEPLISAV subjects (32.3%) and Engerix-B subjects (37.4%). Table 18 presents an analysis of specific systemic post-injection reactions by treatment group and severity. The most frequent systemic post-injection reactions in both treatment groups were headache (HEPLISAV: 20.1%; Engerix-B: 25.3%), and fatigue (HEPLISAV: 21.4%; Engerix-B: 25.1%). Fever was infrequent (HEPLISAV: 1.7%; Engerix-B: 3.4%).

Table 18: Percent of Subjects With Specific Systemic Post-injection Reactions by Treatment Group (Phase 3 Safety Population)

	Treatment Group	
	HEPLISAV (N = 3777)	**Engerix-B (N = 1087)**
Subjects with systemic reactions (%)	(32.3)	(37.4)
Fatigue		
n	3762	1084
Subjects with Fatigue	(21.4)	(25.1)
Severe	(1.6)	(2.4)
Headache		
n	3762	1084
Subjects with Headache	(20.1)	(25.3)
Severe	(1.5)	(2.0)
Malaise		
n	3762	1084
Subjects with Malaise	(13.8)	(16.0)
Severe	(1.1)	(2.1)
Fever		
n	3733	1076
Subjects with fever (≥ 38°C)	(1.7)	(3.4)
Severe (39°C to 40°C)	(0.2)	(0.9)

Data Source: ISS Table 2.7.4-9 and ISS Table 2.7.4-15.

6.4.1.3 Time Course of Post-injection Reactions

Local post-injection reactions tended to peak in frequency between 1 and 3 days after injection in both groups. Systemic post-injection reactions tended to peak between 1 and 2 days after injection in both groups. The time course of post-injection reactions is shown in Appendix 5.

6.4.2 Adverse Events and Withdrawals

6.4.2.1 Adverse Events

AEs were similar in types and frequency for HEPLISAV (55.3%) and Engerix-B (58.0%). No specific AE occurred significantly more frequently for HEPLISAV than for Engerix-B. As shown in Table 19, the 3 most frequently reported AEs in each group by preferred term were:

- Nasopharyngitis (HEPLISAV: 10.1%; Engerix-B: 11.5%)
- Headache (HEPLISAV: 6.9%; Engerix-B: 7.0%)
- Back pain (HEPLISAV: 3.4%; Engerix-B: 3.5%)

These 3 preferred terms were in the 2 most frequently reported system organ classes (SOCs): infections and infestations (HEPLISAV: 25.7%; Engerix-B: 27.3%) and musculoskeletal and connective tissue disorders (HEPLISAV: 14.1%; Engerix-B: 15.5%). Other common AEs were similar in frequency between treatment groups.

Syncope occurred at a low frequency and occurred at a similar rate in both treatment groups (HEPLISAV: 0.1%; Engerix-B: 0.1%). Injection site haematoma, a theoretical risk based on known class effects of PS ODNs on coagulation, occurred at similar frequency in the HEPLISAV group (0.3%) and the Engerix-B group (0.2%).

Table 19: Percent of Subjects With Adverse Events Reported by 2% or More of HEPLISAV Subjects, by Preferred Term (Phase 3 Safety Population)

	Treatment Group	
Preferred Term	**HEPLISAV (N = 3777)**	**Engerix-B (N = 1087)**
Subjects with any AE	(55.3)	(58.0)
Nasopharyngitis	**(10.1)**	**(11.5)**
Headache	**(6.9)**	**(7.0)**
Back Pain	**(3.4)**	**(3.5)**
Sinusitis	(2.9)	(2.4)
Upper Respiratory Infection	(2.8)	(3.5)
Oropharyngeal Pain	(2.7)	(3.2)
Arthralgia	(2.5)	(2.9)
Cough	(2.4)	(2.3)
Diarrhoea	(2.0)	(2.0)
Bronchitis	(1.8)	(1.8)

Data Source: ISS Table 2.7.4-21.
AE = adverse event
Note: Peak frequency for each injection is in **bold**.

6.4.2.2 Related Adverse Events

In subjects 18 years and older, the frequency of AEs considered by an investigator to be related was low and similar between treatment groups (HEPLISAV: 6.2%; Engerix-B: 6.0%) (Appendix 6). Table 20 presents AEs considered by the investigator to be possibly or probably related to treatment in subjects 18 years and older by treatment group. AEs that occurred in 5 or more subjects in a treatment group are presented.

The most frequent related AEs were injection site erythema (HEPLISAV: 0.7%; Engerix-B: 0.4%), headache (HEPLISAV: 0.5%; Engerix-B: 0.4%), and nasopharyngitis (HEPLISAV: 0.4%; Engerix-B: 0.6%). The AEs with the greatest percentage difference between treatment groups were injection site erythema (HEPLISAV: 0.7%; Engerix-B: 0.4%) and nausea (HEPLISAV: 0.3%; Engerix-B: 0.6%).

Table 20: Percent of Subjects With Related Adverse Events in 5 or More Subjects, by Treatment Group, DV2-HBV-10 and DV2-HBV-16 (Pooled Safety Population)

	Treatment Group	
Preferred Term	**HEPLISAV (N = 3777)**	**Engerix-B (N = 1087)**
Subjects with any related AE	(6.2)	(6.0)
Injection Site Erythema	(0.7)	(0.4)
Headache	(0.5)	(0.4)
Nasopharyngitis	(0.4)	(0.6)
Myalgia	(0.4)	(0.5)
Fatigue	(0.3)	(0.4)
Diarrhoea	(0.3)	(0.3)
Nausea	(0.3)	(0.6)
Injection Site Swelling	(0.3)	(0.2)
Back Pain	(0.2)	(0.1)
Injection Site Haematoma	(0.2)	(0.2)
Injection Site Pain	(0.2)	(0.1)
Pain In Extremity	(0.2)	(0.0)
Dizziness	(0.2)	(0.2)
Oropharyngeal Pain	(0.2)	(0.0)
Post Procedural Haematoma	(0.2)	(0.3)
Arthralgia	(0.2)	(0.0)
Injection Site Pruritus	(0.1)	(0.1)
White Blood Cell Count Increased	(0.1)	(0.0)

Data Source: ISS Table 12.7.4-22.
AE = adverse event.

6.4.2.3 Adverse Events Leading to Study Withdrawal

Withdrawals due to an AE were infrequent and were similar between treatment groups (HEPLISAV: 3/3777, 0.08%; Engerix-B: 2/1087, 0.18%).

Table 21 lists the 5 subjects who withdrew due to an AE in the pivotal phase 3 trials. Among the HEPLISAV subjects, there were 3 AEs leading to withdrawal: Hyponatremia, Guillain-Barré Syndrome 5 days following influenza vaccination and 110 days following the last HEPLISAV

dose, and pulmonary embolism. All 3 events were SAEs and were considered by the investigator to be unrelated to study treatment. A narrative for the event of Guillain-Barré Syndrome is provided in Appendix 6. The 2 AEs leading to withdrawal in the Engerix-B group were vision blurred and arthritis. The investigator considered the arthritis to be possibly related to treatment.

Table 21: Adverse Events Leading to Study Withdrawal in DV2-HBV-10 and DV2-HBV-16

Study	Age/Sex	MedDRA Preferred Term	Days Since Last Active Dose	SAE	Severity	Outcome	Relationship to Treatment
HEPLISAV							
DV2-HBV-10	35/F	Guillain-Barré Syndrome	110	Yes	3	Resolved	Probably not related[a]
DV2-HBV-10	26/M	Pulmonary Embolism	41	Yes	3	Resolved	Not related
DV2-HBV-16	67/F	Hyponatremia	24	Yes	3	Resolved	Not related
Engerix-B							
DV2-HBV-10	49/F	Vision Blurred	3	No	2	Resolved	Probably not related
DV2-HBV-10	35/F	Arthritis	8	No	2	Resolved	Possibly related

Data Source: ISS Table 2.4.7-29.
CSR = clinical study report; F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.
[a] "Probably not related" was considered the same as "not related".
Note: Severity: 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Life-threatening or disabling, 5 = Death.

6.4.3 Serious Adverse Events and Deaths

6.4.3.1 Serious Adverse Events

SAEs were similar in type and frequency between HEPLISAV subjects (2.8%) and Engerix-B subjects (3.3%) ≥ 18 years old, as shown in Table 22. When analyzed by SOC, the most frequent categories of events in the pivotal trials were:

- Injury, poisoning and procedural complications (HEPLISAV: 0.6%; Engerix-B: 0.5%)
- Musculoskeletal and connective tissue disorders (HEPLISAV: 0.6%; Engerix-B: 0.6%)
- Neoplasms (HEPLISAV: 0.4%; Engerix-B: 0.5%)

Table 22: Percent of Subjects With Serious Adverse Events, by System Organ Class and Treatment Group (Phase 3 Safety Population)

System Organ Class	HEPLISAV (N = 3777)	Engerix-B (N = 1087)
Subjects with any SAE (%)[a]	(2.8)	(3.3)
Cardiac Disorders	(0.2)	(0.6)
Gastrointestinal Disorders	(0.2)	(0.3)
Infections and Infestations	(0.2)	(0.3)
Injury, Poisoning and Procedural Complications	(0.6)	(0.5)
Metabolism and Nutrition Disorders	(0.2)	(0.1)
Musculoskeletal and Connective Tissue Disorders	(0.6)	(0.6)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	(0.4)	(0.5)
Respiratory, Thoracic and Mediastinal Disorders	(0.3)	(0.3)

Data Source: ISS Table 11.1.4.3 and ISS Appendix Risk Ratios for SAE.
CI = confidence interval; SAE = serious adverse event; SOC = system organ class.
[a] Relative Risk 0.83 (95%CI, 0.57 to 1.21).
Note: This table presents SOCs in which >0.1% HEPLISAV subjects had an event.

Appendix 7 provides the SAEs by Preferred Term. The RR of an SAE in the HEPLISAV group (2.8%) compared with the Engerix-B group (3.3%) was 0.83 (95% CI: 0.57, 1.21). The frequency of SAEs by SOC was similar between treatment groups.

The frequencies of SAEs from all subjects who received 1018 ISS Adjuvant [HEPLISAV (ALL)] were similar in both treatment groups [HEPLISAV (ALL): 2.7%; Engerix-B: 3.7%). The RR of an SAE in the HEPLISAV (ALL) group compared with the Engerix-B group was 0.74 (95% CI: 0.54, 1.03).

6.4.3.2 Related Serious Adverse Events

Two SAEs were considered by the site investigator to be related to vaccination; 1 (0.03%) HEPLISAV subject (GPA, formerly known as Wegener's granulomatosis) and in 1 (0.09%) Engerix-B subject (bronchial hyperreactivity) in DV2-HBV-16 (Table 23). Both SAEs occurred in subjects ≥ 40 years old. Narratives for the 2 SAEs which were considered by the site investigator to be related to study product are in Appendix 6, Section A6.1.

Table 23: Related Serious Adverse Events by Treatment Group (Phase 3 Safety Population)

Study	Age/Sex	MedDRA Preferred Term	Days Since Last Active Dose	SAE	Severity	Outcome	Relationship to Treatment
HEPLISAV (n = 1)							
DV2-HBV-10	55/F	Granulomatosis with polyangitis	72	Yes	3	Ongoing	Possibly related
Engerix-B (n = 1)							
DV2-HBV-16	50/F	Bronchial Hyperreactivity	42	Yes	3	Resolved	Possibly related

Data Source: ISS Listing 3.1 (Appendix 5).
F = female; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.
Note: Severity: 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Life-threatening or disabling, 5 = Death.

6.4.3.3 Deaths

There were no deaths in the supporting trials or in the pivotal phase 3 trial DV2-HBV-10. As shown in Table 24, 2 deaths were reported in DV2-HBV-16: 1 due to an unrelated SAE of pulmonary embolism in the HEPLISAV group (1 of 3777 subjects, 0.03%) and 1 due to an unrelated SAE of myocardial infarction in the Engerix-B group (1 of 1087 subjects, 0.09%). Narratives for the 2 SAEs resulting in death are provided in Appendix 6 , Section A6.2.

Table 24: Deaths During the Clinical Development of HEPLISAV

Study	Subject ID	Age	Sex	MedDRA Preferred Term	Days Since Last Active Dose	Relationship to Treatment
HEPLISAV (n = 1)						
DV2-HBV-16	22-003	45	M	Pulmonary Embolism	46	Not related
Engerix-B (n = 1)						
DV2-HBV-16	92-638	64	M	Myocardial Infarction	43	Not related
Supportive Trials (n = 0)						

Data Source: ISS Table 2.7.4-24 (ISS Listing 1.1, ISS Listing 3.1, and DV2-HBV-16 CSR, Listing 16.5).
CSR = clinical study report; ID = identification; M = male; MedDRA = Medical Dictionary for Regulatory Activities.
Full narratives are provided in the DV2-HBV-16 CSR, Section 14.3 (Subjects 22-003 and 92-638).

6.5 Autoimmune Adverse Events

Three broad assessments of autoimmunity were conducted during the HEPLISAV clinical program and were not restricted to particular disease entities:

- Adverse Events of Special Interest: Identification, categorization, and analysis of AEs in the entire safety database were conducted, using a list of MedDRA terms corresponding to autoimmune and inflammatory conditions (Appendix 6, Section A6.3).

- Adjudicated Autoimmune Events: Enhanced surveillance for autoimmune events was conducted in DV2-HBV-16 through: (1) administration of a questionnaire soliciting signs and symptoms of autoimmune disorders at each clinic visit (Appendix 8); (2) evaluation of potential autoimmune events by a local independent expert; (3) blinded adjudication of potential autoimmune events by the SEAC; and, (4) unblinded evaluation of all adjudicated autoimmune events by the DSMB.

- Autoantibodies: Laboratory assessments of autoantibodies pre- and post-vaccination, including ANA, anti-dsDNA, and ANCA.

6.5.1 Summary of Autoimmune Adverse Events

- AESIs were infrequent and occurred at similar rates in HEPLISAV subjects (0.23%) and in Engerix-B subjects (0.35%).

- There was no difference between HEPLISAV and Engerix-B with respect to either overall autoimmune safety findings or exacerbations of PEAI disease in subjects identified with pre-existing event of special interest (HEPLISAV: 2.3%; Engerix-B: 4.3%).

- In DV2-HBV-16, 3 new-onset autoimmune AEs were identified in 1968 HEPLISAV subjects and 0 in 481 Engerix-B subjects.

- Rates changes in autoantibodies (ANA, anti-dsDNA, ANCA) were similar for HEPLISAV and Engerix-B subjects. For all trials, rates of development of autoantibodies were similar between recipients of HEPLISAV or HEPLISAV (All) and recipients of Engerix-B, including ANA (HEPLISAV: 5.7%; Engerix-B: 5.3%), and anti-dsDNA (HEPLISAV: 1.6%; Engerix-B: 1.8%). Retrospective testing for ANCA revealed no additional subjects with ANCA antibody in either treatment group beyond the 2 subjects with ANCA-associated vasculitis in DV2-HBV-10.

- The rates of autoimmune events were similar in the HEPLISAV and Engerix-B treatment groups.

6.5.2 Adverse Events of Special Interest

AESIs considered appropriate for the assessment of autoimmunity were identified from the safety database using a list of MedDRA terms corresponding to autoimmune and inflammatory conditions across multiple organ systems and mechanisms. Dynavax developed the list of events and terms from regulatory guidances, published literature, and other sponsors' protocols. These events were:

- Neuroinflammatory disorders: Optic neuritis, multiple sclerosis, demyelinating disease, transverse myelitis, Guillain-Barré syndrome, myasthenia gravis, encephalitis, neuritis, and Bell's palsy
- Musculoskeletal disorders: Systemic lupus erythematosus, cutaneous lupus, Sjogren's syndrome, scleroderma, dermatomyositis, polymyositis, rheumatoid arthritis, juvenile rheumatoid arthritis, polymyalgia rheumatica, reactive arthritis, psoriatic arthropathy, ankylosing spondylitis, and spondylarthropathy
- Gastrointestinal disorders: Crohn's disease, ulcerative colitis, and celiac disease
- Metabolic disease: Autoimmune thyroiditis, Grave's or Basedow's disease, Hashimoto thyroiditis, type 1 diabetes mellitus, and Addison's disease
- Skin disorders: Psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, and autoimmune bullous skin diseases
- Others: Anti-neutrophil cytoplasmic vasculitis, autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, antiphospholipid syndrome, temporal arteritis, Behcet's syndrome, pernicious anemia, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosis, cholangitis, autoimmune glomerulonephritis, autoimmune uveitis, autoimmune cardiomyopathy, renal vasculitis, sarcoidosis, Stevens-Johnson syndrome, and granulomatosis with polyangiitis

Based on these identified events, a list of preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA, version 14.0) was generated and used to identify AESIs from the database of coded AEs.

6.5.2.1 Findings for Adverse Events of Special Interest

In the pivotal phase 3 trials, a total of 14 AESIs occurred in 12 subjects: 8 events in 8 of 3777 (0.21%) HEPLISAV subjects; and, 6 events in 4 of 1087 (0.37%) Engerix-B subjects. One

subject in the Engerix-B group experienced 3 AESIs: ANCA positive vasculitis, mixed connective tissue disease, and scleroderma. Two additional AESIs occurred in HEPLISAV recipients in the supporting trials, for rates of 10 of 4425 (0.23%) in HEPLISAV [ALL] recipients and 5 of 1420 (0.35%) in Engerix-B recipients.

As shown in Table 25, the most frequent AESIs were musculoskeletal disorders. Narratives for AESIs are provided in Appendix 6, Section A6.3.

Table 25: Adverse Events of Special Interest by Category, Preferred Term, and Treatment Group (Phase 3 Safety Population and All Trials Safety Population)

	Phase 3 Safety Population		All Trials Safety Population	
	HEPLISAV (N = 3777)	**Engerix-B (N = 1087)**	**HEPLISAV [ALL] (N =4425)**	**Engerix-B (N = 1420)**
Category/Preferred Term				
Subjects with any AESI n, (%)	8 (0.2)	4 (0.4)	10 (0.2)	5 (0.4)
Nervous System Disorders	2 (0.1)	1 (0.1)	3 (0.1)	1 (0.1)
Guillain-Barré Syndrome	1 (0.0)	0	1 (0.0)	0
VIIth Nerve Paralysis (Bell's Palsy)	1 (0.0)	1 (0.1)	2 (0.0)	1 (0.1)
Musculoskeletal and Connective Tissue Disorders	2 (0.1)	1 (0.1)	3 (0.1)	2 (0.1)
Mixed Connective Tissue Disease	0	1 (0.1)	0	1 (0.1)
Rheumatoid Arthritis	1 (0.0)	0	2 (0.0)	1 (0.1)
Scleroderma	0	1 (0.1)	0	1 (0.1)
Systemic Lupus Erythematosus	1 (0.0)	0	1 (0.0)	0
Gastrointestinal Disorders	0	0	0	0
Metabolic Disorders	1 (0.0)	1 (0.1)	1 (0.0)	1 (0.1)
Basedow's Disease	1 (0.0)	1 (0.1)	1 (0.0)	1 (0.1)
Skin Disorders	2 (0.1)	1 (0.1)	2 (0.1)	1 (0.1)
Erythema Nodosum	1 (0.0)	0	1 (0.0)	0
Vitiligo	1 (0.0)	0	1 (0.0)	0
Raynaud's Phenomenon	0	1 (0.1)	0	1 (0.1)
Other Disorders	1 (0.0)	1 (0.1)	1 (0.0)	1 (0.1)
Anti-Neutrophil Cytoplasmic Antibody Positive Vasculitis	0	1 (0.1)	0	1 (0.1)
Granulomatosis with polyangiitis (Wegener's granulomatosis)	1 (0.0)	0	1 (0.0)	0

Data Source: ISS Table 2.7.4-32.
AESI = Adverse event of special interest.

Table 26 presents individual AESIs by treatment group. Serious AESIs occurred in 2 of 3777 subjects (0.05%) in the HEPLISAV group: Guillain-Barré Syndrome and granulomatosis with polyangiitis; and in 1 of 1087 subjects (0.09%) in the Engerix-B group: ANCA positive vasculitis. Narratives for these SAEs are in Appendix 6 , Sections A6.1 and A6.3.

Table 26: Adverse Events of Special Interest by Treatment Group in DV2-HBV-10 and DV2-HBV-16 (Pooled Safety Population)

Age/ Sex	MedDRA Preferred Term	Days Since Last Active Dose	SAE	Severity	Outcome	Relationship to Treatment
HEPLISAV						
DV2-HBV-10						
41/F	Basedow's Disease	43	No	3	Ongoing	Probably not related[a]
52/F	Systemic Lupus Erythematosus	84	No	0	Resolved	Not related
36/F	Guillain-Barré Syndrome	110	Yes	3	Resolved	Probably not related[a]
55/F	Granulomatosis with polyangitis (Wegener's granulomatosis)	150	Yes	3	Ongoing	Possibly related
42/F	Rheumatoid Arthritis	239	No	1	Resolved	Not related
DV2-HBV-16						
62/M	Erythema Nodosum	19	No	2	Resolved	Possibly related
59/M	VIIth Nerve Paralysis	270	No	1	Resolved	Not related
69/M	Vitiligo	1	No	1	Ongoing	Possibly related
Engerix-B						
DV2-HBV-10						
44/F[b]	ANCA Positive Vasculitis	126	Yes	3	Resolved	Not related
	Mixed Connective Tissue Disease	316	No	1	Ongoing	Not related
	Scleroderma	126	No	1	Ongoing	Not related
34/M	VIIth Nerve Paralysis	121	No	2	Resolved	Not related
30/F	Basedow's Disease	77	No	2	Ongoing	Not related
46/M	Raynaud's Phenomenon	32	No	1	Ongoing	Not related

Data Source: ISS Table 2.7.4-33 and Listing 4.1.

Table 26: Adverse Events of Special Interest by Treatment Group in DV2-HBV-10 and DV2-HBV-16 (Pooled Safety Population) (Cont'd, Table Footnotes)

ANCA = anti-neutrophil cytoplasmic antibody; F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.
Note: For SAEs, Days Since Last Active Dose is based on when the event initially met the criteria for seriousness.
[a] The assessment of "Probably Not Related" used in DV2-HBV-10 was considered equivalent to "Not Related" for analysis purposes.
[b] Note: Three events for this subject.

6.5.2.2 Subjects With Pre-existing Events of Special Interest

There is a theoretical risk that immune stimulation by adjuvants may exacerbate a pre-existing event of special interest. To examine this risk, subjects who had a pre-existing event of special interest were retrospectively identified, using the AESI list of MedDRA preferred terms to review medical history.

In the pivotal trials, 93 of 3777 (2.5%) HEPLISAV subjects and 23 of 1087 (2.1%) Engerix-B subjects with pre-existing events of special interest were identified. These subjects included 10 subjects in DV2-HBV-16 with pre-existing hypothyroidism (HEPLISAV: 8 [0.4%]); Engerix-B: 2 (0.2%)]. Skin disorders were the most frequent category of pre-existing event of special interest (HEPLISAV: 40 [1.1%]); Engerix-B: 11 [1.0%]), and psoriasis was the most frequent pre-existing event of special interest disorder (HEPLISAV: 30 [0.8%]); Engerix-B: 11 [1.0%]).

The percentage of subjects with pre-existing events of special interest who experienced an AE was higher in both treatment groups (HEPLISAV: 63.6%; Engerix-B: 69.6%) than in the phase 3 Safety Population overall (HEPLISAV: 55.3%; Engerix-B: 58.0%). When analyzed by SOC, the types of AEs in subjects with pre-existing events of special interest were similar to the types of AEs in the phase 3 Safety Population.

Among subjects with pre-existing events of special interest, 2.3% (2/88) HEPLISAV subjects experienced AESIs that were exacerbations of pre-existing disease. These events were systemic lupus erythematosus and rheumatoid arthritis. In the Engerix-B group, 4.3% (1/23) of subjects with pre-existing events of special interest who experienced an AESI had an exacerbation of a pre-existing disease. This event was mixed connective tissue disease.

6.5.3 Adjudicated Autoimmune Adverse Events in DV2-HBV-16

Dynavax implemented active surveillance and independent review of AIAEs to increase the sensitivity for detection and improve the specificity of diagnosis of such events. Investigators used a questionnaire to solicit signs and symptoms of potential AIAEs at each visit (Appendix 8).

Investigators were instructed to notify Dynavax within 24 hours after becoming aware of such an event and refer the subject for local expert evaluation. If the evaluation confirmed the diagnosis, the event was categorized as a potential autoimmune AE and was submitted to an independent SEAC.

The SEAC was established to increase the specificity of the assessment of events as autoimmune. It was comprised of 2 experts in autoimmune disease and 1 expert in infectious disease, external to Dynavax and not otherwise involved in the conduct of the trials. The SEAC was blind to treatment group and adjudicated all potential autoimmune events for both autoimmune etiology and relatedness to study treatment. The SEAC based its adjudication on the preponderance of evidence in their expert judgment. Events confirmed as autoimmune by the SEAC were reported to the trial's Data Safety Monitoring Board.

6.5.3.1 Findings for Adjudicated Autoimmune Events

A total of 9 non-serious AEs suspected to be autoimmune in nature were reported to the SEAC (Table 27). Two of these events, microscopic colitis and hypothyroidism, were adjudicated as not autoimmune and subsequently reassessed by the investigator as not potentially autoimmune and were withdrawn from the adjudication process. The SEAC adjudicated 5 of the remaining 7 events as autoimmune AEs: Hypothyroidism (n = 4) and vitiligo (n = 1). The 2 events that were not adjudicated as autoimmune were erythema nodosum and VIIth cranial nerve paralysis. All 5 events adjudicated as autoimmune were mild or moderate in severity and non-serious. Narratives for adjudicated autoimmune events are in Appendix 6, Section A6.4.

Testing was performed on banked baseline serum from the 4 adjudicated subjects with hypothyroidism. Two of these subjects were found to have a high thyroid stimulating hormone (TSH) and low free thyroxine-4 (T4) at screening, demonstrating pre-existing hypothyroidism, and 2 subjects had normal thyroid panels at screening. Based on this additional information, the SEAC concluded that 2 of the 4 AEs of hypothyroidism were new-onset.

In summary, 3 new-onset adjudicated autoimmune AEs were reported in DV2-HBV-16; 2 events of hypothyroidism and 1 event of vitiligo. All events occurred in the HEPLISAV group and were mild or moderate in severity and were non-serious. The event of vitiligo was already identified as an AESI. Therefore, this process identified 2 additional autoimmune events.

Table 27: Adverse Events Adjudicated by Safety Evaluation and Adjudication Committee in DV2-HBV-16

Age/ Sex	MedDRA Preferred Term	SAE	Relatedness As Considered by Investigator	As Adjudicated by SEAC			AESI?
				Related	AI	New-Onset	
58/F	Hypothyroidism	No	Possibly Related	No	**Yes**	**Yes**	**No**
53/F	Hypothyroidism	No	Not Related	No	**Yes**	**Yes**	**No**
69/M	Vitiligo[a]	No	Possibly Related	No	**Yes**	**Yes**	**Yes**
59/F	Hypothyroidism	No	Not Related	No	Yes	No[b]	No
57/M	Hypothyroidism	No	Possibly Related	No	Yes	No[b]	No
62/M	Erythema nodosum[a]	No	Possibly Related	Yes	No	Yes	Yes
59/M	VIIth nerve paralysis	No	Not related	No	No	Yes	Yes
43/F	Hypothyroidism[c]	No	Possibly Related	No	No	Yes	No
52/F	Microscopic colitis[c]	No	Not related	No	No	Yes	No

Data Source: DV2-HBV-16 CSR Table 12-15, DV2-HBV-16 CSR Listings 16.5 and 16.14.2.
AI = autoimmune; AESI = adverse event of special interest; CSR = clinical study report; F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; SEAC = safety and evaluation adjudication committee; TSH = thyroid-stimulating hormone.

[a] Events with MedDRA preferred terms corresponding to AESIs, which are therefore also included in the analysis of AESIs

[b] Post-study testing of baseline serum showed a low free T4 and a high TSH level.

[c] Event was initially reported as a potential autoimmune adverse event and subsequently modified to a non-autoimmune diagnosis (BLA 125428, SEQ 0007, dated 28 September 2012).

6.5.4 Relative Risk of Adverse Events of Special Interest and New-onset Adjudicated Autoimmune Events

To assess the risk of autoimmunity in HEPLISAV relative to Engerix-B, RRs were calculated for AESIs and for the combination of AESIs and new-onset adjudicated autoimmune events for all exposures to HEPLISAV or 1018 ISS Adjuvant. Relative risks are expressed as the risk in HEPLISAV recipients divided by the risk in Engerix-B recipients.

As shown in Table 28, in the phase 3 Safety Population, the RR for AESIs was 0.57 (95% CI: 0.17, 1.91). Across all trials, the RR for AESIs was 0.64 (95% CI: 0.22, 1.87).

Table 28: Relative Risk of Adverse Events of Special Interest

	Phase 3 Safety Population		All Trials Safety Population	
	HEPLISAV (N = 3777)	**Engerix-B (N = 1087)**	**HEPLISAV (ALL) (N = 4425)**	**Engerix-B (N = 1420)**
AESI (%)	**(0.21)**	**(0.37)**	**(0.23)**	**(0.35)**
Relative Risk (RR)[a]	0.57		0.64	
2-tailed 95% Confidence Interval[b]	0.17-1.91		0.22-1.87	

Data Source: ISS Table 2.7.4-40.
Risk Ratios for AESI. AESI = adverse event of special interest; CI = confidence interval; RR = relative risk.
[a] The point estimate of the relative risk is expressed as HEPLISAV/Engerix-B; a relative risk less than 1 indicates a lower point estimate for HEPLISAV risk than for Engerix-B risk.
[b] The 95% CI is the estimated 95% CI for relative risk between 2 cohorts.
Note: The relative risk and its CI were calculated by SAS PROC FREQ. The confidence level was computed by rounding down (1-alpha/2)*100%, where alpha was an option in TABLE statement set to the closest whole percentage point where the upper limit of the CI was at 1 or below.

As shown in Table 29, with the addition of the 2 new-onset adjudicated autoimmune events in DV2-HBV-16, the RR of all autoimmune events in the phase 3 Safety Population was 0.72 (95% CI: 0.23, 2.29), and the RR across all trials was 0.77 (95% CI: 0.27, 2.18).

Based on the observed AESIs and new-onset adjudicated autoimmune events in the pivotal trials, the rate of autoimmune events was similar in HEPLISAV recipients and Engerix-B recipients.

Table 29: Relative Risk of Adverse Events of Special Interest and Adjudicated Autoimmune Events

	DV2-HBV-10 and DV2-HBV-16 (Phase 3 Safety Population)		All Trials Safety Population	
	HEPLISAV (N = 3777)	**Engerix-B (N = 1087)**	**HEPLISAV (ALL) (N = 4425)**	**Engerix-B (N = 1420)**
AESI (%) or Adjudicated Autoimmune Events (%)	**(0.26)**	**(0.37)**	**(0.27)**	**(0.35)**
Relative Risk (RR)[a]	0.72		0.77	
2-tailed 95% Confidence Interval[b]	0.23-2.29		0.27-2.18	

Data Source: ISS Table 2.7.4-40.
Risk Ratios for AESI. AESI = adverse event of special interest; CI = confidence interval; RR = relative risk.
[a] The point estimate of the relative risk is expressed as HEPLISAV/Engerix-B; a relative risk less than 1 indicates a lower point estimate for HEPLISAV risk than for Engerix-B risk..
[b] The 95% CI is the estimated 95% CI for relative risk between 2 cohorts.
Note: The relative risk and its CI were calculated by SAS PROC FREQ. The confidence level was computed by rounding down (1-alpha/2)*100%, where alpha was an option in TABLE statement set to the closest whole percentage point where the upper limit of the CI was at 1 or below.

6.5.5 Laboratory Assessments of Autoimmunity and Inflammation

Laboratory assays for autoantibodies were performed as safety biomarkers related to autoimmunity. These assessments were performed independently of processes for clinical evaluation of predefined AESIs or adjudicated autoimmune events. ANA and anti-dsDNA testing were performed as a protocol-specified assessment in both pivotal phase 3 trials. ANCA testing was performed retrospectively on available banked specimens from study DV2-HBV-10 based on the occurrence of 2 events of ANCA-associated vasculitis in that trial.

6.5.5.1 Antinuclear Antibodies

The frequency of development of ANAs or increase in titers of pre-existing ANAs was similar between treatment groups. As shown in Table 30, the percentage of subjects with positive pre-vaccination ANA results was 7.5% in the HEPLISAV group and 9.1% in the Engerix-B group. The percentage of subjects with positive post-vaccination ANA results was 8.6% in the HEPLISAV group and 9.1% in the Engerix-B group. The percentage of subjects converting from a negative to a positive ANA result was similar between groups (HEPLISAV: 5.7%; Engerix-B: 5.3%). In both groups, most subjects with a positive pre-vaccination ANA result had a negative post-vaccination result (HEPLISAV: 55.9%; Engerix-B: 52.6%). The percentage of subjects with a positive pre-vaccination result and a post-treatment rise in titer was also similar between groups (HEPLISAV: 15.4%; Engerix-B: 16.8%).

Table 30: Antinuclear Antibody Results by Treatment Group (Phase 3 Safety Population)

Antinuclear Antibodies	HEPLISAV	Engerix-B
Pre-Vaccination, N	3772	1085
Negative (< 1:160), n (%)	3490 (92.5)	986 (90.9)
Positive (1:160 and above) n (%)	282 (7.5)	99 (9.1)
Post-Vaccination, N	3583	1038
Negative (< 1:160), n (%)	3274 (91.4)	944 (90.9)
Positive (1:160 and above) n (%)	309 (8.6)	94 (9.1)
Negative Pre-Vaccination, N[a]	3333	950
Positive Post-Vaccination, n (%)	189 (5.7)	50 (5.3)
Positive Pre-Vaccination, N[a]	272	95
Negative post-vaccination, n (%)	152 (55.9)	50 (52.6)
Lower titer post-vaccination, n (%)	35 (12.9)	13 (13.7)
Higher Titer Post-Vaccination, n (%)	42 (15.4)	16 (16.8)

Data Source: ISS Table 14.2.7.4-42, ad-hoc report "ana_results6.docx."
[a] Includes only subjects with evaluable (non-missing) pre-treatment and post-treatment results.

6.5.5.2 Anti-double-stranded Deoxyribonucleic Acid Antibodies

The rate of development of anti-dsDNA antibodies in recipients of HEPLISAV was similar to recipients of Engerix-B. As shown in Table 31, the percentage of subjects with a positive post-treatment anti-dsDNA result was 1.6% in the HEPLISAV group and 1.8% in the Engerix-B group. The percentage of subjects converting from a negative to a positive titer was 1.2% in the HEPLISAV group and 0.9% in the Engerix-B group. The percentage of subjects converting from a positive to a negative result was 52.6% in the HEPLISAV group and 43.8 % in the Engerix-B group.

Table 31: Anti-double Stranded Deoxyribonucleic Acid Results by Treatment Group (Phase 3 Safety Population)

Anti-dsDNA	HEPLISAV	Engerix-B
Pre-Vaccination, N	3767	1082
Positive, n (%)	38 (1.0)	16 (1.5)
Post-Vaccination, N	3581	1038
Positive, n (%)	57 (1.6)	19 (1.8)
Negative Pre-Vaccination, N	3729	1066
Positive Post-Vaccination, n (%)	44 (1.2)	10 (0.9)
Positive Pre-Vaccination, N	38	16
Negative Post-Vaccination, n (%)	20 (52.6)	7 (43.8)

Data Source: ISS Table 2.7.4-43, ad-hoc report "ana_results6.docx."
Anti-dsDNA = antibody to double-stranded DNA.

6.5.5.3 Anti-neutrophil Cytoplasmic Antibodies

An ELISA assay was used for screening followed by confirmatory IFA for any positive ELISA result. Specimens that were negative by both screening ELISAs were not tested further. Denominators in Table 32 are based on the number of subjects with evaluable pre- and post-vaccination results. From DV2-HBV-10, a total of 1780 HEPLISAV subjects and 596 Engerix-B subjects were analyzed. A total of 3 of 1780 HEPLISAV subjects (0.17%) and 2 of 96 Engerix-B subjects (0.34%) had a positive screening ELISA; all were positive before vaccination. All confirmatory IFA testing in DV2-HBV-10 was negative.

Table 32: Anti-neutrophil Cytoplasmic Antibody Testing Results by Treatment Group in DV2-HBV-10

Age range	11 to 55 years	
	HEPLISAV (N = 1780)	**Engerix-B (N = 596)**
Pre-Treatment, n (%)		
Anti-PR3 positive	2 (0.1)	2 (0.3)
c-ANCA positive	0 (0.0)	0 (0.0)
Anti-MPO positive	1 (0.1)	0 (0.0)
p-ANCA positive	0 (0.0)	Not done[a]
Post-Treatment, n (%)		
Anti-PR3 positive	2 (0.1)	2 (0.3)
c-ANCA positive	0 (0.0)	0 (0.0)
Anti-MPO positive	0 (0.0)	0 (0.0)
p-ANCA positive	Not done[a]	Not done[a]

Data Source: ISS Table 2.7.4-44; HEPLISAV Clinical Technical Report (CTR-HBV-01, Determination of Anti-neutrophil Cytoplasmic Antibody [ANCA] and C-reactive protein [CRP] Levels from HEPLISAV Clinical Studies).
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 only subjects who had evaluable pre- and post-treatment time points.
Note: If no screening test was positive no confirmatory test was performed.

6.6 Safety Summary

Safety data from phase 3 pivotal trials DV2-HBV-10 and DV2-HBV-16 demonstrate a similar safety profile for HEPLISAV when compared with Engerix-B. HEPLISAV was generally well tolerated with a safety profile similar to Engerix-B, a widely used, licensed hepatitis B vaccine considered to be very safe. HEPLISAV and Engerix-B had similar rates of local and systemic post-injection reactions, AEs, SAEs, and deaths. Intensive surveillance for autoimmune events revealed similar rates for AESIs, exacerbation of pre-existing events of special interest, autoimmune events, and autoantibody development. Lastly, the safety profile of HEPLISAV was similar across all subpopulations studied, including different age subgroups, races, smokers, and in subjects with diabetes or who were obese.

7.0 BENEFIT/RISK

7.1 Benefits

HEPLISAV has a favorable benefit/risk profile for the vaccination of adults at risk for hepatitis B infection. The immunogenicity is consistently higher than that of Engerix-B and the 2-dose, 1-month regimen has the potential to improve adherence. The combination of the higher immunogenicity and potential to improve adherence should result in higher seroprotection rates in actual use across all populations at risk for hepatitis B infection. The similarity of the safety profile of HEPLISAV to Engerix-B has been demonstrated in an integrated analysis of the HEPLISAV clinical studies. A comprehensive analysis of autoimmunity showed no increased rate of autoimmunity over Engerix-B.

7.1.1 Medical Need

Despite the success of hepatitis B vaccination in children, there remains a significant unmet need in adults at risk for hepatitis B infection. This group includes those at risk because of behavioral factors: Men having multiple sex partners, MSM, injection drug users; additionally at risk in this group are healthcare workers and others who in the course of their work are exposed to blood and other body fluids, and people who need rapid protection because they travel to areas where the incidence of HBV infection is high. Finally, certain medical conditions also predispose individuals to greater risk: Diabetes, chronic liver disease, HIV infection, and chronic kidney disease.

The unmet medical need in adults is also the result of limitations of currently available hepatitis B vaccines:

- The current 3-dose, 6-month schedule needed to achieve seroprotection for most persons makes adherence difficult and results in significant proportions of individuals receiving fewer than the required 3 doses, thus remaining unprotected.

- There are populations who are hyporesponsive to currently available hepatitis B vaccines, including older adults, men, persons who are obese, and smokers.

- The 6-month schedule for the currently licensed hepatitis B vaccines means that even a majority of subjects who receive all 3 doses as scheduled do not achieve seroprotection for at least 6 months.

HEPLISAV, with its improved immunogenicity and shorter dosing schedule, and similar safety profile has the potential to meet this medical need.

7.1.2 Demonstrated Benefits

Two doses of HEPLISAV over 1 month met not only the primary objective of noninferiority in the 2 pivotal phase 3 trials but also demonstrated that HEPLISAV induced significantly higher antibody levels than Engerix-B. HEPLISAV induced significantly higher peak seroprotection than Engerix-B in every comparison evaluated. HEPLISAV induced significantly higher SPRs at each early time point with a median time to seroprotection 20 weeks before that for Engerix-B.

In every subpopulation evaluated, HEPLISAV induced significantly higher peak SPRs than Engerix-B. This includes key populations with a high risk of HBV infection such as men, blacks, and individuals with diabetes. In addition, it includes those populations who are hyporesponsive to current vaccines such as older adults, persons who are obese, and smokers.

7.1.3 Potential Benefits

There is an important potential adherence benefit to HEPLISAV's 2-dose, 1-month schedule. The excellent adherence observed in the phase 3 trials is not what occurs in actual use. The VSD Study provides an example of real-world adherence across 3 age groups in a medical care setting. Rates of adherence to 2 doses of vaccine over 1 month were higher than rates of adherence to 3 doses over 6 months (Nelson, Bittner et al. 2009). Combining adherence data from VSD Study with SPR data from clinical trials results in the effective SPR; that is, the SPR expected in the real world. In the VSD Study of over 88000 enrollees in medical care organizations, adherence ranged from 74.3% of adults 18 to 29 years of age receiving 2 doses of hepatitis B vaccine and 53.1% receiving 3 doses to 84.9% of adults 50 to 64 years of age and older receiving 2 doses and 71.2% receiving 3 doses. Using adherence rates from VSD Study and SPRs from the pooled mITT population in the Dynavax pivotal phase 3 trials, it may be expected that the effective SPRs in the HEPLISAV groups are similar in all 3 age groups (83% to 84%) while the effective SPRs in the Engerix-B groups decrease from 63% in the youngest age group to 55% in the oldest age group. The difference in effective SPRs between the HEPLISAV and Engerix-B groups ranges from 20% to 28% (Appendix 3).

The impact of HEPLISAV in practice has the potential to be even greater than that of Engerix-B if one considers the combination of the significantly higher immunogenicity in a hyporesponsive population and a 2-dose schedule.

The CDC has published a model of the potential impact of implementation of the recent ACIP recommendation for routine hepatitis B vaccination of individuals with diabetes who are younger than 60 years of age. The CDC has reported on the lifetime outcomes of a hypothetical vaccination program of 5% of all unvaccinated adults with diabetes younger than 60 years of age in the United States (Sawyer and Hoerger 2011). According to that report, vaccinating the

estimated 528047 adults with diabetes would be expected to prevent 4271 HBV infections resulting in the prevention of 467 hospitalizations, 256 cases of chronic hepatitis B infection, 33 cases of hepatocellular carcinoma, 13 liver transplants, and 130 deaths. Outcomes of this model can highlight the potential benefit of HEPLISAV over Engerix-B. Using results for HEPLISAV and Engerix-B in diabetics from the Dynavax clinical trials and adherence data from the VSD Study, HEPLISAV would have 27.5% better seroprotection and 15.5% better adherence resulting in an overall benefit of 32.1% in effective seroprotection. Thus in this population of 528047 individuals, HEPLISAV would be expected to prevent 7359 HBV infections resulting in the prevention of 805 hospitalizations, 441 cases of chronic hepatitis B infection, 57 cases of liver cancer, 22 liver transplants, and 224 deaths. HEPLISAV would be expected to prevent 3088 more HBV infections than Engerix-B. HEPLISAV would result in 338 fewer hospitalizations, 185 fewer cases of chronic hepatitis B infection, 24 fewer cases of liver cancer, 9 fewer liver transplants, and 94 fewer deaths than would be expected if Engerix-B were used.

The final potential benefit of HEPLISAV is its shorter 2-dose, 1-month schedule. Unlike currently licensed vaccines that require more than 6 months to induce seroprotection in most people, HEPLISAV induced seroprotection in 92.0% of subjects by Week 12 while Engerix-B induced seroprotection in only 20.9% of subjects. While early seroprotection may not have a large public health benefit, for individuals who need rapid protection, the risk of exposure to HBV could be imminent, and the longer time to seroprotection increases the risk of infection.

The benefits of HEPLISAV over Engerix-B are notable, and they are achieved without an increase in risk.

7.2 Risks

The safety profile of HEPLISAV was similar to that of Engerix-B with respect to AEs.

7.2.1 Demonstrated Risks

The demonstrated risks of HEPLISAV are primarily mild to moderate post-injection reactions. HEPLISAV induces local and systemic post-injection reactions. The post-injection reaction profile of HEPLISAV was similar to that of Engerix-B. The post-injection reaction profile of HEPLISAV is consistent with a short-term, local immune response and is similar to that of Engerix-B. As with other injectable vaccines, syncope may occur with intramuscular injection of HEPLISAV.

7.2.2 Potential Risks

There are limited data on the use of HEPLISAV in pregnant women so the risks of use in pregnancy are unknown. A summary of the use of HEPLISAV in pregnant women is in

Appendix 9. Though not seen in the development program, because the HBsAg used in HEPLISAV is manufactured using yeast, HEPLISAV has the potential to cause hypersensitivity reaction in persons with an allergy to yeast and is therefore contraindicated in this population. This is consistent with the licensed hepatitis B vaccines that are also manufactured using yeast. The Institute of Medicine found a causal relationship between anaphylaxis and currently licensed hepatitis B vaccines in yeast sensitive persons with a rate of 1.1 per million doses.

8.0 CONCLUSION

Hepatitis B remains a public health problem in adults in the United States. Current vaccines provide over 90% seroprotection in the pediatric population but less well in adults, particularly in some subgroups at high risk for infection. Adherence to a 3-dose, 6-month schedule is very challenging for some of the highest risk groups and often results in high rates of noncompliance. Lastly, the delayed time to achieve seroprotective levels of antibody leaves some persons without seroprotection and at unnecessarily prolonged risk for infection. Clinicians need another option to overcome these limitations.

HEPLISAV stimulates a pathway in the innate immune system that is an element of the natural response to an infection. By doing so, compared with current vaccines, HEPLISAV: (1) induces significantly higher levels of seroprotection; (2) should increase adherence by virtue of its shorter 2-dose schedule over 1 month; (3) induces high levels of seroprotection in populations hyporesponsive to currently available vaccines, as well as in populations with good responses; and, (4) provides earlier seroprotection which might be beneficial to certain high risk persons in need of rapid protection.

The safety profile of HEPLISAV was similar to Engerix-B. Despite enhanced safety surveillance for autoimmunity, there was no observed increase in the occurrence of local and systemic post injections, new onset autoimmune disease, exacerbation of pre-existing autoimmune disease, or induction of autoantibodies in HEPLISAV recipients over that observed in Engerix-B recipients.

Based on these considerations, the approval of HEPLISAV would benefit adults 18 through 70 years old who are at risk for HBV infection.

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APPENDIX 1: MANUFACTURE OF 1018 ISS ADJUVANT, HBsAg DRUG SUBSTANCE, AND HEPLISAV DRUG PRODUCT

Manufacturing and testing of the 1018 ISS Adjuvant are performed at:

NITTO DENKO, Avecia Inc. (formerly Avecia Biotechnology, Inc.)
155 Fortune Boulevard
Milford, MA 01757
USA

Manufacturing and testing of the HBsAg Drug Substance are performed at:

Rhein Biotech GmbH
Eichsfelder Straße 11
40595 Düsseldorf
Germany

Formulation and fill of the 1018 ISS-HBsAg Drug Product are performed at:

Rentschler Biotechnologie GmbH
Erwin Rentschler Straße 21
88471 Laupheim
Germany

1018 ISS Adjuvant and HBsAg Drug Substance Production and Control

HEPLISAV Drug Product (1018 ISS-HBsAg) is produced as an aqueous solution containing 6000 mcg/mL of 1018 ISS Adjuvant and 40 mcg/mL of HBsAg Drug Substance in phosphate buffered saline at pH 7 with 0.01% Polysorbate 80 (w/w). All clinical study material manufactured to date has been filled into 2-mL glass vials.

The 1018 ISS Adjuvant is synthesized on a controlled-pore glass support using an automated synthesizer, following current Good Manufacturing Practices (cGMPs). The required oligodeoxynucleotide (ODN) sequence, containing phosphorothioate linkages, is assembled using the standard beta-cyanoethylphosphoramidite approach of detritylation, coupling, oxidation (thiolation), and capping. The NITTO DENKO, Avecia Inc. process produces freeze-dried 1018 ISS ODN as an adjuvant.

The HBsAg Drug Substance is produced following cGMPs in yeast *Hansenula polymorpha* cells. The process produces HBsAg Drug Substance as a liquid that requires storage at 2°C to 8°C. The Drug Substance is alum free.

HEPLISAV Drug Product is formulated by Rentschler Biotechnologie GmbH (Germany) in an 8 mM sodium phosphate/154 mM sodium chloride/0.01% w/w polysorbate 80/pH 7.0 buffer. Drug Product is supplied as 40 mcg/mL of HBsAg and 6000 mcg/mL of 1018 ISS in a 2-mL vial containing 0.7 mL of sterile solution (28 mcg of HBsAg and 4200 mcg of 1018 ISS per vial) of which a 0.5 mL dose is administered. Vials must be stored at 2°C to 8°C. The Drug Product is alum free.

HEPLISAV Drug Product Stability

Available stability data indicate that HEPLISAV Drug Product is stable for up to 24 months when stored at 2°C to 8°C, the recommended storage temperature. Additional stability studies are ongoing.

Preparation and Administration of HEPLISAV Drug Product

Preparation and administration of the HEPLISAV vaccine must be followed according to the instructions provided in the study protocol. The HEPLISAV is supplied as a single-dose vial and must be used within 8 hours of removing from refrigeration for injection preparation.

Hansenula polymorpha is the yeast used to express the rHBsAg for Crucell's hepatitis B vaccine, Hepavax-Gene. "Since its introduction in 1996, more than 596 million doses have been sold in over 90 countries making it the third most used hepatitis B vaccine in the world (Crucell press release dated 08 December 2012)." The safety and immunogenicity of hepatitis B vaccines that use rHBsAg produced in *Hansenula* have been demonstrated to be comparable to that of Engerix-B (Rebedea, Diaconescu et al. 2006; Tregnaghi, Voelker et al. 2010)

APPENDIX 2: COMPLETED CLINICAL TRIALS OF HEPLISAV

Table 33: Completed Trials of HEPLISAV

Phase/ Study No.	Study Design	HEPLISAV Dose/Schedule/N	Comparator Dose/Schedule/N	Key Immunogenicity/ Safety Endpoint(s)
Phase 1 Clinical Trials				
HBV0001	Observer-blind, randomized, dose-escalation trial of the 1018 ISS Adjuvant component of vaccine in healthy, seronegative adults 18 to 55 years old conducted in Canada	• HBsAg: constant at 20 mcg, plus 1018 ISS Adjuvant at: 300 mcg 650 mcg 1000 mcg 3000 mcg • Schedule: 0, 8 weeks • N = 32	• HBsAg: 20 mcg alone • N = 8 • 1018 ISS Adjuvant alone: 300 mcg, 650 mcg, 1000 mcg, 3000 mcg • N = 8	• Anti-HBs measured after vaccination
Phase 2 Clinical Trials				
DV2-HBV-02	Observer-blind, randomized, parallel-group trial of hypo- and non-responders to licensed hepatitis B vaccine in adults 18 to 65 years old conducted in Canada	• HEPLISAV (F1): 20 mcg/3000 mcg • Schedule: single injection • N = 30	• Engerix-B: 20 mcg HBsAg • Schedule: single injection • N = 29	• SPR at Week 4
DV2-HBV-03	Observer-blind, randomized, parallel-group trial in adults 18 to 28 years old conducted in Canada	• HEPLISAV (F1): 20 mcg/3000 mcg • Schedule: 0, 8 weeks (placebo/ meningococcal vaccine at 24 weeks) • N = 48	• Engerix-B: 20 mcg HBsAg • Schedule: 0, 8, 24 weeks • N = 51	• SPR at Week 28
DV2-HBV-05	Double-blind, randomized, parallel-group trial in adults 40 to 70 years old in Singapore	• HEPLISAV (F2) • Schedule: 0, 8, 24 weeks • N = 48	• Engerix-B • Schedule: 0, 4, 24 weeks • N = 47	• AEs (25 weeks) • SAEs (50 weeks) • Local and systemic post-injection reactions (7 days following each injection) • Clinical laboratory tests (serum chemistry, hematology, ANA, and anti-dsDNA), vital signs; and concomitant medication use

Table 33: Completed Trials of HEPLISAV (Cont'd)

Phase/ Study No.	Study Design	HEPLISAV Dose/Schedule/N	Comparator Dose/Schedule/N	Key Immunogenicity/ Safety Endpoint(s)
Phase 2 Clinical Trials (continued)				
DV2-HBV-08	Double-blind, randomized, parallel-group trial in adults 18 to 39 years old in Canada	HEPLISAV (F2) • Schedule: 0, 4 weeks and 0, 8 weeks HEPLISAV (F2) Half Dose (10 mcg/1500 mcg) • Schedule: 0, 4 weeks • N = 61	• None	• AEs (12 weeks) • SAEs (32 weeks) • Local and systemic post-injection reactions (7 days following each injection) • Clinical laboratory tests (serum chemistry, hematology, urinalysis, ANA); vital signs; and concomitant medication use
DV2-HBV-14[a]	Open-label trial in healthy subjects 11 to 55 years old conducted in the US	• HEPLISAV (F3): 20 mcg/3000 mcg • Schedule: 0, 4 weeks • N = 207	• None	• SPR at Weeks 4, 8, 12, and 28 • GMC at Weeks 4, 8, 12, and 28
Phase 3 Clinical Trials				
DV2-HBV-04	Double-blind, randomized, parallel-group trial in adults 40 to 70 years old in South Korea, Philippines, and Singapore	• HEPLISAV (F2) • Schedule: 0, 8, 24 weeks (placebo at 4 weeks) • N = 206	• Engerix-B • Schedule: 0, 4, 24 weeks (placebo at 8 weeks) • N = 206	• AEs (28 weeks) • SAEs (50 weeks) • Local and systemic post-injection reactions (7 days following each injection) • Clinical laboratory tests (serum chemistry, hematology); vital signs; and concomitant medication use
DV2-HBV-10 (Pivotal Trial)	Observer-blind, randomized, active-controlled, parallel-group, multicenter trial in healthy subjects 11 to 55 years old conducted in Canada and Germany	• HEPLISAV (F3): 20 mcg/3000 mcg • Schedule: 0, 4 weeks (placebo at 24 weeks) • N = 1820	• Engerix-B: 20 mcg HBsAg • Schedule: 0, 4, 24 weeks • N = 608	• Primary Endpoint • SPR at Week 12 for HEPLISAV and Week 28 for Engerix-B

Table 33: Completed Trials of HEPLISAV (Cont'd)

Phase/ Study No.	Study Design	HEPLISAV Dose/Schedule/N	Comparator Dose/Schedule/N	Key Immunogenicity/Safety Endpoint(s)
Phase 3 Clinical Trials (continued)				
DV2-HBV-16 (Pivotal Trial)	Observer-blind, randomized, active-controlled, parallel-group, multicenter trial in healthy adults 40 to 70 years old conducted in the US and Canada	• HEPLISAV (F3): 20 mcg/3000 mcg • Schedule: 0, 4 weeks (placebo at 24 weeks) • N = 1969	• Engerix-B: 20 mcg HBsAg • Schedule: 0, 4, 24 weeks • N = 483	• Primary Endpoint • SPR at Week 12 for HEPLISAV and Week 32 for Engerix-B • Lot consistency of HEPLISAV measured by GMC at Week 8

Data Sources: CSRs for HBV0001, DV2-HBV-02, DV2-HBV-03, DV2-HBV-04, DV2-HBV-05, DV2-HBV-08, DV2-HBV-10, DV2-HBV-14, and DV2-HBV-16.
ANA = antinuclear antibody; anti-dsDNA = antibody against double-stranded deoxyribonucleic acid; anti-HBs = antibody against hepatitis B surface antigen; CSR = clinical study report; GMC = geometric mean concentration; HBsAg = hepatitis B virus surface antigen; HEPLISAV = proposed commercial formulation of HEPLISAV comprises 20 mcg recombinant HBsAg subtype *adw* and 3000 mcg 1018 ISS Adjuvant in a single-vial presentation; HEPLISAV (F1) = 20 mcg recombinant HBsAg subtype *adw* and 3000 mcg 1018 ISS Adjuvant in a 2-vial presentation; 1018 ISS Adjuvant = 1018 immunostimulatory sequence; N = number of randomized subjects; a dose of Engerix-B comprises 20 mcg recombinant HBsAg and 500 mcg aluminum hydroxide; SPR = seroprotection rate.
[a] No subject < 18 years old was enrolled in DV2-HBV-14.

Three formulations of HEPLISAV have been tested during the clinical development program:

- HEPLISAV (F1), which comprises 20 mcg HBsAg subtype *adw* and variable concentrations of 1018 ISS Adjuvant in a 2-vial presentation;
- HEPLISAV (F2), which comprises 20 mcg HBsAg subtype *adr* and 3000 mcg 1018 ISS Adjuvant in a single-vial or 2-vial presentation; and,
- HEPLISAV, also known as HEPLISAV (F3), which comprises 20 mcg HBsAg subtype *adw* and 3000 mcg 1018 ISS Adjuvant in a single-vial presentation and is the proposed commercial formulation.

APPENDIX 3: VACCINE DATALINK STUDY

The potential adherence benefit of HEPLISAV was calculated using adherence rates from the VSD and SPRs from the Dynavax pivotal phase 3 trials.

Table 34 presents adherence data from the VSD Study by age group (Nelson, Bittner et al. 2009). Adherence was lowest in young adults and highest in older adults. Of individuals 18 to 29 years of age in the VSD Study, 74.3% received at least 2 doses of licensed hepatitis B vaccine and 53.1% received the complete series of 3 doses over the 8-year study period. Among those 50 to 64 years of age, 84.9% of individuals received at least 2 doses of hepatitis B vaccine and 71.2% received all 3 doses.

Table 34: Percentage of Participants in Vaccine Safety Datalink Study in Each Adherence Category for Hepatitis B Vaccine by Age Group

Age Subgroup (years)	N	Received 3 Doses (n)[a]	Received 3 Doses (%)	Received Only 2 Doses (n)	Received Only 2 Doses (%)	Received Only 1 Dose (n)	Received Only 1 Dose (%)
18 - 29	23179	12308	53.1	4914	21.2	5957	25.7
30 - 49	41359	27090	65.5	6783	16.4	7486	18.1
50 - 64	18776	13369	71.2	2572	13.7	2835	15.1

Source: (Nelson, Bittner et al. 2009).
n = number of individuals who received specified number of doses in age group; N = number of individuals in each age group.
[a] Received all 3 doses over the 8-year study period.

For estimates of the differences in SPRs by age group and dose between HEPLISAV and Engerix-B, SPR data from all subjects (18 years of age and older) in the pooled analysis of DV2-HBV-10 and DV2-HBV-16 were used. Table 35 presents data on SPRs following dose 1 and 2 for both vaccines, and dose 3 for Engerix-B for each age group. The SPR following the first injection was measured at Week 4 prior to the second dose of vaccine. The highest SPR following 2 doses was measured at Week 24 for both vaccines.

Table 35: Seroprotection Rate by Dose and Age Group for HEPLISAV and Engerix-B (pooled mITT population)

Visit/ Age Stratum	HEPLISAV[a] n/N	HEPLISAV[a] % (95% CI)[c]	Engerix-B[b] n/N	Engerix-B[b] % (95% CI)[c]	% Difference HEPLISAV - Engerix-B (95% CI)[d]
Week 4					
Following 1 dose					
18 - 29	109/311	35.0 (29.7, 40.6)	7/100	7.0 (2.9, 13.9)	28.0 (19.5, 34.5)
30 - 49	414/1767	23.4 (21.5, 25.5)	21/566	3.7 (2.3, 5.6)	19.7 (17.0, 22.1)
50 - 64	265/1415	18.7 (16.7, 20.9)	16/362	4.4 (2.5, 7.1)	14.3 (11.0, 17.0)
Week 24					
Following 2 doses					
18 - 29	305/306	99.7 (98.2, 100.0)	55/95	57.9 (47.3, 68.0)	41.8 (32.2, 51.8)
30 - 49	1680/1717	97.8 (97.0, 98.5)	152/551	27.6 (23.9, 31.5)	70.3 (66.3, 73.9)
50 - 64	1303/1375	94.8 (93.5, 95.9)	73/357	20.4 (16.4, 25.0)	74.3 (69.6, 78.3)
Week 28					
Following 3 doses					
18 - 29			89/96	92.7 (85.6, 97.0)	
30 - 49			429/548	78.3 (74.6, 81.7)	
50 - 64			254/355	71.5 (66.5, 76.2)	

Data Source: Ad hoc SPR by Visit by Age Group.
anti-HBs = antibody against hepatitis B surface antigen; CI = confidence interval; mITT = modified intent-to-treat; n = number of subjects with post-injection anti-HBsAg greater than or equal to 10 mIU/mL; N = number of subjects in the analysis population in the group; 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.
[c] 95% CIs of seroprotection rates were calculated using the Clopper-Pearson method.
[d] 95% CIs of the difference in seroprotection rates between the HEPLISAV group and the Engerix-B group were calculated using the Newcombe score method with continuity correction.

The effective SPRs, or the SPRs that might be expected in actual use of HEPLISAV, were calculated by combining the adherence data from the VSD Study with the SPR data from the HEPLISAV pivotal trials for each age group (Table 36). For example, in persons 18 to 29 years of age, multiplying the SPR following 1 dose of HEPLISAV (25.7%) times the adherence rate

(35.0%) results in an effective SPR of 9%. The results by age group are summarized in Table 37. The effective SPRs in the HEPLISAV groups are similar in all 3 age groups (83% to 84%) while the effective SPRs in the Engerix-B groups decrease from 63% in the youngest age group to 55.6% in the oldest age group. The difference in effective SPRs between the HEPLISAV and Engerix-B groups ranges from 20% to 28%.

Table 36: Comparison of Effective Seroprotection Rates by Age Group and Maximum Doses Received in Individuals Who Received HEPLISAV or Engerix-B

	HEPLISAV			Engerix-B			
Maximum Number of Doses Received	**% of Subjects Receiving Number of Doses [a]**	**SPR (%) [b]**	**Effective SPR (%) [c]**	**% of Subjects Receiving Number of Doses [d]**	**SPR (%) [b]**	**Effective SPR (%) [c]**	**Difference in Effective SPRs (%) (HEPLISAV – Engerix-B)**
18 – 29 years							
Only 1 Dose	25.7	35.0[e]	9	25.7	7.0[e]	2	
Only 2 Doses	74.3	99.7[f]	74	21.2	57.9[f]	12	
3 Doses	NA	NA	NA	53.1	92.7[g]	49	
Total			83			63	20
30 – 49 years							
Only 1 Dose	18.1	23.4	4	18.1	3.7	1	
Only 2 Doses	81.9	97.8	80	16.4	27.6	5	
3 Doses	NA	NA	NA	65.5	78.3	51	
Total			84			57	27
50 – 64 years							
Only 1 Dose	15.1	18.7	3	15.1	4.4	1	
Only 2 Doses	84.9	94.8	80	13.7	20.4	3	
3 Doses	NA	NA	NA	71.2	71.5	51	
Total			83			55	28

Data Source: Ad hoc SPR by Visit by Age Group.
mITT = modified intent-to-treat; NA = not applicable; SPR = seroprotection rate.

[a] Percentage of subjects receiving vaccine was derived from data in (Nelson, Bittner et al. 2009). Percentage of subjects receiving 2 doses of HEPISAV is the sum of the percentage of subjects who received 2 doses of Engerix-B and 3 doses of Engerix-B in (Nelson, Bittner et al. 2009).

[b] SPRs are shown for subjects 18 years of age and older who participated in DV2-HBV-10 and DV2-HBV-16 (Pooled Pivotal Trials mITT Analysis Population).

[c] Effective SPR is defined as the product of the percentage of individuals receiving the indicated number of doses multiplied by the SPR for that number of doses.

[d] Percentage of subjects receiving vaccine is from (Nelson, Bittner et al. 2009).

[e] SPR is based on SPR after 1 dose of study treatment measured at Week 4 in the Pooled Pivotal Trials mITT Analysis Population.

[f] SPR is based on highest SPR after 2 doses of vaccine measured at Week 24 in the Pooled Pivotal Trials mITT Analysis Population.

[g] SPR is based on highest SPR after 3 doses of Engerix-B measured at Week 28 in the Pooled Pivotal Trials mITT Analysis Population.

Table 37: Summary of Effective Seroprotection Rates by Age Group in Individuals Who Received HEPLISAV or Engerix-B

	HEPLISAV			Engerix-B			
Age Group	**Subjects Receiving 2 Doses (%)[a]**	**SPR (%)[b]**	**Effective SPR (%)[c]**	**Subjects Receiving 3 Doses (%)[a]**	**SPR (%)[b]**	**Effective SPR (%)[c]**	**Difference in Effective SPRs (%) (HEPLISAV – Engerix-B)**
18 – 29	74.3	99.7	83	53.1	92.7	63	20
30 – 49	81.9	97.8	84	65.5	78.3	57	27
50 – 64	84.9	94.8	83	71.2	71.5	55	28

Data Source: Ad hoc SPR by Visit by Age Group.
mITT = modified intent-to-treat; SPR = seroprotection rate; VSD = Vaccine Safety Datalink.
[a] Percentage of subjects receiving indicated number of doses vaccine was derived from VSD data in (Nelson, Bittner et al. 2009). Percentage of subjects receiving 2 doses of HEPISAV is the sum of the percentage of subjects who received 2 doses of Engerix-B and 3 doses of Engerix-B in (Nelson, Bittner et al. 2009).
[b] SPRs shown are the peak SPR for each vaccine in each age group of subjects who participated in DV2-HBV-10 and DV2-HBV-16 (Pooled Pivotal Trials mITT Analysis Population).
[c] Effective SPR total for each age group for each vaccine in Table 36.

APPENDIX 4: SUBGROUP IMMUNOGENICITY ANALYSES

Geometric Mean Concentrations

In the DV2-HBV-10 PP population, the GMC was significantly higher in the HEPLISAV group than in the Engerix-B group at each visit from Week 4 through Week 24. At Week 28, the GMC in the HEPLISAV group was 320.0 mIU/mL which was similar to the GMC in the Engerix-B group of 348.2 mIU/mL with the ratio of GMCs = 0.92. The GMC in those subjects 18 to 39 years old was higher in the Engerix-B group than in the HEPLISAV group, and in those 40 to 55 years old, the GMC was similar in both groups.

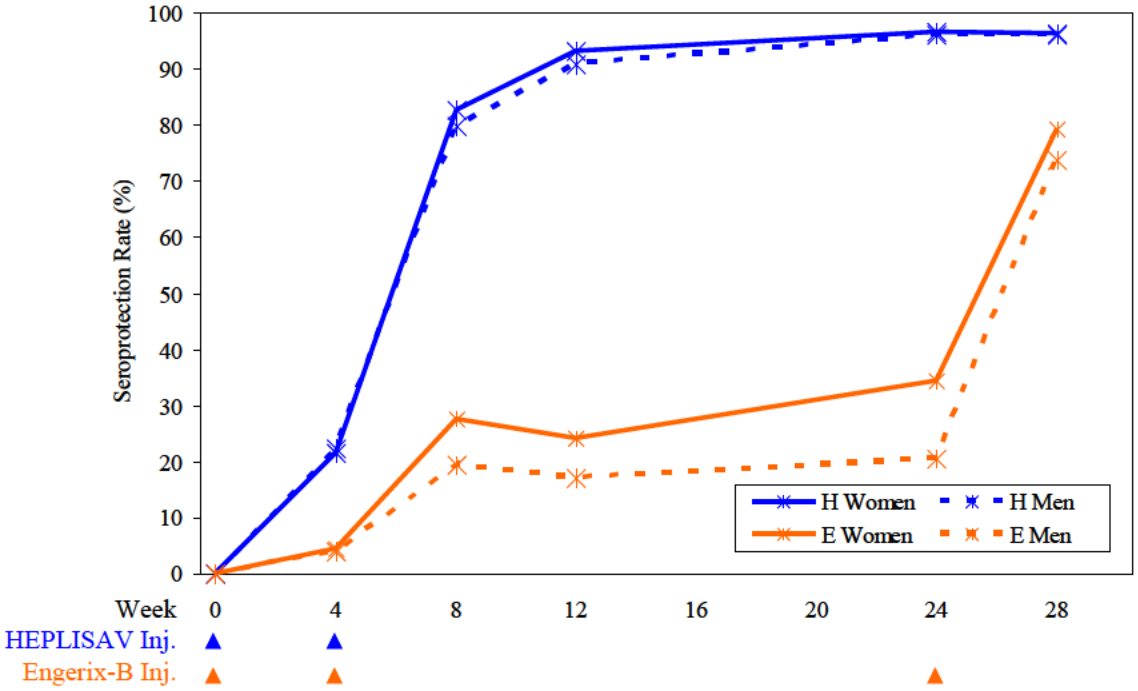
In DV2-HBV-16, the GMC was significantly higher in the HEPLISAV group than in the Engerix-B group at each visit from Week 4 through Week 52. At Week 24, the GMC in the HEPLISAV group was 232.7 mIU/mL, and at Week 28 the GMC in the Engerix-B group was 88.5 mIU/mL.

SPR by Sex

In both men and women, the peak SPR in the HEPLISAV group was significantly higher than in the Engerix-B group. For both men and women, seroprotection was achieved earlier with HEPLISAV than with Engerix-B (Figure 5).

In men, the peak SPR of 96.1% in the HEPLISAV group was significantly higher than the peak SPR of 73.7% in the Engerix-B group. In women the peak SPR of 96.6% in the HEPLISAV group was significantly higher than the peak SPR of 79.3% in women in the Engerix-B group (Table 38). In addition, the SPR at each visit in both men and women who received HEPLISAV was significantly higher than in men and women, respectively, who received Engerix-B.

Figure 5: Seroprotection Rates by Sex and Visit in DV2-HBV-10 and DV2-HBV-16 (Pooled mITT Analysis Population)



Data Source: BLA Section 2.7.3, Figure 2.7.3-8.
E = Engerix-B; H = HEPLISAV; inj = injection; mITT = modified intent-to-treat.

Table 38: Seroprotection Rates by Sex and Visit in DV2-HBV-10 and DV2-HBV-16 (Pooled mITT Analysis Population)

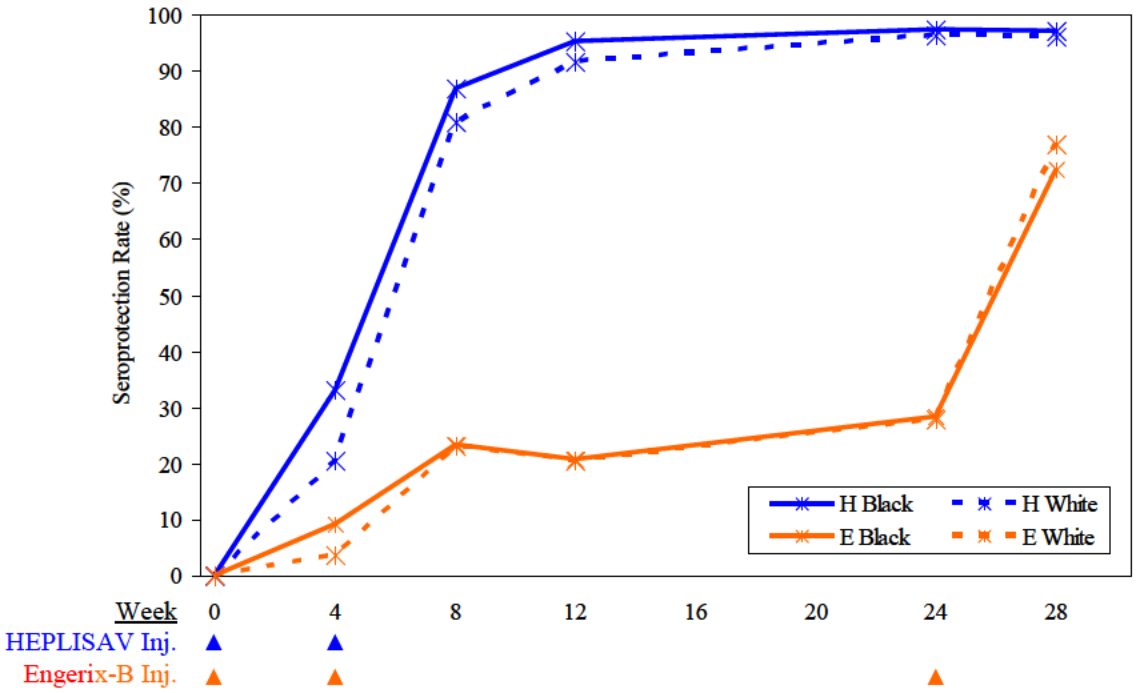
Sex/ Visit	HEPLISAV[a] n/N	HEPLISAV[a] SPR (%) (95% CI)[c]	Engerix-B[b] n/N	Engerix-B[b] SPR (%) (95% CI)[c]	Difference in SPRs (%) (HEPLISAV-Engerix-B) (95% CI)[d]
Men					
Peak[e]	1644/1711	96.1 (95.1, 97.0)	356/483	73.7 (69.5, 77.6)	22.4 (18.5, 26.6)
Week 4	395/1767	22.4 (20.4, 24.4)	20/494	4.0 (2.5, 6.2)	18.3 (15.5, 20.7)
Week 8	1394/1747	79.8 (77.8, 81.7)	95/490	19.4 (16.0, 23.2)	60.4 (56.2, 64.1)
Week 12	1574/1735	90.7 (89.3, 92.0)	83/485	17.1 (13.9, 20.8)	73.6 (69.7, 76.9)
Week 24	1644/1711	96.1 (95.1, 97.0)	99/483	20.5 (17.0, 24.4)	75.6 (71.6, 79.0)
Women					
Peak[e]	1845/1909	96.6 (95.7, 97.4)	448/565	79.3 (75.7, 82.6)	17.4 (14.1, 21.0)
Week 4	418/1956	21.4 (19.6, 23.3)	26/583	4.5 (2.9, 6.5)	16.9 (14.2, 19.2)
Week 8	1605/1939	82.8 (81.0, 84.4)	158/575	27.5 (23.9, 31.3)	55.3 (51.1, 59.1)
Week 12	1792/1925	93.1 (91.9, 94.2)	139/576	24.1 (20.7, 27.8)	69.0 (65.1, 72.4)
Week 24	1845/1909	96.6 (95.7, 97.4)	196/569	34.4 (30.5, 38.5)	62.2 (58.1, 66.1)

Data Source: BLA Section 2.7.3, Table 2.7.3-13.
CI = confidence interval; n = Number of subjects with anti-HBs ≥ 10 mIU/mL in the treatment group; N = Number of subjects in the treatment group; SPR = seroprotection rate (proportion of subjects with anti-HBs ≥ 10 mIU/mL).
[a] Study injections were given at Weeks 0, 4, and 24 (placebo).
[b] Study injections were given at Weeks 0, 4, and 24.
[c] 95% CIs of SPRs were calculated using Clopper-Pearson method.
[d] 95% CI of difference in SPRs was calculated using Newcombe score method with continuity correction.
[e] Peak SPR occurred in HEPLISAV subjects at Week 24 and in Engerix-B subjects at Week 28.

SPR by Race

In white subjects and black subjects, HEPLISAV induced higher peak SPRs and higher SPRs at each visit than Engerix-B, thereby providing earlier seroprotection in both white subjects and black subjects. Figure 6 and Table 39 present a comparison of SPRs by race and visit for the pooled analysis of HBV-10 and HBV-16. The small number of subjects who were Asian or "Other" who received Engerix-B in these studies limits the usefulness of the comparative data from these 2 racial subgroups. Peak SPRs in Asians and subjects of "Other" race who received HEPLISAV were generally similar to peak SPRs in white subjects and black subjects.

Figure 6: Seroprotection Rates by Race and Visit in DV2-HBV-10 and DV2-HBV-16 (Pooled mITT Analysis Population)



Data Source: BLA Section 2.7.3, Figure 2.7.3-9.
E = Engerix-B; H = HEPLISAV; inj = injection; mITT = modified intent-to-treat.

In white subjects, the peak SPR induced by HEPLISAV, which occurred at Week 24, was 96.3% and the peak SPR induced by Engerix-B, which occurred at Week 28, was 77.0% with a difference in SPRs of 19.3% (95% CI: 16.6%, 22.2%). In black subjects, the peak SPR after 2 doses of HEPLISAV was 97.4% and the peak SPR after 3 doses of Engerix-B was 72.5% with a difference in SPRs of 24.9% (95% CI: 16.0%, 35.6%) (Table 39). In addition, the SPR at each visit in both whites and blacks who received HEPLISAV was significantly higher than in whites and blacks, respectively, who received Engerix-B.

Table 39: Seroprotection Rates by Race and Visit in DV2-HBV-10 and DV2-HBV-16 (Pooled mITT Analysis Population)

Visit Race	HEPLISAV[a]		Engerix-B[b]		Difference in SPRs (%) (HEPLISAV-Engerix-B) (95% CI)[d]
	n/N	SPR (%) (95% CI)[c]	n/N	SPR (%) (95% CI)[c]	
Week 24/28[e]					
White	3078/3196	96.3 (95.6, 96.9)	713/926	77.0 (74.1, 79.7)	19.3 (16.6, 22.2)
Black	296/304	97.4 (94.9, 98.9)	58/80	72.5 (61.4, 81.9)	24.9 (16.0, 35.6)
Asian	61/63	96.8 (89.0, 99.6)	23/26	88.5 (69.8, 97.6)	8.4 (-2.0, 26.3)
Other[f]	54/57	94.7 (85.4, 98.9)	10/16	62.5 (35.4, 84.8)	32.2 (11.8, 55.9)
Week 4					
White	674/3271	20.6 (19.2, 22.0)	34/949	3.6 (2.5, 5.0)	17.0 (15.1, 18.8)
Black	108/327	33.0 (28.0, 38.4)	8/86	9.3 (4.1, 17.5)	23.7 (14.3, 30.5)
Asian	19/65	29.2 (18.6, 41.8)	4/26	15.4 (4.4, 34.9)	13.8 (-6.9, 28.5)
Other[f]	12/60	20.0 (10.8, 32.3)	0/16	0.0 (0.0, 20.6)	20.0 (-2.4, 32.4)
Week 8					
White	2623/3245	80.8 (79.4, 82.2)	217/937	23.2 (20.5, 26.0)	57.7 (54.5, 60.6)
Black	279/321	86.9 (82.7, 90.4)	20/86	23.3 (14.8, 33.6)	63.7 (52.8, 71.9)
Asian	55/65	84.6 (73.5, 92.4)	13/26	50.0 (29.9, 70.1)	34.6 (13.9, 53.5)
Other[f]	42/55	76.4 (63.0, 86.8)	3/16	18.8 (4.0, 45.6)	57.6 (30.0, 71.6)
Week 12					
White	2955/3223	91.7 (90.7, 92.6)	192/937	20.5 (17.9, 23.2)	71.2 (68.3, 73.8)
Black	299/314	95.2 (92.2, 97.3)	17/82	20.7 (12.6, 31.1)	74.5 (64.0, 82.0)
Asian	62/65	95.4 (87.1, 99.0)	9/26	34.6 (17.2, 55.7)	60.8 (39.9, 75.8)
Other[f]	50/58	86.2 (74.6, 93.9)	4/16	25.0 (7.3, 52.4)	61.2 (34.3, 76.2)
Week 24					
White	3078/3196	96.3 (95.6, 96.9)	259/929	27.9 (25.0, 30.9)	68.4 (65.4, 71.3)
Black	296/304	97.4 (94.9, 98.9)	23/81	28.4 (18.9, 39.5)	69.0 (58.0, 77.6)
Asian	61/63	96.8 (89.0, 99.6)	8/26	30.8 (14.3, 51.8)	66.1 (45.2, 79.9)
Other[f]	54/57	94.7 (85.4, 98.9)	5/16	31.3 (11.0, 58.7)	63.5 (37.6, 79.8)
Week 28					
White	3061/3185	96.1 (95.4, 96.8)	713/926	77.0 (74.1, 79.7)	19.1 (16.4, 22.0)
Black	287/296	97.0 (94.3, 98.6)	58/80	72.5 (61.4, 81.9)	24.5 (15.6, 35.2)
Asian	60/62	96.8 (88.8, 99.6)	23/26	88.5 (69.8, 97.6)	8.3 (-2.2, 26.2)
Other[f]	55/58	94.8 (85.6, 98.9)	10/16	62.5 (35.4, 84.8)	32.3 (12.0, 56.0)

Table 39: Seroprotection Rates by Race and Visit in DV2-HBV-10 and DV2-HBV-16 (Pooled mITT Analysis Population) (Cont'd, Table Footnotes)

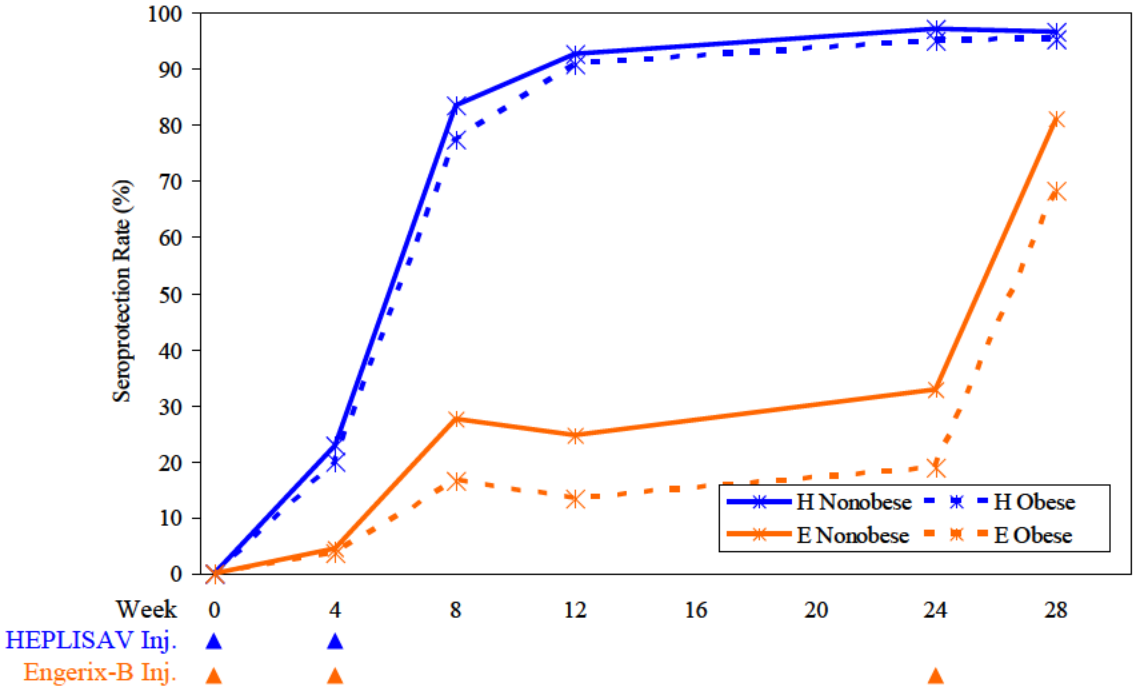
Data Source: BLA Section 2.7.3, Table 2.7.3-14.
CI = confidence interval; mITT = modified intent-to-treat; n = number of subjects with post-injection anti-HBs ≥10 mIU/mL; N = number of subjects in the population in the group; SPR = seroprotection rate.

[a] Study injections were given at Weeks 0, 4, and 24 (placebo).
[b] Study injections were given at Weeks 0, 4, and 24.
[c] 95% CIs of seroprotection rates were calculated using the Clopper-Pearson method.
[d] 95% CIs of the difference in seroprotection rates between the HEPLISAV group and the Engerix-B group were calculated using the Newcombe score method with continuity correction.
[e] In white and black subjects who received HEPLISAV, the peak SPR occurred at Week 24. In Asian and other subjects who received HEPLISAV, the peak SPR occurred at Week 28. In subjects who received Engerix-B, the peak SPR occurred at Week 28.
[f] "Other" race includes American Indian/Alaska Native, Native Hawaiian or other Pacific Islander, and other race.

SPR by Body Mass Index

In obese (BMI $\geq 30 kg/m^2$) and nonobese (BMI $< 30 kg/m^2$) subjects, HEPLISAV induced a significantly higher peak SPR and significantly higher SPRs at each visit, thereby providing earlier seroprotection than did Engerix-B. Figure 7 and Table 40 presents SPRs in obese and non-obese subjects by visit.

Figure 7: Seroprotection Rates by Body Mass Index and Visit in Subjects in DV2-HBV-10 and DV2-HBV-16 (Pooled mITT Analysis Population)



Data Source: BLA Section 2.7.3, Figure 2.7.3-11.
E = Engerix-B; H = HEPLISAV; inj = injection; mITT = modified intent-to-treat.

In obese subjects, the peak SPR in the HEPLISAV group (95.3%) was significantly higher than the peak SPR in the Engerix-B group (68.3%); the difference in SPRs was 27.0% (95% CI: 22.2%, 32.1%). In nonobese subjects, the peak SPR in the HEPLISAV group (97.1%) was significantly higher than the peak SPR in the Engerix-B group (81.2%); the difference in SPRs was 15.9% (95% CI: 13.1%, 19.1%).

In obese subjects, at Week 4, after 1 dose of study treatment, the SPR in those who received HEPLISAV was 19.9% and in those who received Engerix-B was 3.8%. At Week 8 after 2 study injections, the SPR in the HEPLISAV group was 77.4%, and was not only significantly higher than the SPR in the Engerix-B group at Week 8 (16.5%; difference = 60.9%, 95% CI: 56.1%, 65.0%), but was also higher than the peak SPR in the Engerix-B group at Week 28 (68.3%) (Table 40).

Table 40: Seroprotection Rates in Obese and Nonobese Subjects by Visit in DV2-HBV-10 and DV2-HBV-16 (Pooled mITT Analysis Population)

	HEPLISAV[a]		Engerix-B[b]		
Visit/ Obese/ Non-obese	n/N	SPR (%) (95% CI)[c]	n/N	SPR (%) (95% CI)[c]	Difference in SPRs (%) (HEPLISAV-Engerix-B) (95% CI)[d]
Obese					
Week 4	260/1307	19.9 (17.8, 22.2)	14/370	3.8 (2.1, 6.3)	16.1 (12.9, 18.8)
Week 8	1001/1294	77.4 (75.0, 79.6)	60/364	16.5 (12.8, 20.7)	60.9 (56.1, 65.0)
Week 12	1160/1277	90.8 (89.1, 92.4)	49/362	13.5 (10.2, 17.5)	77.3 (73.0, 80.8)
Week 24	1205/1268	95.0 (93.7, 96.2)	68/358	19.0 (15.1, 23.4)	76.0 (71.4, 79.9)
Week 28[e]	1205/1265	95.3 (93.9, 96.4)	243/356	68.3 (63.1, 73.1)	27.0 (22.2, 32.1)
Non-obese					
Week 4	550/2411	22.8 (21.2, 24.5)	32/705	4.5 (3.1, 6.3)	18.3 (15.8, 20.4)
Week 8	1993/2387	83.5 (81.9, 85.0)	192/699	27.5 (24.2, 30.9)	56.0 (52.3, 59.5)
Week 12	2201/2378	92.6 (91.4, 93.6)	172/697	24.7 (21.5, 28.1)	67.9 (64.4, 71.1)
Week 24	2279/2347	97.1 (96.3, 97.7)	226/692	32.7 (29.2, 36.3)	64.4 (60.8, 67.9)
Week 28[e]	2253/2331	96.7 (95.8, 97.3)	560/690	81.2 (78.0, 84.0)	15.5 (12.6, 18.7)

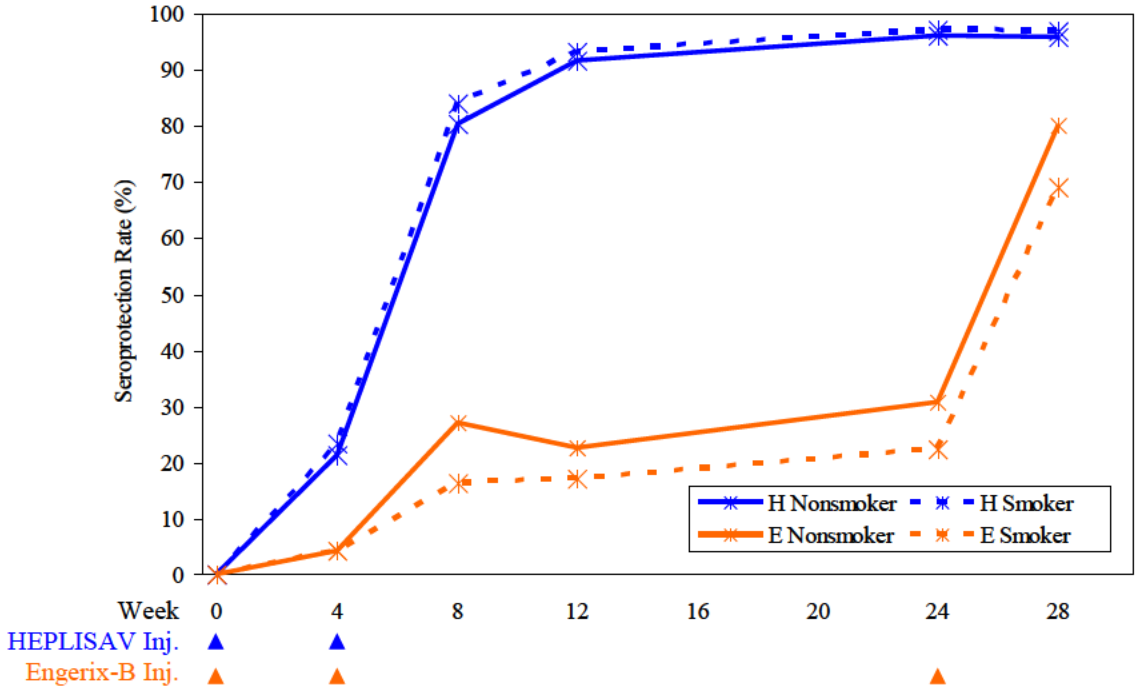
Data Source: ISE Table 33.
BMI = body mass index; CI = confidence interval; mITT = modified intent-to-treat; n = number of subjects with post-injection anti-HBs ≥10 mIU/mL; N = number of subjects in the population in the group; SPR = seroprotection rate.
Subjects with a BMI ≥ 30 kg/m^2 were considered obese.
[a] Study injections were given at Weeks 0, 4, and 24 (placebo).
[b] Study injections were given at Weeks 0, 4, and 24.
[c] 95% CIs of seroprotection rates were calculated using the Clopper-Pearson method.
[d] 95% CIs of difference in SPRs were calculated using Newcombe score method with continuity correction.
[e] The peak SPR occurred at Week 28 in both the HEPLISAV and Engerix-B groups of obese and non-obese subjects.

SPR by Smoking Status in the Prior Year

In smokers and nonsmokers, HEPLISAV induced a significantly higher peak SPR and significantly higher SPRs at each visit than Engerix-B, thereby providing earlier seroprotection.

Figure 8 and Table 41 present SPRs by smoking status (did or did not smoke regularly in the prior year) and by visit.

Figure 8: Seroprotection Rates by Smoking Status in the Prior Year and Visit in Pivotal Trials DV2-HBV-10 and DV2-HBV-16 (Pooled mITT Analysis Population)



Data Source: BLA Section 2.7.3, Figure 2.7.3-12.
E = Engerix-B; H = HEPLISAV; inj = injection; mITT = modified intent-to-treat.

In smokers, the peak SPR in the HEPLISAV group (97.2%) was significantly higher than the peak SPR in the Engerix-B group (69.0%); the difference in SPRs was 28.2% (95% CI: 23.2%, 33.5%). In nonsmokers, the peak SPR in the HEPLISAV group (96.1%) was significantly higher than the peak SPR in the Engerix-B group (80.1%); the difference in SPRs was 16.0% (95% CI: 13.1%, 19.1%) (Table 41).

In smokers, at Week 4, after 1 dose of study treatment, the SPR in those who received HEPLISAV was 23.4%, and in those who received Engerix-B it was 4.2%. At Week 8, after 2 study injections, the SPR in the HEPLISAV group was 84.0% and was not only significantly higher than the SPR in the Engerix-B group at Week 8 (16.2%; difference = 67.8%, 95% CI: 62.8%, 72.0%), but was also higher than the peak SPR in the Engerix-B group at Week 28 (69.0%) (Table 41).

Table 41: Seroprotection Rates by Smoking Status During the Prior Year and by Visit in Pivotal Trials DV2-HBV-10 and DV2-HBV-16 (Pooled mITT Analysis Population)

Smoker/ Nonsmoker Visit	HEPLISAV[a] n/N	HEPLISAV[a] SPR (%) (95% CI)[c]	Engerix-B[b] n/N	Engerix-B[b] SPR (%) (95% CI)[c]	Difference in SPRs (%) (HEPLISAV-Engerix-B) (95% CI)[d]
Smoker					
Week 24/28[e]	991/1020	97.2 (95.9, 98.1)	220/319	69.0 (63.6, 74.0)	28.2 (23.2, 33.5)
Week 4	249/1063	23.4 (20.9, 26.1)	14/336	4.2 (2.3, 6.9)	19.3 (15.6, 22.4)
Week 8	875/1042	84.0 (81.6, 86.2)	53/328	16.2 (12.3, 20.6)	67.8 (62.8, 72.0)
Week 12	966/1038	93.1 (91.3, 94.5)	56/329	17.0 (13.1, 21.5)	76.0 (71.3, 80.0)
Week 24	991/1020	97.2 (95.9, 98.1)	72/324	22.2 (17.8, 27.1)	74.9 (69.9, 79.2)
Week 28	975/1007	96.8 (95.5, 97.8)	220/319	69.0 (63.6, 74.0)	27.9 (22.9, 33.2)
Non-Smoker					
Week 24/28[e]	2498/2600	96.1 (95.9, 98.1)	584/729	80.1 (77.0, 82.9)	16.0 (13.1, 19.1)
Week 4	564/2660	21.2 (19.7, 22.8)	32/741	4.3 (3.0, 6.0)	16.9 (14.6, 18.9)
Week 8	2124/2644	80.3 (78.8, 81.8)	200/737	27.1 (24.0, 30.5)	53.2 (49.5, 56.6)
Week 12	2400/2622	91.5 (90.4, 92.6)	166/732	22.7 (19.7, 25.9)	68.9 (65.5, 71.9)
Week 24	2498/2600	96.1 (95.3, 96.8)	223/728	30.6 (27.3, 34.1)	65.4 (61.9, 68.8)
Week 28	2488/2594	95.9 (95.1, 96.6)	584/729	80.1 (77.0, 82.9)	15.8 (12.9, 18.9)

Data Source: BLA Section 2.7.3, ISE Table 28; ISE Table 34.
CI = confidence interval; mITT = modified intent-to-treat; n = number of subjects with post-injection anti-HBs ≥10 mIU/mL; N = number of subjects in the population in the group; 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.
[c] 95% CIs of seroprotection rates were calculated using the Clopper-Pearson method.
[d] 95% CIs of the difference in seroprotection rates between the HEPLISAV group and the Engerix-B group at each visit were calculated using the Newcombe score method with continuity correction.
[e] Peak SPR occurred in HEPLISAV subjects at Week 24 and in Engerix-B subjects at Week 28.

APPENDIX 5: TIME COURSE OF POST-INJECTION REACTIONS

Reactions were assessed daily for 7 days following each injection. As shown in Table 42, local post-injection reactions peaked in frequency between Day 1 and Day 3 after each injection. Overall, local post-injection reactions to HEPLISAV injection peaked in frequency approximately 1 day later than those for Engerix-B. By Day 7, local post-injection reactions were infrequent. Injection-site pain remained the most frequent reaction at Day 7 in both treatment groups.

Table 42: Daily Profile of Local Post-injection Reactions by Injection Number in Subjects at Least 18 Years Old; Percent of Subjects in DV2-HBV-10 and DV2-HBV-16 (Pooled Safety Population)

	Percent (%) of Subjects							
	Time After Injection							
Reaction (injection #)	**30 Min**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Redness								
HEPLISAV								
Injection 1	(0.1)	(0.1)	(1.0)	**(1.9)**	(1.3)	(0.6)	(0.4)	(0.3)
Injection 2	(0.2)	(0.4)	(1.0)	**(1.1)**	(0.9)	(0.5)	(0.3)	(0.2)
Engerix-B								
Injection 1	(0.1)	(0.1)	**(0.3)**	**(0.3)**	(0.0)	(0.0)	(0.0)	(0.0)
Injection 2	(0.3)	**(0.3)**	**(0.3)**	(0.1)	(0.1)	(0.0)	(0.0)	(0.0)
Injection 3	(0.1)	(0.1)	(0.2)	**(0.3)**	(0.1)	(0.1)	(0.1)	(0.1)
Swelling								
HEPLISAV								
Injection 1	(0.1)	(0.4)	(0.7)	**(0.8)**	(0.6)	(0.1)	(0.1)	(0.1)
Injection 2	(0.1)	(0.4)	**(0.6)**	(0.5)	(0.4)	(0.2)	(0.1)	(0.1)
Engerix-B								
Injection 1	(0.2)	**(0.4)**	**(0.4)**	(0.2)	(0.1)	(0.1)	(0.1)	(0.1)
Injection 2	(0.1)	(0.1)	**(0.3)**	(0.1)	(0.1)	(0.0)	(0.0)	(0.0)
Injection 3	(0.0)	(0.1)	**(0.3)**	**(0.3)**	(0.1)	(0.1)	(0.1)	(0.1)
Pain								
HEPLISAV								
Injection 1	(6.3)	(13.5)	**(22.5)**	(11.3)	(3.3)	(1.3)	(0.7)	(0.6)
Injection 2	(4.9)	(15.2)	**(22.6)**	(12.2)	(4.8)	(2.1)	(0.9)	(0.5)
Engerix-B								
Injection 1	(7.5)	**(18.6)**	(13.3)	(4.2)	(1.5)	(0.4)	(0.0)	(0.1)
Injection 2	(5.5)	**(15.5)**	(11.0)	(3.6)	(2.0)	(1.0)	(0.7)	(0.3)
Injection 3	(5.6)	**(12.9)**	(9.6)	(4.5)	(1.7)	(0.8)	(0.2)	(0.3)

Data Source: ISS Table 7.1.4.3 and BLA Section 2.7.4, Table 2.7.4-17.
Note: Peak frequency for each injection is in **bold.**

As shown in Table 43, fever was the least frequent systemic post-injection reaction and it peaked on Day 1 and Day 2 after HEPLISAV injections and between Day 3 and Day 6 after Engerix-B injections. All other systemic post-injection reactions peaked on Day 1 or Day 2. By Day 7, fatigue was the most frequent systemic post-injection reaction in both groups.

Within each treatment group, the daily profile of post-injection reactions was similar across injections. The daily profile of HEPLISAV in each age subgroup was similar to the daily profile in subjects 18 and over.

Table 43: Daily Profile of Systemic Post-injection Reactions by Injection Number in Subjects at Least 18 Years Old; Percent of Subjects in DV2-HBV-10 and DV2-HBV-16 (Pooled Safety Population)

	Percent (%) of Subjects							
	Time After Injection							
Reaction (injection #)	**30 Min**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Fever								
HEPLISAV								
Injection 1	(0.0)	(0.3)	**(0.3)**	(0.2)	(0.2)	(0.1)	(0.1)	(0.1)
Injection 2	(0.0)	**(0.3)**	**(0.3)**	(0.2)	(0.2)	(0.1)	(0.1)	(0.2)
Engerix-B								
Injection 1	(0.0)	(0.2)	(0.3)	(0.6)	**(0.7)**	(0.5)	**(0.7)**	(0.3)
Injection 2	(0.0)	(0.5)	(0.2)	**(0.6)**	(0.5)	(0.4)	(0.5)	(0.1)
Injection 3	(0.0)	(0.2)	(0.0)	(0.3)	(0.0)	(0.3)	**(0.5)**	(0.3)
Malaise								
HEPLISAV								
Injection 1	(0.5)	(2.3)	**(3.2)**	(2.9)	(2.2)	(2.1)	(1.9)	(1.3)
Injection 2	(0.3)	(3.0)	**(3.6)**	(2.3)	(1.8)	(1.6)	(1.2)	(1.0)
Engerix-B								
Injection 1	(0.4)	(2.9)	**(4.1)**	(2.9)	(2.6)	(2.1)	(2.3)	(2.0)
Injection 2	(0.5)	(2.8)	**(3.0)**	(2.2)	(2.0)	(1.0)	(0.9)	(0.8)
Injection 3	(0.3)	(2.7)	**(3.2)**	(2.3)	(1.6)	(1.6)	(1.5)	(1.0)
Headache								
HEPLISAV								
Injection 1	(0.7)	(4.3)	**(5.5)**	(4.4)	(3.5)	(3.0)	(3.1)	(2.0)
Injection 2	(0.5)	(3.7)	**(4.4)**	(3.6)	(2.7)	(2.1)	(1.6)	(1.2)
Engerix-B								
Injection 1	(0.6)	(5.1)	**(5.3)**	(4.9)	(4.5)	(3.4)	(2.8)	(3.0)
Injection 2	(0.7)	**(5.1)**	(4.4)	(3.1)	(2.6)	(2.5)	(2.2)	(1.1)
Injection 3	(0.6)	(3.2)	**(3.8)**	**(3.8)**	(2.8)	(2.6)	(2.1)	(0.8)
Fatigue								
HEPLISAV								
Injection 1	(1.1)	(5.9)	**(7.0)**	(6.0)	(4.2)	(3.7)	(3.0)	(2.6)
Injection 2	(0.4)	(6.2)	**(6.5)**	(4.3)	(2.8)	(2.5)	(2.2)	(1.6)
Engerix-B								
Injection 1	(1.6)	**(6.3)**	**(6.3)**	(5.0)	(5.1)	(4.3)	(4.2)	(3.6)
Injection 2	(1.3)	**(6.2)**	(5.9)	(3.8)	(3.2)	(3.4)	(3.1)	(2.3)
Injection 3	(0.5)	(5.0)	**(5.4)**	(4.1)	(3.0)	(2.5)	(3.0)	(1.8)

Data Source: ISS Table 7.1.4.3 and BLA Section 2.7.4, Table 2.7.4-17.
Note: Peak frequency for each injection is in **bold**.

APPENDIX 6: NARRATIVES OF SELECTED ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A6.1 Narratives of SAEs Considered by the Site Investigator to Be Related to Study Product

DV2-HBV-10 Subject 24-057: c-ANCA positive vasculitis (Wegener's granulomatosis) Treatment Arm: HEPLISAV

DV2-HBV-10 Subject 24-057 was a 55-year-old white woman from Germany with no pre-existing AI disease. She received her first HEPLISAV injection on 3 July 2007, with post-injection reactions of mild injection site redness and injection site pain. On 21 July 2007, 18 days after the first injection, the subject had onset of moderate, non-serious AEs of hypersensitivity and urticaria associated with an allergic reaction (widespread urticarial reaction) which subsided spontaneously after 3 hours and which was attributed by the investigator to the consumption of herring fish. The subject received a second HEPLISAV injection on 2 August 2007, with a post-injection reaction of mild malaise. On 13 August 2007, 11 days after the second injection, the subject had onset of moderate, non-serious AE of vocal cord disorder, with a symptom of hoarseness. She was treated with Locabiosol (inhaled fusafungin). The event resolved on 26 August 2007.

On 13 October 2007, approximately 2.5 months after the second HEPLISAV injection, the subject had onset of sinusitis. She reported never having had similar episodes before. On 8 November 2007, a computerized tomography (CT) scan confirmed the diagnosis of sinusitis and also showed moderate septal deviation. The subject was hospitalized on 21 November 2007 for septal plastic surgery with drainage of the left paranasal sinus and was discharged on 24 November 2007. The sinusitis was considered by the investigator to be resolved at the time of the subject's study visit on 11 December 2007. On 26 December 2007, the subject experienced a recurrence of her sinusitis, and on 12 January 2008, the subject underwent a second surgery for sinusitis.

On 15 January 2008, during a scheduled follow-up study visit, the subject had a fever of 101.8°F (38.8°C). A follow-up thoracic CT scan on 21 January 2008 detected pneumonia in the right upper lobe, at which point the subject was again hospitalized. During this hospitalization the subject developed pericardial effusion and was admitted to an intensive care unit from 7 February 2008 to 18 February 2008. A pericardiocentesis showed an exudate. In addition, the subject had pulmonary infiltrates and bilateral pleural effusion. She was also found to have proteinuria, and the possibility of glomerulonephritis was considered. On 14 February 2008, an ELISA test was positive for proteinase-3 and a c-ANCA test was positive, with a titer of 1:128. The c-ANCA test was repeated at 2 outside reference laboratories with comparable results.

Having this laboratory result, a diagnosis of Wegener's granulomatosis was made by her attending physician at the local hospital, and the subject was started on corticosteroids and cyclophosphamide. She was discharged on 27 February 2008. No action was taken regarding the investigational product, as all treatment visits were complete. The AE of Wegener's granulomatosis was considered by the investigator to be clinically stable on 30 June 2008. The subject had negative pre- and post-vaccination ANA and anti-dsDNA results. Retrospective anti-HBsAg testing performed in conjunction with evaluation of this SAE showed a peak anti-HBsAg concentration of 102.5 mIU/mL on 25 September 2007. The event was considered by the investigator to be serious, severe, and possibly related to study vaccine.

DV2-HBV-16 Subject 28-352: Bronchial Hyperreactivity
Treatment Arm: Engerix-B

DV2-HBV-16 Subject 28-352 was a 50-year-old white woman with a history of environmental allergies who was randomized to the Engerix-B group, received 3 injections, and experienced an SAE of reactive airway disease (MedDRA preferred term = bronchial hyperreactivity) 42 days after her third injection. During the evaluation of this subject, Churg-Strauss syndrome was considered in the differential diagnosis. Serologic workup, including p-ANCA and c-ANCA, was negative. The sponsor submitted documentation of this case to a rheumatologist who is an expert on Churg-Strauss syndrome for independent evaluation on 18 May 2011. Based on a review of the available records, the rheumatologist gave the opinion that in the absence of asthma, peripheral eosinophilia, evidence of vasculitis, or chest radiographic abnormalities, this subject did not fulfill the definition of Churg-Strauss syndrome. This event was considered by the investigator to be possibly related to treatment. The consultation letter from the independent rheumatologist is in the DV2-HBV-16 CSR Appendix 16.1.17.

A6.2 Narratives of SAEs Resulting in Death

DV2-HBV-16 Subject 22-003: Pulmonary embolism
Treatment Arm: HEPLISAV

Subject 22-003 was a 46-year-old white man with no relevant medical history including no prior history of coagulation disorder. There was no pre-disposing cause for pulmonary embolism; he was an active adult without preceding trauma to cause pulmonary embolism.

He was not taking any concomitant medications.

The subject received study injections on 12 March 2010 and 9 April 2010. On b(6) b(6) days after his second study injection, the subject experienced swelling and leg pain, right

pressure in his chest, and shortness of breath; he had been playing softball and collapsed. He was resuscitated on the field by emergency medical technicians but died on his way to the hospital. An emergency medical technician report was not available; a copy of the autopsy report was requested repeatedly but not received. The only source document available supporting the diagnosis of pulmonary embolism was a report about a telephone conversation between study site personnel and the subject's friend.

The subject's laboratory results at Visit 3 on 8 May 2010 were within normal limits.

The investigator assessed the event of pulmonary embolism as fatal and not related to study treatment.

DV2-HBV-16 Subject 92-638: Heart failure
Treatment Arm: Engerix-B

Subject 92-638 was a 64-year-old black or African American man with a medical history that included gout since 1998, hypertension since 2000, reflux since 2006, and osteoarthritis in both knees since 2009.

Concomitant medications included perindopril, amlodipine, allopurinol, indomethacin, rabeprazole, diclofenac, bisoprolol, ventolin, and deglycyrrhizinated licorice root extract.

The subject received study injections on 12 May 2010 and 10 June 2010. On 23 July 2010, 43 days after his second and last study injection, the subject was hospitalized in critical condition following a heart attack. On b(6), the subject experienced pulmonary arrest and ventricular fibrillation. The subject received emergency cardiac medications and cardioversion, but his heart continued to fail. On b(6) the subject expired; no autopsy was performed.

The subject's laboratory results at screening on 10 May 2010 were normal except for creatinine 110.5 mg/dL (< 103.0 mg/dL), neutrophils 77.0% (43.0 - 73.0%), and platelets 108×10^9/L ($145 - 390 \times 10^9$/L).

The investigator assessed the event of heart failure as an important medical event that required hospitalization, resulted in death, and was not related to study treatment.

A6.3 Narratives of Adverse Events of Special Interest

DV2-HBV-10 Subject 08-038 was a 41-year-old white woman with no pre-existing AI disease. She received HEPLISAV injections on 27 March 2007 and 25 April 2007. She experienced post-injection reactions of mild injection site pain after each active injection. On 7 June 2007, approximately 6 weeks after the second HEPLISAV injection, the subject experienced the onset of a severe, non-serious AE of **Basedow's disease**, with onset of a severe AE of tachycardia on the same date. These AEs occurred 1 day following an elective procedure of rhinoplasty for a deviated nasal septum. The subject received ablative therapy with radioactive iodine on 6 July 2007, with a subsequent improvement in her tachycardia. She was started on atenolol on 8 August 2007, with further improvement of her tachycardia. She experienced a moderate, non-serious AE of heart arrhythmia on 18 August 2007. She began thyroid replacement with levothyroxine on 14 September 2007. The subject received her third (placebo) injection on 18 September 2007, at which time her HR was 56 bpm. The subject completed the study on 16 October 2007. Additional follow-up by the investigator revealed the Basedow's disease to be ongoing and stable as of 21 March 2008. This subject had a positive pre-vaccination ANA titer of 1:320, which was unchanged at her last study visit (Week 28). Pre- and post-vaccination anti-dsDNA results were negative. In addition, in retrospective pre- and post-vaccination testing, ANCA was negative and C-reactive protein (CRP) was less than 0.8. This subject's peak anti-HBsAg response was 3670 mIU/mL at Week 28 (16 October 2007), approximately 6 months after the second injection and approximately 4.5 months after the onset of the event. The AE of Basedow's disease was considered by the investigator to be probably not related to study vaccine. This event was retrospectively identified as an AESI, and, therefore, no SAE narrative is available in the DV2-HBV-10 CSR.

DV2-HBV-10 Subject 10-060 was a 52-year-old white woman with a pre-existing AI disease of systemic lupus erythematosus since 2007 (verbatim term: "**Lupus profundus**") and previous history of hypothyroidism and sulfa allergy who was randomized to the HEPLISAV group. She received HEPLISAV injections on 16 May 2007 and 14 June 2007. She experienced no post-injection reactions and reported an AE of mild injection site bruising after the second injection. On 6 September 2007, approximately 2.5 months after the second injection, the subject experienced the onset of a non-serious AE of SLE. The severity of this AE was reported as "unknown" by the investigator. The symptoms associated with the AE are not known. This AE resolved on 15 September 2007. Subsequently, on 22 October 2007, the subject began treatment for her SLE with hydroxychloroquine. The subject received her third (placebo) injection on 15 November 2007. This subject had a negative pre-vaccination ANA titer of less than 1:160 and a positive post-vaccination titer of 1:640. Her pre- and post-vaccination anti-dsDNA results were negative. In retrospective pre- and post-vaccination testing, ANCA was negative and CRP was less than 0.8. This subject's peak anti-HBsAg response was 108 mIU/mL at Week 24 (15 November 2007), approximately 5 months after the second injection and 2

months after the onset of the event. The AE of SLE was considered by the investigator to be not related to study vaccine. This event was retrospectively identified as an AESI and therefore no SAE narrative is available in the DV2-HBV-10 CSR.

DV2-HBV-10 Subject 11-168 was a 36-year-old white woman with no pre-existing AI disease and a medical history of splenectomy for unknown reasons. She received HEPLISAV injections on 11 July 2007 and 9 August 2007. No AEs were noted during this period. The subject received an influenza vaccination on 22 November 2007. On 27 November 2007, approximately 3.5 months after the second HEPLISAV injection, and 5 days after the influenza vaccination, the subject experienced the onset of a severe SAE of **Guillain-Barré Syndrome**. The subject was hospitalized complaining of progressive weakness that progressed to respiratory failure. The diagnosis of Guillain-Barré Syndrome was subsequently made. The subject's hospitalization was prolonged by the diagnosis of a follicular variant of papillary carcinoma (thyroid) and bilateral pulmonary embolism. She also experienced multiple urinary tract infections. While hospitalized, she was treated with anticoagulants, antibiotics, immunoglobulins, and plasmapheresis, resulting in noticeable improvement. She was discharged on 15 February 2008. 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. In retrospective pre-vaccination testing, ANCA was negative and CRP was positive at 0.83. Post-vaccination testing for ANCA and CRP was not performed. This subject's peak anti-HBsAg response was less than 5 mIU/mL at Week 8 (9 August 2007); no subsequent results are available. 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.

DV2-HBV-10 Subject 25-141 was a 42-year-old white woman with a pre-existing AI disease of rheumatoid arthritis since 2007. She received her first HEPLISAV injection on 28 June 2007, with a post-injection reaction of mild injection site redness. On 3 July 2007, 5 days after the first injection, the subject experienced onset of a mild, non-serious AE of musculoskeletal pain (verbatim term: "**Worsening of rheumatic pain**"), which was treated with etoricoxib and resolved 6 days later on 9 July 2007. She received her second injection on 27 July 2007, with post-injection reactions of mild malaise and fatigue. She received her third (placebo) injection on 6 December 2007. On 13 December 2007, the subject experienced a mild, non-serious AE of rheumatoid arthritis (verbatim term: "**Worsening of rheumatoid arthritis**"), which was treated with diclofenac and resolved 7 days later on 20 December 2007. This subject had a positive pre-vaccination ANA titer of 1:160 and a negative post-vaccination titer of less than 1:160. Her pre- and post-vaccination anti-dsDNA results were negative. In retrospective pre- and post-vaccination testing, ANCA was negative and CRP was less than 0.8. This subject's peak anti-HBsAg response was 489 mIU/mL at Week 24 (6 December 2007), approximately 4.5 months after the second HEPLISAV injection and 1 week before the onset of the event. The

AE of rheumatoid arthritis was considered by the investigator to be not related to study vaccine. This event was retrospectively identified as an AESI and therefore no SAE narrative is available in the DV2-HBV-10 CSR.

DV2-HBV-16 Subject 28-615 was a 62-year-old white man with no pre-existing AI disease. He received his first HEPLISAV injection on 26 April 2010, with no post-injection reactions. He received a second HEPLISAV injection on 24 May 2010, also with no post-injection reactions. On 12 June 2010, 19 days after the second injection, the subject experienced the onset of a moderate, non-serious AE of **erythema nodosum**. The subject was referred for dermatology evaluation. A biopsy confirmed the diagnosis. This AE was treated with prednisone and resolved on 11 August 2010. The subject did not receive the third (placebo) injection. The subject had negative pre- and post-vaccination ANA and anti-dsDNA results. This subject's peak anti-HBsAg response was 86.7 mIU/mL at Week 8 (21 June 2010), approximately 4 weeks after the second HEPLISAV injection and 9 days after the onset of the event. The AE of erythema nodosum was considered by the investigator to be a potential AIAE possibly related to study vaccine. This event was adjudicated by the SEAC as not autoimmune and as related to study vaccine.

DV2-HBV-16 Subject 30-352 was a 59-year-old white man with no pre-existing AI disease. He received his first HEPLISAV injection on 26 April 2010, with no post-injection reactions. He received his second HEPLISAV injection on 24 May 2010, again with no post-injection reactions. The subject received a third (placebo) injection on 11 October 2010, also with no post-injection reactions. The subject received a trivalent inactivated seasonal influenza vaccination on 18 January 2011. On 18 February 2011, approximately 9 months after the last HEPLISAV injection and 1 month after influenza vaccination, the subject experienced the onset of a mild, non-serious AE of VIIth nerve paralysis (verbatim term: "**Bell's palsy** left eye"). The subject was referred for rheumatology evaluation and the diagnosis was confirmed. This AE was treated with valacyclovir and prednisone and resolved on 28 March 2011. The subject had negative pre- and post-vaccination ANA and anti-dsDNA results. No ANCA or CRP testing was performed. This subject's peak anti-HBsAg response was 1070 mIU/mL at Week 36 (3 January 2011), approximately 7.5 months after the last HEPLISAV injection and 6 weeks before the onset of the event. The AE of VIIth nerve paralysis was considered by the investigator to be a potential AIAE and not related to study vaccine. The SEAC adjudicated this event as not an AIAE and not related to study vaccine.

DV2-HBV-16 Subject 41-624 was a 69-year-old white man with a pre-existing AI disease of psoriasis. He received his first HEPLISAV injection on 10 March 2010, with no post-injection reactions. He received his second HEPLISAV injection on 7 April 2010, also with no post-injection reactions. On 8 April 2010, 1 day after the second HEPLISAV injection, the subject experienced the onset of a mild, non-serious AE of **vitiligo**. Findings included multiple small

rounded pink patches without pigmentation on both cheeks, noted following sun exposure. The diagnosis was confirmed by dermatology referral. The AE was treated with topical hydrocortisone and Elidel and was ongoing when the subject completed the study. The subject also experienced a moderate, non-serious AE of phlebitis of the left leg from 23 June 2010 to 23 September 2010. This subject had negative pre- and post-vaccination ANA and anti-dsDNA results. This subject's peak anti-HBsAg response was 11.1 mIU/mL at Week 24 (26 August 2010), approximately 4.5 months after the second HEPLISAV injection and the onset of the event. The event of vitiligo was considered by the investigator to be a potential AIAE possibly related to study vaccine. The SEAC adjudicated the event as an AIAE and not related to study vaccine. The SEAC also considered that the temporal relationship to vaccination was unclear, since the subject's sun exposure may have led to post-vaccination recognition of an event with an earlier onset. The subject received his third (placebo) injection on 26 August 2010.

DV2-HBV-10 Subject 06-083 was a 44-year-old white woman with a pre-existing AI disease of mixed connective tissue disease since approximately 1997 and an additional history of osteoarthritis (hand and shoulders), neck pain, food allergy, myopia, presbyopia, constipation, headache, and tension headache. She received an influenza vaccination in December 2005. She received her first Engerix-B injection on 15 February 2007, with no post-injection reactions. She received her second Engerix-B injection on 14 March 2007, also with no post-injection reactions. In July 2007, while on a trip to Brazil, the subject had fever and malaise. Upon returning home, she was prescribed antibiotics by her general practitioner for presumed pneumonia. After about 10 days there was no improvement and she developed pleuritic pain. As a result, she visited the emergency room on 15 July 2007. Results of a chest x-ray were normal, and the subject was sent home with pain medication. On 18 July 2007, approximately 4 months following her second Engerix-B injection, the subject experienced onset of a severe, serious AE 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 performed during this admission showed pulmonary hemorrhage. A chest CT scan disclosed bilateral diffuse air space consolidation, which is also consistent with pulmonary hemorrhage. She was discharged from the intensive care unit after 17 days on oxygen therapy. At that time there was extreme proximal weakness attributed to steroid myopathy. 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 on 16 August 2007, when the event of p-ANCA associated vasculitis was considered to be resolved. The subject's study injections were discontinued as a result of the SAE. She did not receive her third Engerix-B injection.

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. This subject's peak anti-HBsAg response was 7.7 mIU/mL at Week 12 (10 May 2007), approximately 2 months after the second Engerix-B injection and 2 months before the onset of the event. The p-ANCA associated vasculitis was considered by the investigator to be severe, serious and not related to study vaccine.

DV2-HBV-10 Subject 06-360 was a 34-year-old Asian man with no pre-existing AI disease. He received his first Engerix-B injection on 21 June 2007, with a post-injection reaction of moderate malaise. He received his second Engerix-B injection on 19 July 2007, with a post-injection reaction of mild injection site pain. On 17 November 2007, approximately 4 months after the second Engerix-B injection, the subject experienced the onset of a moderate, non-serious AE of VIIth nerve paralysis (verbatim term: "**Bell's palsy** left side"). This AE was treated with prednisone. The subject received his third Engerix-B injection on 6 December 2007, with no post-injection reactions. The AE of VIIth nerve paralysis resolved on 25 December 2007. This subject had negative pre- and post-vaccination ANA and anti-dsDNA results. In retrospective pre- and post-vaccination testing, ANCA was negative and CRP was less than 0.8. This subject's anti-HBsAg response was less than 5 mIU/mL at all available timepoints. The AE was considered by the investigator to be not related to study vaccine. The event did not meet the criteria for seriousness and was retrospectively identified as an AESI; therefore, no SAE narrative is available in the DV2-HBV-10 CSR.

DV2-HBV-10 Subject 11-153 was a 30-year-old white woman with no pre-existing AI disease and a history of postpartum thyroiditis and tachycardia in 2007. She received her first Engerix-B injection on 9 July 2007, with no post-injection reactions. She received her second Engerix-B injection on 6 August 2007, also with no post-injection reactions. On 2 October 2007, the subject had onset of a moderate, non-serious AE of (verbatim term: "**Left eye change – hyper-reflexia**"), resulting in a thyroid scan. On 22 October 2007, approximately 3.5 months after the second injection of Engerix-B, the subject was reported to have the onset of a moderate, non-serious AE of **Basedow's disease**. No treatment was initiated for this AE. On 28 December 2007, the subject received her third Engerix-B injection, again with no post-injection reaction. The AE of Basedow's disease was ongoing when the subject completed the study on 29 January 2008. This subject had negative pre- and post-vaccination ANA and anti-dsDNA results. Retrospective pre- and post-vaccination testing for ANCA was negative. Retrospective CRP testing was 0.8 prevaccination, was positive at 0.86 on 6 September 2007 and 2.57 on 2 October 2007, and was less than 0.8 on 29 January 2008. This subject's peak anti-HBsAg response was 330 mIU/mL at Week 28 (29 January 2008), approximately 1 month after the third Engerix-B injection and 3 months after the onset of the event. The event of Basedow's disease was considered by the investigator to be not related to study vaccine. The event did not meet the

criteria for seriousness and was retrospectively identified as an AESI; therefore, no SAE narrative is available in the DV2-HBV-10 CSR.

DV2-HBV-10 Subject 12-119 was a 46-year-old white man with no pre-existing AI disease and a history of "cervical disc bulging" since 2005 and carpal tunnel syndrome since 2006. He received his first Engerix-B injection on 15 June 2007, with no post-injection reactions. He received his second Engerix-B injection on 16 July 2007, also with no post-injection reactions. He received his third Engerix-B injection on 3 December 2007, again with no post-injection reactions. On 4 January 2008, approximately 1 month after the third Engerix-B injection, the subject had onset of mild, non-serious AE of **Raynaud's phenomenon**. No treatment was initiated. The AE began on the day when the subject completed the study, and was therefore reported as ongoing. This subject had negative pre- and post-vaccination ANA and anti-dsDNA results. In retrospective pre- and post-vaccination testing, ANCA was negative and CRP was less than 0.8. This subject's peak anti-HBsAg response was 12.3 mIU/mL at Week 28 (4 January 2008), 1 month after the third Engerix-B injection and coincident with the onset of the event. The event of Raynaud's phenomenon was considered by the investigator to be not related to study vaccine. The event did not meet the criteria for seriousness and was retrospectively identified as an AESI; therefore, no SAE narrative is available in the DV2-HBV-10 CSR.

DV2-HBV-04 Subject 11-050 was a 53-year-old Asian woman with no pre-existing AI disease and a history of tinnitus and hearing disturbance. She received her first HEPLISAV (F2) injection on 15 September 2005, with no post-injection reactions. On 23 September 2005, the subject experienced a tingling sensation in the hand. She visited a neurology clinic and was treated with ginkgo biloba extract, amitriptyline hydrochloride, and mecobalamin from 23 September 2005 to 25 September 2005. On 30 September 2005, 15 days after the first HEPLISAV (F2) injection, the subject had onset of a moderate, serious AE of VIIth nerve paralysis (verbatim term: "**Bell's palsy**"). She was treated with prednisolone, ranitidine hydrochloride, and magnesium hydroxide. She then started acupuncture treatment without medication on 5 October 2005 and was recovering gradually. She had subsequent injections of placebo on 13 October 2005 and HEPLISAV (F2) on 9 November 2005, and 2 March 2006, with no post-injection reactions. This AE was resolving but ongoing when the subject completed the study on 1 September 2006. This subject had no laboratory tests performed for ANA, anti-dsDNA, ANCA, or CRP. This subject's peak anti-HBsAg response was 218.6 mIU/mL at Week 28 (29 March 2007), approximately 4 weeks after the last HEPLISAV (F2) injection and 5 months after the onset of the event. The AE of VIIth nerve paralysis was considered by the investigator to be probably not related to study vaccine. Based on additional follow-up, the AE resolved 1 year after the first injection.

HBV0001 Subject 006 was a 35-year-old white woman with a pre-existing AI disease of rheumatoid arthritis. She received her first injection of HEPLISAV (F1) on 12 December 2000,

with post-injection reactions of severe headache, mild arm pain, mild injection site warmth, and mild diarrhea. On 3 January 2001, approximately 3 weeks after the first injection, the subject experienced the onset of a moderate, non-serious AE of rheumatoid arthritis (verbatim term: "**Exacerbation of arthritis of both hands**"). Results of a bone scan were consistent with an early inflammatory arthropathy. She was treated with rofecoxib and ibuprofen. She received her second HEPLISAV (F1) injection on 5 February 2001, with post-injection reactions of moderate headache and mild injection site tenderness. The AE of rheumatoid arthritis was ongoing at the end of the study. This subject had negative pre- and post-vaccination ANA results and positive pre- and post-vaccination anti-dsDNA results. The event was considered by the investigator to be unrelated to study vaccine. The event did not meet the criteria for seriousness and was retrospectively identified as an AESI; therefore, no further SAE narrative is available in the DV2-HBV-04 CSR.

DV2-HBV-04 Subject 13-002 was a 56-year-old Asian man with a history of hyperthyroidism and hand pain. He received his first Engerix-B injection on 12 August 2005, with a post-injection reaction of injection site redness. On 1 September 2005, approximately 3 weeks after his first injection, the subject had onset of a mild, non-serious AE of **rheumatoid arthritis**. The subject received additional injections of Engerix-B on 8 September 2005, 14 October 2005, and 8 February 2006. The AE of rheumatoid arthritis was ongoing when the subject completed the study on 8 August 2006. This subject had no laboratory tests performed for ANA, anti-dsDNA, ANCA, or CRP. This subject's peak anti-HBsAg response was 11580 mIU/mL at Week 28 (23 February 2006), approximately 2 weeks after the last Engerix-B injection and 5.5 months after the onset of the event. The event was considered by the investigator to be not related to study vaccine. The event did not meet the criteria for seriousness and was retrospectively identified as an AESI; therefore, a full SAE narrative is not available in the DV2-HBV-04 CSR.

A6.4 Narratives of Adjudicated Autoimmune Adverse Events in DV2-HBV-16

DV2-HBV-16 Subject 20-312 was a 58-year-old white woman with a medical history that included depression, hypoglycemia, fatigue, and anemia. The subject was randomized to HEPLISAV and received 2 study injections. Two days after receiving the second injection, the subject was seen by her primary care physician with complaints of low blood pressure, dizziness, fatigue, and weakness for the previous 6 days. She was referred to a cardiologist for work up of bradycardia and hypotension. When seen by her cardiologist, a diagnosis of **hypothyroidism** was made based on an elevated TSH and decreased T4 (results not provided). Subsequent testing by her primary care provider 43 days after her initial complaints revealed a thyroid peroxidase antibody level of 167 IU/mL (0 to 34 IU/mL) and an antithyroid antibody level of 881 IU/mL (0 to 40 IU/mL). The event was considered by the investigator to be mild and possibly related to treatment. The event was adjudicated by the SEAC as autoimmune and not

related to treatment. The subject received her third injection because the third injection would have been either placebo (HEPLISAV group) or Engerix-B and autoimmune events are not a contraindication to receiving Engerix-B. This subject had negative ANA and anti-dsDNA titers at baseline and Week 52. Post-trial testing of baseline serum showed a low free T3 and a normal TSH and free T4.

DV2-HBV-16 Subject 30-317 was a 53-year-old white woman with a medical history that included obesity, anxiety, vasomotor symptoms, and alopecia. Over the year prior to enrollment, the subject had noted cold intolerance, fatigue, weight gain, brittle fingernails, and amenorrhea. The subject had no prior history of thyroid or autoimmune disease. One month prior to the initial injection, the subject had seen her primary care physician and requested thyroid testing. She was referred to an endocrinologist. She was randomized to the HEPLISAV group and received 2 study injections. When seen by the endocrinologist 29 days following her second injection, the subject was diagnosed with **hypothyroidism** based on a T4 of 0.8 ng/dL (0.0 to 1.8 ng/dL), TSH of 7.56 mIU/mL (0.35 to 5.50 mIU/mL), and thyroid peroxidase antibody less than 5 IU (0 to 4 IU) and she was placed on levothyroxine. The event was considered by the investigator to be mild and not related to study vaccine. The event was adjudicated by the SEAC as autoimmune and not related to study vaccine. The subject did not receive her third injection. This subject had an ANA titer of less than1:40 at baseline and 1:80 with a speckled pattern at Week 52. Anti-dsDNA was negative at baseline and Week 52. Post-trial testing of baseline serum showed a normal thyroid panel.

DV2-HBV-16 Subject 41-624 was a 69-year-old white man with a history of a PEAI of psoriasis as well as eczema, acne, and osteoarthritis. He was randomized to the HEPLISAV group and received 2 study injections. One day after the second injection, the subject noted pink patches on both cheeks after sun exposure. Forty days following the second injection, the subject was seen by a dermatologist, and the diagnosis of **vitiligo** was made. The event was considered by the investigator to be mild and possibly related to treatment. The SEAC adjudicated the event as autoimmune and not related to treatment. The SEAC also considered that the temporal relationship to vaccination was unclear, since the subject's sun exposure may have led to post-vaccination recognition of an event with an earlier onset. The subject received his third injection because the third injection would have been either placebo (HEPLISAV group) or Engerix-B and autoimmune events are not a contraindication to receiving Engerix-B. This subject had negative ANA and anti-dsDNA titers at baseline and Week 52. A full narrative is provided in the DV2-HBV-16 CSR.

DV2-HBV-16 Subject 20-320 was a 59-year-old white woman with medical history that included sulfa allergy and allergic rhinitis, and she had a family history of hypothyroidism. She was randomized to the HEPLISAV group and received 3 study injections. Forty-nine days after the second injection, the subject experienced generalized edema, abdominal bloating, and

symptoms of a urinary tract infection resulting in emergency room visits. Approximately 2 weeks after the third (placebo) injection, the subject went to her primary care physician with complaints of fatigue and cold intolerance and was diagnosed with **hypothyroidism** based on a TSH of 57.99 mIU/mL (0.27 to 4.20 mIU/mL) and T4 of 0.4 mg/dL (0.9 to 1.8 mg/dL). The event was considered by the investigator to be moderate and not related to study vaccine. The SEAC adjudicated the event as autoimmune and not related to study vaccine. ANA and anti-dsDNA titers were negative at baseline and Week 52. Post-trial testing of baseline serum showed a low free T4 and a high TSH, providing laboratory evidence of pre-existing hypothyroidism.

DV2-HBV-16 Subject 29-307 was a 57-year-old black man who had a medical history that included allergic rhinitis. The subject was randomized to HEPLISAV and received 2 injections. Approximately 10 days after the second injection, the subject started amoxicillin for an upper respiratory infection, and approximately 5 weeks after this injection, the subject was experiencing fatigue for which he saw his primary care physician for a routine physical examination. Routine laboratory testing demonstrated **hypothyroidism** with a T4 of 0.7 ng/dL (0.8 to 1.8 ng/dL) and a TSH of 6.31 mIU/mL (0.4 to 4.5 mIU/mL). The event was considered by the investigator to be mild in severity and possibly related to treatment. The SEAC adjudicated the event as autoimmune and not related to treatment. The subject received his third injection because the third injection would have been either placebo (HEPLISAV group) or Engerix-B, and autoimmune events are not a contraindication to receiving Engerix-B. ANA and anti-dsDNA titers were negative at baseline and Week 52. Post-trial testing of baseline serum showed a low free T4 and a high TSH, providing laboratory evidence of pre-existing hypothyroidism.

DV2-HBV-16 Subject 28-615 was a 62-year-old white man with no pre-existing AI disease. He received his first HEPLISAV injection on 26 April 2010, with no post-injection reactions. He received a second HEPLISAV injection on 24 May 2010, also with no post-injection reactions. On 12 June 2010, 19 days after the second injection, the subject experienced the onset of a moderate, non-serious AE of **erythema nodosum**. The subject was referred for dermatology evaluation. A biopsy confirmed the diagnosis. This AE was treated with prednisone and resolved on 11 August 2010. The subject did not receive the third (placebo) injection. The subject had negative pre- and post-vaccination ANA and anti-dsDNA results. This subject's peak anti-HBsAg response was 86.7 mIU/mL at Week 8 (21 June 2010), approximately 4 weeks after the second HEPLISAV injection and 9 days after the onset of the event. The AE of erythema nodosum was considered by the investigator to be a potential AIAE possibly related to study vaccine. This event was adjudicated by the SEAC as not autoimmune and as related to study vaccine.

DV2-HBV-16 Subject 30-352 was a 59-year-old white man with no pre-existing AI disease. He received his first HEPLISAV injection on 26 April 2010, with no post-injection reactions. He received his second HEPLISAV injection on 24 May 2010, again with no post-injection reactions. The subject received a third (placebo) injection on 11 October 2010, also with no post-injection reactions. The subject received a trivalent inactivated seasonal influenza vaccination on 18 January 2011. On 18 February 2011, approximately 9 months after the last HEPLISAV injection and 1 month after influenza vaccination, the subject experienced the onset of a mild, non-serious AE of VIIth nerve paralysis (verbatim term: "**Bell's palsy** left eye"). The subject was referred for rheumatology evaluation and the diagnosis was confirmed. This AE was treated with valacyclovir and prednisone and resolved on 28 March 2011. The subject had negative pre- and post-vaccination ANA and anti-dsDNA results. No ANCA or CRP testing was performed. This subject's peak anti-HBsAg response was 1070 mIU/mL at Week 36 (3 January 2011), approximately 7.5 months after the last HEPLISAV injection and 6 weeks before the onset of the event. The AE of VIIth nerve paralysis was considered by the investigator to be a potential AIAE and not related to study vaccine. The SEAC adjudicated this event as not an AIAE and not related to study vaccine.

APPENDIX 7: SERIOUS ADVERSE EVENTS BY PREFERRED TERM

Table 44: Summary of Serious Adverse Events in Adults 18 to 70 Years of Age by System Organ Class, Preferred Term, and Study

Study	DV2-HBV-16		DV2-HBV-10	
Age Group, years	40 - 70		18 - 55	
System Organ Class Preferred Term	**HEPLISAV (N = 1968)**	**Engerix-B (N = 481)**	**HEPLISAV (N = 1809)**	**Engerix-B (N = 606)**
Subjects with any SAE n (%)	76 (3.9)	23 (4.8)	28 (1.5)	13 (2.1)
Blood And Lymphatic System Disorders	0	1 (0.2)	0	0
Anaemia	0	1 (0.2)	0	0
Cardiac Disorders	7 (0.4)	4 (0.8)	1 (0.1)	2 (0.3)
Acute Myocardial Infarction	2 (0.1)	1 (0.2)	0	0
Angina Pectoris	1 (0.1)	0	1 (0.1)	0
Angina Unstable	0	1 (0.2)	0	0
Atrial Fibrillation	1 (0.1)	0	0	1 (0.2)
Cardiac Failure	0	1 (0.2)	0	0
Cardiomyopathy	1 (0.1)	0	0	0
Coronary Artery Disease	2 (0.1)	1 (0.2)	0	0
Coronary Artery Stenosis	0	1 (0.2)	0	0
Supraventricular Tachycardia	0	0	0	1 (0.2)
Ear And Labyrinth Disorders	1 (0.1)	0	0	0
Vertigo	1 (0.1)	0	0	0
Gastrointestinal Disorders	7 (0.4)	2 (0.4)	1 (0.1)	1 (0.2)
Abdominal Hernia	1 (0.1)	0	0	0
Barrett's Oesophagus	0	1 (0.2)	0	0
Erosive Oesophagitis	1 (0.1)	0	0	0
Gastric Haemorrhage	0	1 (0.2)	0	0
Gastric Ulcer	1 (0.1)	0	0	0
Gastritis	0	0	1 (0.1)	0
Gastrooesophageal Reflux Disease	1 (0.1)	0	0	0
Haematemesis	1 (0.1)	0	0	0
Inguinal Hernia	1 (0.1)	0	0	0
Pancreatitis	0	0	0	1 (0.2)
Small Intestinal Obstruction	1 (0.1)	0	0	0
General Disorders And Administration Site Conditions	3 (0.2)	2 (0.4)	1 (0.1)	0
Chest Pain	0	1 (0.2)	0	0
Device Dislocation	0	0	1 (0.1)	0

Table 44: Summary of Serious Adverse Events in Adults 18 to 70 Years of Age by System Organ Class, Preferred Term, and Study (Cont'd)

Study	DV2-HBV-16		DV2-HBV-10	
Age Group, years	40 - 70		18 - 55	
System Organ Class Preferred Term	HEPLISAV (N = 1968)	Engerix-B (N = 481)	HEPLISAV (N = 1809)	Engerix-B (N = 606)
Hepatobiliary Disorders	1 (0.1)	0	1 (0.1)	0
Cholecystitis	1 (0.1)	0	0	0
Immune System Disorders	0	0	0	1 (0.2)
Anti-Neutrophil Cytoplasmic Antibody Positive Vasculitis	0	0	0	1 (0.2)
Infections And Infestations	7 (0.4)	1 (0.2)	1 (0.1)	2 (0.3)
Cavernous Sinus Thrombosis	1 (0.1)	0	0	0
Diverticulitis	1 (0.1)	0	0	0
Gastroenteritis Salmonella	0	1 (0.2)	0	0
Liver Abscess	0	0	0	1 (0.2)
Localised Infection	1 (0.1)	0	0	0
Perirectal Abscess	1 (0.1)	0	0	0
Pneumonia	1 (0.1)	0	0	0
Post Procedural Infection	1 (0.1)	0	0	0
Salpingo-Oophoritis	0	0	0	1 (0.2)
Septic Shock	0	0	0	1 (0.2)
Staphylococcal Infection	1 (0.1)	0	0	0
Tonsillitis	0	0	1 (0.1)	0
Urinary Tract Infection	0	0	0	0
Injury, Poisoning And Procedural Complications	13 (0.7)	3 (0.6)	8 (0.4)	2 (0.3)
Alcohol Poisoning	2 (0.1)	0	0	0
Ankle Fracture	2 (0.1)	0	1 (0.1)	0
Contusion	1 (0.1)	0	0	0
Delayed Recovery From Anaesthesia	0	1 (0.2)	0	0
Fall	1 (0.1)	0	0	0
Femur Fracture	0	0	0	1 (0.2)
Fibula Fracture	1 (0.1)	0	0	0
Foot Fracture	1 (0.1)	0	0	0
Gun Shot Wound	1 (0.1)	0	0	0
Jaw Fracture	0	0	2 (0.1)	0
Joint Dislocation	0	0	0	1 (0.2)
Joint Injury	1 (0.1)	1 (0.2)	0	0
Meniscus Lesion	1 (0.1)	1 (0.2)	1 (0.1)	0

Table 44: Summary of Serious Adverse Events in Adults 18 to 70 Years of Age by System Organ Class, Preferred Term, and Study (Cont'd)

Study	DV2-HBV-16		DV2-HBV-10	
Age Group, years	40 - 70		18 - 55	
System Organ Class Preferred Term	**HEPLISAV (N = 1968)**	**Engerix-B (N = 481)**	**HEPLISAV (N = 1809)**	**Engerix-B (N = 606)**
Muscle Strain	1 (0.1)	0	0	0
Patella Fracture	0	0	1 (0.1)	0
Post Procedural Complication	0	0	1 (0.1)	0
Postoperative Ileus	0	0	0	0
Sternal Fracture	0	0	1 (0.1)	0
Tendon Rupture	0	0	1 (0.1)	0
Thermal Burn	1 (0.1)	0	0	0
Tibia Fracture	1 (0.1)	0	0	0
Ulna Fracture	0	0	1 (0.1)	0
Metabolism And Nutrition Disorders	6 (0.3)	1 (0.2)	0	0
Dehydration	0	1 (0.2)	0	0
Diabetic Ketoacidosis	1 (0.1)	0	0	0
Hyperglycaemia	1 (0.1)	0	0	0
Hypokalaemia	1 (0.1)	0	0	0
Hyponatraemia	2 (0.1)	0	0	0
Water Intoxication	1 (0.1)	0	0	0
Musculoskeletal And Connective Tissue Disorders	19 (1.0)	5 (1.0)	2 (0.1)	1 (0.2)
Bursitis	0	1 (0.2)	1 (0.1)	0
Gouty Arthritis	0	0	1 (0.1)	0
Intervertebral Disc Degeneration	1 (0.1)	1 (0.2)	0	0
Intervertebral Disc Protrusion	4 (0.2)	0	0	1 (0.2)
Loose Body In Joint	1 (0.1)	0	0	0
Lumbar Spinal Stenosis	1 (0.1)	1 (0.2)	0	0
Musculoskeletal Chest Pain	1 (0.1)	0	0	0
Neck Pain	1 (0.1)	0	0	0
Osteoarthritis	9 (0.5)	2 (0.4)	0	0
Spinal Column Stenosis	2 (0.1)	0	0	0
Spondylolisthesis	1 (0.1)	0	0	0

Table 44: Summary of Serious Adverse Events in Adults 18 to 70 Years of Age by System Organ Class, Preferred Term, and Study (Cont'd)

Study	DV2-HBV-16		DV2-HBV-10	
Age Group, years	40 - 70		18 - 55	
System Organ Class Preferred Term	**HEPLISAV (N = 1968)**	**Engerix-B (N = 481)**	**HEPLISAV (N = 1809)**	**Engerix-B (N = 606)**
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	9 (0.5)	5 (1.0)	5 (0.3)	0
Brain Neoplasm	1 (0.1)	0	0	0
Breast Cancer	1 (0.1)	2 (0.4)	2 (0.1)	0
Breast Cancer Recurrent	0	0	1 (0.1)	0
Colon Adenoma	2 (0.1)	0	0	0
Colon Cancer Stage IV	1 (0.1)	0	0	0
Inflammatory Carcinoma Of The Breast	1 (0.1)	0	0	0
Meningioma	0	0	1 (0.1)	0
Non-Small Cell Lung Cancer Metastatic	1 (0.1)	0	0	0
Prostate Cancer	1 (0.1)	3 (0.6)	0	0
Thyroid Cancer	0	0	1 (0.1)	0
Uterine Leiomyoma	1 (0.1)	0	0	0
Nervous System Disorders	2 (0.1)	1 (0.2)	2 (0.1)	0
Benign Intracranial Hypertension	0	1 (0.2)	0	0
Cerebral Ischaemia	0	0	1 (0.1)	0
Guillain-Barre Syndrome	0	0	1 (0.1)	0
Spondylitic Myelopathy	1 (0.1)	0	0	0
Subarachnoid Haemorrhage	1 (0.1)	0	0	0
Syncope	0	0	0	0
Psychiatric Disorders	1 (0.1)	0	2 (0.1)	1 (0.2)
Delirium Tremens	0	0	0	1 (0.2)
Depression	0	0	2 (0.1)	0
Major Depression	1 (0.1)	0	0	0
Renal And Urinary Disorders	0	0	1 (0.1)	0
Renal Failure	0	0	1 (0.1)	0
Reproductive System And Breast Disorders	2 (0.1)	1 (0.2)	1 (0.1)	2 (0.3)
Endometriosis	1 (0.1)	0	0	0
Haemorrhagic Ovarian Cyst	0	1 (0.2)	0	0
Menorrhagia	0	0	0	1 (0.2)
Menstruation Irregular	1 (0.1)	0	0	0
Ovarian Cyst	0	0	0	1 (0.2)

Table 44: Summary of Serious Adverse Events in Adults 18 to 70 Years of Age by System Organ Class, Preferred Term, and Study (Cont'd)

Study	DV2-HBV-16		DV2-HBV-10	
Age Group, years	40 - 70		18 - 55	
System Organ Class Preferred Term	**HEPLISAV (N = 1968)**	**Engerix-B (N = 481)**	**HEPLISAV (N = 1809)**	**Engerix-B (N = 606)**
Prostatitis	0	0	1 (0.1)	0
Respiratory, Thoracic And Mediastinal Disorders	5 (0.3)	2 (0.4)	5 (0.3)	1 (0.2)
Asthma	2 (0.1)	0	0	1 (0.2)
Bronchial Hyperreactivity	0	1 (0.2)	0	0
Chronic Obstructive Pulmonary Disease	1 (0.1)	1 (0.2)	0	0
Hypoxia	1 (0.1)	0	0	0
Pneumothorax	0	0	2 (0.1)	0
Pulmonary Embolism	2 (0.1)	0	3 (0.2)	0
Vascular Disorders	3 (0.2)	1 (0.2)	1 (0.1)	0
Deep Vein Thrombosis	2 (0.1)	1 (0.2)	0	0
Hypertension	1 (0.1)	0	0	0
Wegener's Granulomatosis[a]	0	0	1 (0.1)	0

Data Source: DV2-HBV-10 CSR, Table 12-13 and DV2-HBV-16, Table 12/14.
PSAP = primary safety analysis population; SAE = serious adverse event.
[a] The event of Wegener's granulomatosis in DV2-HBV-10 was originally coded in MedDRA version 12.1 with a primary system organ class of respiratory and mediastinal disorder.

APPENDIX 8: AUTOIMMUNE QUESTIONNAIRE

Autoimmune Event Questionnaire DV2-HBV-16

This questionnaire must be filled out by the attending staff at every visit.

Has the subject:	YES	NO	Comments
Experienced stiffness in or around the joints, in the morning and lasting for at least 1 hour?			
Noticed at least 3 joints simultaneously swollen?			
Noticed at least one area swollen as described above involving his/her wrist, hand or fingers?			
Experienced simultaneous involvement of joint swelling as described above in both sides of the body?			
Noticed nodules under his/her skin?			
Heard about a blood test named Rheumatoid Factor (RF)?			
Ever been tested for RF?			Not applicable
If so, was it Positive?			Not applicable
Ever had an X-ray taken of his/her hands/wrists?			
Was it abnormal?			Not applicable
Ever had painful or painless oral ulcers or purulent or bloody nasal discharge that required medical attention?			
Had a chest X-Ray showing the presence of nodules, fixed infiltrates, or cavities?			
Had blood in his/her urine?			
Had any pain, irritation or discharge from the eye?			
Had a skin rash as a result of unusual reaction to sunlight, which required medical attention?			
Had a facial rash (flat or raised) that affected the mid-section of the face (over the malar eminences, tending to spare the nasolabial folds)?			
Ever had a skin rash (red raised patches with follicular plugging OR atrophic scarring)?			
Ever experienced tenderness, swelling, or effusion involving 2 or more peripheral joints?			
Ever had seizures (in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance)?			
Ever been diagnosed with psychiatric disorder, especially psychosis (in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance)?			
Ever told s/he had Hemolytic anemia--with reticulocytosis OR Low leukocytes count (Leukopenia--less than 4,000/mm^3 total on 2 or more occasions)			

Has the subject:	YES	NO	Comments
Experienced stiffness in or around the joints, in the morning and lasting for at least 1 hour?			
OR Low lymphocyte count (Lyphopenia--less than 1,500/mm^3 on 2 or more occasions) OR Low platelet count (Thrombocytopenia--less than 100,000/mm^3) in the absence of offending drugs			
Ever heard about a test named Antinuclear Antibody or ANA?			
Ever been tested for ANA?			Not applicable
Comments from Investigator (state if the subject is referred for expert evaluation):			

Data Source: CSR DV2-HBV-16: 2.3.2 Study Ops Manual, Section 2.10.9.

APPENDIX 9: HEPLISAV USE IN PREGNANT WOMEN

Pregnancy was an exclusion criterion for all clinical trials of HEPLISAV. No trials were conducted specifically to assess the safety of HEPLISAV in pregnancy. Table 45 presents reported pregnancies and outcomes during the clinical development program, during which 19 pregnancies were reported (HEPLISAV: n = 14; Engerix-B: n = 5).

In the pivotal trials DV2-HBV-10 and DV2-HBV-16, there were 13 pregnancies (HEPLISAV: n = 10; Engerix-B: n = 3). In the HEPLISAV group, 6 subjects had healthy term deliveries, 1 subject had a healthy premature delivery, 2 subjects had elective terminations, and 1 subject was lost to follow up. Repeated attempts to contact this subject for follow up were not successful. In the Engerix-B group, 2 subjects had healthy term deliveries and 1 subject had an elective termination.

In the supportive trials, 6 pregnancies were reported (HEPLISAV: n = 4; Engerix-B: n = 2). In the HEPLISAV group, 3 subjects had healthy term deliveries and 1 subject with a history of chronic hypertension had a stillbirth that was reported as an SAE. The stillbirth occurred at 23 weeks gestational age, which was almost 5 months after the subject received her last injection. The fetal death certificate noted that the pre-existing maternal chronic hypertension most likely began the sequence of events resulting in fetal death. In the Engerix-B group, 1 subject had a healthy term delivery and 1 subject had an elective termination.

Table 45: Reported Pregnancies During the Clinical Development Program

Trial	Last Active Injection	LMP Date	Resolution Date	Outcome	Gestation Age	AE	SAE
HEPLISAV (n = 14)							
HBV-10	5 Mar 07	16 Apr 07	b(6)	Elective Termination	6 weeks	No	No
HBV-10	15 May 07	Jun 07		Elective Termination	7 weeks	No	No
HBV-10	28 Jun 07	Jul 07		Healthy Term Delivery	Term	No	No
HBV-10	27 Mar 07	25 Jun 07		Healthy Term Delivery	Term	No	No
HBV-10	11 Jul 07	15 Aug 07		Healthy Term Delivery	Term	No	No
HBV-10	9 Aug 07	5 Oct 07		Healthy Term Delivery	Term	No	No
HBV-10	19 Jun 07	15 Jul 07		Healthy Term Delivery	Term	No	No
HBV-10	6 Jul 07	11 Jan 08		Healthy Premature Delivery	37 weeks	No	No
HBV-10	18 Jul 07	30 Jun 07		Healthy Term Delivery	Term	No	No
HBV-16[a]	16 Apr 10	NA	NA	NA	NA	No	No
HBV-14	NA[b]	NA	b(6)	Healthy Term Delivery	Term	No	No
HBV-14	NA[c]	23 Jul 07		Stillborn	23 weeks	Yes	Yes
HBV0001	5 Feb 00	NA	NA	Healthy Term Delivery	Term	No	No
HBV0001	27 Mar 01	23 Oct 01	b(6)	Healthy Term C/S Delivery	Term	No	No
Engerix-B (n = 5)							
HBV-10	NA[d]	20 Sep 07	b(6)	Healthy Term Delivery	Term	No	No
HBV-10	18 Dec 07	Jul 07		Elective Termination	NA	No	No
HBV-10	18 Dec 07	19 Dec 07		Healthy Term Delivery	Term	No	No
HBV-04	9 Feb 06	30 Jan 06	b(6)	Elective Termination	NA	Yes	Yes
HBV-03	22 Jul 03	24 Aug 04		Healthy Term Delivery	Term	No	No

Data Source: ISS Listing 5.1, DV2-HBV-14 Subject 03-048 SAE narrative.
AE = adverse event; C/S = Cesarean section; LMP = last menstrual period; NA = not available; SAE = serious adverse event

[a] Repeated attempts to contact this subject for follow-up were not successful.

[b] Dates for Injection #2 (last active injection) and Injection #3 (placebo) are not available. Injection #1: 15 Jun 07.

[c] Dates for Injection #2 (last active injection) and Injection #3 (placebo) are not available. Injection #1: 14 Aug 07. The SAE of stillbirth occurred almost 5 months after the subject received her last injection. The AE database was locked when the trial site was informed of the SAE. It was not included in the adverse event tables and listings.

[d] Date for Injection #3 (last active injection) not available. Injection #1: 22 Jun 07; Injection #2: 8 Aug 07.