Vaccines and Related Biological Products Advisory Committee Meeting

July 28, 2017

FDA Briefing Document

Heplisav-B (Hepatitis B Vaccine Recombinant and 1018 ISS Adjuvant)

Applicant:

Dynavax Technologies Corporation

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1.0 General Information

1.1 Product: Heplisav (rHBsAg-1018 ISS)

- Recombinant Hepatitis B surface antigen (rHBsAg), subtype *adw*, produced in yeast cells (*Hansenula polymorpha*).
- Combined with a novel cytosine phosphoguanine (CpG) enriched oligodeoxynucleotide (ODN) phosphorothioate immunostimulatory adjuvant. 1018 ISS used in Heplisav is a 22-mer oligonucleotide with the sequence:

  5' TGA CTG TGA ACG TTC GAG ATG A 3'

1.2 Proposed Indication: Active immunization against all subtypes of hepatitis B virus infection in adults 18 years of age and older.

1.3 Dosage and Administration: Each 0.5mL dose contains 20 mcg rHBsAg and 3000 mcg 1018 ISS adjuvant. The dosing regimen is two 0.5 mL doses administered 1 month apart.

2.0 Executive Summary

Dynavax, the Applicant, submitted a Biologics License Application (BLA) for Heplisav on April 26, 2012. Because the vaccine contains a novel adjuvant, a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting was held November 15, 2012. At the time of the November 2012 VRBPAC, the BLA submission included two pivotal phase 3, randomized, active-controlled, immunogenicity and safety studies (DV2-HBV-10 and -16; 3778 Heplisav recipients, 1086 recipients of the licensed hepatitis B vaccine Engerix-B, manufactured by GlaxoSmithKline; GSK), and seven supportive trials, three of which included immunogenicity assessments. Table 1 (see below) provides an overview of studies informing discussion at the November 2012 VRBPAC, as well as studies subsequently submitted to the BLA.

Immunogenicity of Heplisav was assessed by determining the seroprotection rate (SPR): the proportion of subjects with an anti-HBsAg level $\geq$ 10 mIU/mL, an antibody concentration, recognized as conferring protection against hepatitis B virus infection (1, 2). Study DV2-HBV-10 enrolled adolescents and adults 11-55 years of age; Study DV2-HBV-16 enrolled adults 40-70 years of age. Subjects received either two doses of Heplisav at Weeks 0 and 4 and placebo at Week 24 or three doses of Engerix-B at Weeks 0, 4, and 24. In both pivotal studies, the SPR following two doses of Heplisav was non-inferior to the SPR induced by three doses of Engerix-B. At least 90% of healthy adult subjects (defined as 18 years of age and older) maintained seroprotective antibody levels against hepatitis B at 48 weeks after two doses of Heplisav in Study DV2-HBV-16. Subgroup analyses did not reveal clinically significant differences between antibody responses in younger and older subjects, or between males and females. The SPRs were similar among all ethnic groups examined.

The submitted safety database at that time included 5845 subjects (Heplisav n=4425, Engerix-B n=1420) 18 -70 years of age enrolled in the nine aforementioned clinical trials. The safety evaluation comprised an assessment of local and systemic reactogenicity monitored for days 0-6 after vaccination in both pivotal studies. In Study DV2-HBV-10,

unsolicited adverse events (AEs) and serious adverse events (SAEs) were monitored through week 28 (24 weeks following the last dose of Heplisav and 4 weeks following the last dose of Engerix-B). In Study DV2-HBV-16, unsolicited AEs were monitored through week 28 and SAEs and autoimmune events were monitored through week 52 (48 weeks following the last dose of Heplisav and 28 weeks following the last dose of Engerix-B). Anti-dsDNA and anti-nuclear antibody (ANA) levels were measured in both pivotal studies. Due to the different administration schedules for Heplisav and Engerix-B, subjects who received Heplisav were followed for longer after the last dose of Heplisav compared to subjects who received Engerix-B; however, subjects in both arms were followed for the same length of time after the first vaccination.

Most AEs were related to local reactogenicity, were described as mild in intensity, and did not differ noticeably from the licensed comparator, Engerix-B. A numerical imbalance in pulmonary embolism was noted in the integrated safety analysis with five Heplisav subjects and no Engerix-B subjects reporting this SAE. In the pivotal study DV2-HBV-10 two cases of vasculitis were reported: one case of cyotoplasmic-ANCA (c-ANCA) positive granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) in the Heplisav treatment arm and one case of perinuclear-ANCA (p-ANCA) positive vasculitis in a subject with a pre-existing mixed connective tissue disorder in the Engerix-B treatment arm. A case of Guillain-Barré syndrome was also reported in the Heplisav arm (five days after receiving influenza vaccine and 110 days after receiving the second study injection of Heplisav). These events prompted a prospective evaluation for autoimmune adverse events in Study DV2-HBV-16, in which potential autoimmune events were referred to an external Safety Evaluation and Adjudication Committee (SEAC) for review. Three subjects in the Heplisav group (hypothyroidism, n=2; vitiligo, n=1) and no subjects in the Engerix-B group were adjudicated as having a new-onset autoimmune event. One additional subject in Study DV2-HBV-16 was identified as having a possible diagnosis of Tolosa-Hunt syndrome (THS) following vaccination with Heplisav. THS is a painful ophthalmoplegia resulting from granulomatous inflammation of the cavernous sinus. At the time of the November 2012 VRBPAC, FDA had minimal information on the case of THS; therefore the case was not discussed at length at the VRBPAC meeting. Subsequent to the November 2012 VRBPAC, FDA obtained outside consultations from four experts regarding the diagnosis and possible relationship to Heplisav.

At the November 2012 VRBPAC meeting, FDA presented the immunogenicity and safety of Heplisav based on the two pivotal trials and integrated information available. VRBPAC members voted 13:1 that the immunogenicity data submitted in the BLA were adequate to support the effectiveness of Heplisav for the prevention of hepatitis B virus infection in adults 18 - 70 years of age. However, the Committee voted 8:5, with one abstention, that the available data were not adequate to support the safety of Heplisav in the same age group. Committee members noted that there were insufficient numbers of subjects studied to detect relatively infrequently occurring adverse events, especially considering the novel adjuvant contained in Heplisav. Committee members noted that the pre-licensure safety database should be more racially and ethnically diverse to better reflect the U.S. population and those most likely to benefit from the vaccine and that concomitant administration studies were not done.

FDA issued a complete response (CR) letter on February 22, 2013, citing, among other items, the insufficient size of the safety database, as well as the possible occurrence of two rare granulomatous diseases following Heplisav administration, GPA and THS. To address the CR item regarding insufficient safety database, the Applicant conducted Study DV2-HBV-23, an observer-blind, randomized, active controlled trial enrolling subjects 18 to 70 years of age comparing Heplisav and Engerix-B with a randomization ratio of 2:1. As FDA already considered vaccine effectiveness to have been established in Studies DV2-HBV-10 and DV2-HBV-16, FDA did not require an evaluation of immunogenicity in Study DV2-HBV-23. Nonetheless, the Applicant designed the study to include non-inferiority comparisons of seroprotection rates in diabetics (primary endpoint) and all subjects (secondary endpoint). While FDA confirmed that the immunogenicity results in all subjects (secondary analysis) were consistent with those from Studies DV2-HBV-10 and DV2-HBV-16, the results of immunogenicity analyses from Study DV2-HBV-23 are not presented in this briefing document. Medically attended adverse events (MAEs), SAEs, and adverse events of special interest (AESIs) were monitored through Week 56 (52 weeks following the last dose of Heplisav and 32 weeks following the last dose of Engerix-B) in DV2-HBV-23. AESIs were pre-specified by a list of potentially immune-mediated conditions and were referred to an external SEAC for review and adjudication. The solicited reactogenicity data collected in pivotal studies DV2-HBV-10 and -16 were adequate and did not raise safety concerns; therefore, reactogenicity data were not collected during Study DV2-HBV-23.

The Applicant submitted a complete response to the February 22, 2013 CR letter on March 16, 2016, including the Clinical Study Report (CSR) and supporting documents from DV2-HBV-23, and additional information intended to address the other CR Letter items. Further, the March 2016 submission included revised CSRs for Studies DV2-HBV-10 and DV2-HBV-16 that corrected errors in the immunogenicity analyses. The revised immunogenicity data (presented in this briefing document) did not differ substantively from the immunogenicity data presented to VRBPAC in 2012.

In Study DV2-HBV23, the overall rates of all MAEs and SAEs reported in the 56-week study period were similar between the Heplisav and Engerix-B groups. Imbalances between trial arms were noted in deaths, SAEs of myocardial infarctions (MI), and MAEs of herpes zoster. After excluding deaths that were due to overdose or injury, 0.29% of Heplisav (16 subjects) and 0.14% of Engerix-B (4 subjects) recipients experienced fatal SAEs. Based upon the standard Medical Dictionary for Regulatory Activities (MedDRA) query for MI (including the preferred terms acute myocardial infarction, myocardial infarction, coronary artery occlusion, acute coronary syndrome, and angina unstable), 19 Heplisav subjects (0.3%) and 3 Engerix-B subjects (0.1%) reported an SAE of MI. All subjects reporting an MI had at least one cardiovascular risk factor. Cardiovascular risk factors were similar between trial arms at baseline. A discrete risk window was not identified. A difference between trial arms in deaths or MI was not observed in prior studies; however, subjects enrolled in DV2-HBV-23 had more cardiovascular risk factors than those enrolled in prior studies. While the number of SAEs of MI is small, the relative risk is 3.15 (95% exact CI 0.99, 23.11). A comparison of cardiovascular AEs between groups was not prospectively specified, potentially leading to under ascertainment of events. Additionally, there are issues of multiplicity and alpha error inflation in such *post hoc* safety analyses, further complicating interpretation of the

results. On the other hand, with safety one is more concerned with false negatives, at least initially.

In response to questions from FDA concerning the findings, the Applicant submitted a major adverse cardiovascular events (MACE) analysis. This analysis used external expert consultants to perform a blinded adjudication of events of cardiac death, myocardial infarction, and stroke occurring in the three pivotal studies. The relative risk of non-fatal MI and the composite three-point outcome in study DV2-HBV-23 was 6.97 (95% exact confidence interval [CI] 1.00, 184.9) and 2.32 (95% exact CI 0.98, 7.52), respectively. The relative risk of non-fatal MI and the composite three-point outcome in the pivotal studies was 3.30 (95% exact CI 0.84, 33.8) and 1.6 (95% exact CI 0.75, 6.08), respectively. FDA obtained three cardiology consultations (appended to this document) for input in evaluating these analyses.

Based upon review of the events and SEAC assessment, nine subjects in the Heplisav group (0.2%) reported new-onset AESIs without a clear alternative plausible cause (VIIth cranial nerve palsy in five subjects, alopecia areata, ulcerative colitis, polymyalgia rheumatica, and granulomatous dermatitis). One subject in the Engerix-B group (0.03%) reported a confirmed new-onset AESI (VIIth cranial nerve palsy). No events were assessed by the SEAC as related to study vaccination.

A laboratory sub-study was conducted in DV2-HBV-23 based on the safety review of the initial BLA, most notably the observation that five subjects in Heplisav groups and no subjects in the Engerix-B groups in the initial integrated summary of safety reported five SAEs of pulmonary emboli. Two sites enrolled 309 subjects in the sub-study. Review of chemistry, hematology, and urinalysis assessments conducted at time points through the 56-week study period did not identify notable differences between study groups. While no imbalance in venous thromboembolic MAEs was observed, more subjects in the Heplisav group had normal baseline anti-beta2 glycoprotein 1 IgM levels and elevated Week 8 levels (8.3% in the Heplisav group, 1.1% in the Engerix-B group). The significance of one abnormal antiphospholipid antibody level in asymptomatic subjects is unclear.

In summary, Heplisav was shown to have a robust immune response in healthy adults 18-70 years of age in Studies DV2-HBV-10 and-16. Heplisav met pre-specified non-inferiority criteria to an active comparator vaccine, Engerix-B, in these two phase 3 clinical trials. Regarding safety, there appear to be imbalances in deaths and SAEs of MI in DV2-HBV-23, and imbalances in AESIs in DV2-HBV-16 and -23 (the studies that prospectively evaluated these events). Numbers and rates of events are low, and the lack of prospectively defined monitoring and evaluation of cardiac events limits the causal interpretation of these observations.

3.0 Introduction and Background

3.1 Epidemiology

Worldwide, more than 250 million persons are infected with Hepatitis B virus (HBV). Approximately 887,000 deaths worldwide were reported in 2015, mostly due to chronic hepatitis B, and resultant end-stage liver disease and/or hepatocellular carcinoma (3).

In the U.S., universal childhood vaccination has been recommended since 1991. Subsequently, the incidence of HBV infection has substantially decreased from 8.5 per 100,000 (1990) to 1.1 per 100,000 (2015). In the United States 850,000 persons are thought to be living with HBV, although other studies have estimated this number as high as 2.2 million. In 2015, the CDC reported 1,715 deaths in the U.S. noting hepatitis B as an underlying cause, using reported U.S. death certificate data. Also in 2015, incidence of acute hepatitis B was highest for persons aged 30–39 years (2.6 cases/100,000 population); approximately two-thirds of chronic hepatitis B cases are reported in persons 25–55 years of age. While CDC estimates the incidence of acute HBV infections in Asian/Pacific Islanders is low (0.35 per 100,000), unpublished surveillance data from CDC suggest that about one-half of chronic HBV infections were among Asian/Pacific Islanders. Forty-seven to 70% of U.S. residents with chronic HBV infection were born in other countries (4).

Transmission of HBV is by percutaneous and mucosal exposure to infectious blood or body fluids. In the U.S. transmission is primarily sexual, followed by injection drug use. In 2015, 30% of persons with acute hepatitis B infection reported injection drug use (4). Nosocomial transmission between patients and from patients to health care workers (HCW), including in the setting of hemodialysis (HD) and oncology units, has become rare, declining 95% since implementation of routine vaccination and standard precautions for blood-borne pathogens. The prevalence of HBV infection among hemodialysis patients was 1.2% in 2002 (5). In 2015, 0.2% of persons with acute hepatitis B infection reported receipt of dialysis or kidney transplant (4).

3.2 Currently Available Interventions

Two licensed vaccines, both made from yeast-derived recombinant antigen adsorbed to aluminum compounds are currently available for the prevention of HBV in the U.S., Engerix-B (GSK) and Recombivax HB (Merck). There is also one combination vaccine for adults, Twinrix (GSK), which includes a hepatitis A vaccine component. Engerix-B and Recombivax HB are both approved for use in infants, children, adolescents, and adults as a three-dose series to be administered on a 0-, 1-, and 6-month schedule. A two-dose Recombivax HB series, administered at 0, and 4 to 6 months, is also approved for adolescents 11 to 15 years of age. Twinrix is licensed as a three-dose series, administered at months 0, 1, and 6. Additionally an accelerated schedule is licensed for Twinrix—a series of four doses (1 mL each), given on Days 0, 7 and Days 21 to 30, followed by a booster dose at Month 12.

These vaccines are highly effective, as shown in controlled clinical trials of efficacy against acute hepatitis B infection (1) and prospective observational studies (2, 6), and elicit a SPR in approximately 95% of healthy adults. Long-term studies of immunocompetent adults and children indicate that immune memory remains intact for up to two decades and protects against symptomatic acute and chronic HBV infection, even though anti-HBs antibody concentrations may become low or undetectable over time (6).

Breakthrough infections (detected by presence of anti-HBc antibodies or HBV DNA) have occurred in immunized people, but these infections typically are transient and asymptomatic (7, 8). Chronic HBV infection in immunized individuals has been

documented in dialysis patients whose anti-HBsAg antibody concentrations fell below 10 mIU/mL (8). For adults on dialysis, formulations of Recombivax HB and Engerix-B containing 40 mcg HBsAg per dose (standard adult dose is 10 or 20 mcg of HBsAg, respectively) administered in a 3 or 4 dose series, respectively, are approved. In dialysis patients, the need for booster doses is assessed by annual antibody testing, and revaccination is indicated when anti-HBsAg levels decline below 10 mIU/mL (7-9).

3.3 Mechanism of Action of 1018 ISS Adjuvant

Heplisav consists of rHBsAg and a synthetic unmethylated single strand cytosine phosphoguanine oligodeoxynucleotide (CpG ODN) adjuvant, 1018 ISS. There is currently no other licensed vaccine in the U.S. that contains this adjuvant. The mode of action of CpG ODNs is based on the concept that, whereas vertebrate (self) DNA is usually methylated when a cytosine is followed by a guanine, bacterial and viral DNA contain unmethylated CpG sequences, which are recognized as foreign by the innate immune system through interaction with toll-like receptor 9 (TLR9) (10).

TLR9 receptors are located within the cytoplasm of plasmacytoid dendritic cells (pDCs) and B cells, on the surface of the endoplasmic reticulum (ER). They are present to a lesser degree in NK cells. Activation of antigen-presenting pDCs and B-cells occurs when intracellular viral and bacterial pathogens containing unmethylated CpG sequences are recognized by TLR9 receptors. Activated pDCs become antigen presenting cells (APCs) and secrete interferon-alpha (IFN-α), which in turn stimulates a T helper 1 (Th1) immune response, and the secretion of other proinflammatory cytokines that activate macrophages, monocytes, and NK cells (11). Activated B-cells are stimulated to secrete antibodies and contribute to the overall biased Th1 cellular immune response by facilitating opsonization and antibody-dependent cytotoxic T cell responses.

The 1018 ISS adjuvant in Heplisav is thought to have the following effects: (1) activation of pDCs through TLR9, (2) conversion of pDCs into activated dendritic cells that present the processed HBsAg component of Heplisav to CD4+ T cells, and (3) promotion of Th1 T-cell differentiation through the production of IFN-α and IL-12. This activation is thought to result in a high and sustained antibody response, likely due to generation of large numbers of anti-HBsAg-secreting plasmacytes and HBsAg-specific memory cells.

Because of theoretical concerns for TLR-agonist adjuvants, such as CpG, to induce or exacerbate autoimmune disease in humans (12-14), efforts were made to identify clinical cases of autoimmunity and evaluate biomarkers of autoimmunity, such as anti-dsDNA, ANA, and ANCA, in individuals enrolled in studies of Heplisav.

3.4 Non-Clinical Data

Non-clinical toxicology studies were conducted with a vaccine similar to Heplisav or 1018 ISS alone in a number of rodent and non-human primate (NHP) studies.
In a repeat-dose toxicity study, mice were administered three intramuscular doses of a vaccine formulation containing 0.5 mcg HbsAg/mL and 50 mcg 1018 ISS/mL ($1/40^{th}$ and $1/60^{th}$ of the human dose on an absolute basis, respectively). No mortality or clinical toxicity was seen, but mild, transient anemia and associated mild extramedullary hematopoiesis were noted. Microscopically observed epicardial mineralization (a

common spontaneous lesion in mice) was reported in animals receiving both adjuvanted antigen and antigen alone. Serology assessment was not performed.

In a developmental and reproductive toxicity study, rats received 4 subcutaneous doses (two prior to mating and two during gestation) of a vaccine formulation containing 2.5 mcg HbsAg/dose and up to 3000 mcg 1018 ISS/dose ($1/8^{th}$ and 1x the human dose on an absolute basis, respectively). No treatment-related effects on female fertility, fetal development or post-natal development up to the time of weaning were observed.

Tissue distribution studies of other phosphorothioate ODNs in mice, rats and primates primarily showed distribution into kidney, liver, lymph nodes, spleen, and bone marrow. The primary mode of clearance is by degradation (exonuclease activity) in tissues and is slow (measured in days to weeks), because the phosphorothioate backbone resists degradation. Renal clearance is low and elimination from tissues is slow (15-17).

In a repeat-dose toxicity study of 1018 ISS alone rats were administered 8 subcutaneous doses at 12.5 mg/kg 1018 ISS/dose (272-fold clinical multiples on a body weight basis). Transient thrombocytopenia, anemia, lymphocytosis, neutrophilia, and monocytosis, as well as compensatory medullary and extramedullary hematopoiesis were observed. Elevated BUN, renal tubular degeneration, interstitial inflammation and oligonucleotide deposition in the renal proximal tubular epithelial cells was seen, but no effect on renal function and no specific findings of glomerulonephritis or vasculitis were detected. Additionally, congestion, dose-dependent liver atrophy, Kupffer cell hyperplasia and chronic inflammation were observed in the liver; considerable recovery was apparent after the recovery phase. Cardiomyopathy was observed in rats at a similar incidence between treatment and control groups and, given this established background finding in this animal, was assessed as not related to test article.

In another repeat dose toxicity study of 1018 ISS alone, cynomolgus macaques received 8 subcutaneous doses at 12.5 mg/kg 1018 ISS/dose (272-fold clinical multiples on body weight basis). Transient leukopenia, neutropenia, and modest increases in activated partial thromboplastin time were observed. Splenomegaly with lymphoid hyperplasia, hyperplasia of the Kupffer cells with blue granular pigment inclusions in the highest dose group and minimal to mild activation of the alternative complement pathway were observed after the treatment phase. These findings in the liver and spleen were still present after a 4 week recovery period but with decreased severity.

In summary, no significant toxicity was observed in the pre-clinical studies and all effects were thought to reflect previously described class effects of oligodeoxynucleotides, as well as the expected immunostimulatory properties of the vaccine. Non-clinical investigations of the potential for CpGs or Heplisav to induce autoimmunity have been suboptimal given the lack of an appropriate mouse or well-characterized NHP models of human autoimmunity.

3.5 Relevant Prior Human Experience

Limited prior human experience exists for the adjuvant 1018 ISS. More clinical experience is available with other CpG oligonucleotides (ODNs), in particular CpG 7909 (ProMune, Coley Pharmaceuticals), an immunostimulatory synthetic cytosine

phosphoguanine oligonucleotide agonist of TLR9. CPG 7909 has been evaluated in numerous clinical trials, most commonly in the context of use in the cancer patient population. While these studies have been difficult to interpret due to the heterogeneous population of patients evaluated in clinical trials, to date no significant autoimmune signals have been reported (18, 19). Autoantibody seroconversions have been reported in a small proportion of patients treated with CpG ODNs (≤ 10%), specifically anti-dsDNA and ANA, but without evidence of clinical disease (18).

CpG 7909 has been administered with Engerix-B in a double-blind phase 1/2 study in 42 healthy subjects 18-35 years of age (20). The most frequently reported adverse events were injection site reactions, flu-like symptoms and headache. Autoimmune adverse events were not reported. A second, similar study performed in thirty-eight HIV-infected individuals 18-55 years of age (21) failed to reveal any autoimmune adverse events, although transient elevations above normal range for anti-dsDNA were noted in two subjects who received Engerix-B plus CpG 7909 and in two subjects who received CpG 7909 alone. These subjects were ANA negative. In a third study, a phase 1 double-blind study evaluated CpG 7909 and Anthrax Vaccine Adsorbed (BioThrax) in 69 healthy subjects 18-45 years of age. Safety monitoring was performed for six months after the last vaccination. No serious adverse events related to study agents were reported, and the combination was considered to be reasonably well tolerated (22). A follow-up phase 1 study of BioThrax plus CPG 7909 was conducted in 105 healthy adults 18-50 years of age. The most common adverse events (AEs) in the BioThrax alone and BioThrax plus CpG 7909 groups assessed by investigators as related to vaccination were injection site reactions. No autoimmune events were observed in the study (23).

3.6 Dose Selection of 1018 ISS Adjuvant

The rationale for dose selection of 1018 ISS for further clinical development and for the candidate vaccine formulation was based on results from the pilot Study DV2-HBV0001. This was a phase 1, observer-blind, randomized, dose-escalation study performed in healthy, seronegative adults 18-55 years of age, that evaluated the safety, tolerability and immune response to rHBsAg, 20 micrograms (mcg), co-administered by intramuscular injection (IM) with differing doses of 1018 ISS. Doses of 1018 ISS administered were 300, 650, 1000, or 3000 mcg.

Two IM doses of rHBsAg, 20 mcg, combined with the highest dose of 1018 ISS evaluated in this study (3000 mcg) yielded the highest seroprotection rate, based on the limited seroprotective response data presented.

4.0 Overview of Clinical Trials

Studies submitted to the BLA are presented in Table 1.

Table 1. Summary of Completed Studies of Heplisav

	Study Design	Heplisav Dose/Schedule/N	Active Comparator Dose/Schedule/N	Key Endpoint(s)
Pivotal Studies				
HBV-10 Study Period: Dec 2006-March 2008	Phase 3, observer-blind, randomized, active-controlled, parallel group, multi-center study in healthy subjects 11-55 years of age conducted in Canada and Germany	Heplisav: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant Schedule: 0, 4 weeks IM (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 Solicited reactions 7 days following each injection AEs/SAEs Study Week 28
HBV-16 Study Period: Feb 15, 2010-May 25, 2011	Phase 3, observer-blind, randomized, active-controlled, parallel group, multi-center study in healthy adult subjects 40-70 years of age conducted in Canada and US	Heplisav: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant Schedule: 0, 4 weeks IM (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 Solicited reactions 7 days following each injection AEs Study Week 28, SAEs/AESIs Study Week 52
HBV-23 Study Period: April 18, 2014-March 1, 2015	A Phase 3, Observer-Blinded, Randomized, Active-Controlled (Engerix-B), Multicenter Trial of the Safety and Immunogenicity of Heplisav™ in Adults 18 to 70 Years of Age	Heplisav: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant Schedule: Schedule: 0, 4 weeks IM (placebo at 24 weeks) N=5587	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks N=2781	CBER did not concur with the Primary Immunogenicity Endpoint of SPR at Week 28 in subjects with type 2 diabetes mellitus Secondary Endpoint: SPR at Week 24 in Heplisav subjects and at Week 28 in Engerix-B subjects MAEs/SAEs/AESIs Study Week 56

	Study Design	Heplisav Dose/Schedule/N	Active Comparator Dose/Schedule/N	Key Endpoint(s)
Supportive Studies				
HBV0001 Study Period: Dec 6, 2000-May 9, 2002	Phase 1 Observer-blind, randomized, dose-escalation study of the 1018 ISS Adjuvant component of vaccine in healthy, seronegative adults 18-55 years of age conducted in Canada.	Varying doses of 1018 ISS Adjuvant, given in combination with a fixed dose of HBsAg (20 mcg); not the to-be-marketed formulation at 0 and 8 weeks: 300 mcg, ± 20 mcg HBsAg 650 mcg, ± 20 mcg HBsAg 1000 mcg, ± 20 mcg HBsAg 3000 mcg, ± 20 mcg HBsAg Schedule: 0, 8 weeks IM N=32	HBsAg: 20 mcg N=8 1018 ISS Adjuvant Alone: 300, 650, 1000, 3000 mcg N=8	Anti-HBsAg GMC measured after vaccination Solicited AEs 7 days following each injection AEs/SAEs Study Week 62 Serum chemistry, hematology, urinalysis, ANA, anti-dsDNA, anti-ssDNA, ESR
HBV-02 Study Period: Feb 17, 2003-Aug 28, 2004	Phase 2 Observer-blind, randomized, parallel group study of hypo- and non-responders to licensed hepatitis vaccine in adults 18-65 years of age conducted in Canada	Heplisav: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant (not the to-be-marketed formulation) Schedule: Single injection IM N=30	Engerix-B: 20 mcg HBsAg Schedule: Single injection IM N=29	SPR at Week 4 Solicited AEs 7 days following each injection AEs Study Week 4, SAEs Study Week 52 Serum chemistry, hematology, ESR, ANA, anti-dsDNA, anti-ssDNA
HBV-03 Study Period: Aug 13, 2002-May 20, 2004	Phase 2 Observer-blind, randomized, parallel-group study in adults 18-28 years of age conducted in Canada.	Heplisav: 20 mcg HBsAg/ 3000 mcg 1018 ISS adjuvant (not the to-be-marketed formulation) Schedule: 0, 8 weeks IM (placebo/meningococcal vaccine at 24 weeks) N=48	Engerix-B: 20 mcg HBsAg Schedule: 0, 8, 24 weeks IM N=51	SPR at Week 28 Solicited AEs 7 days post-injection(s) AEs Study Week 20 SAEs Study Week 60 Serum chemistry, hematology, ESR, Urinalysis, ANA, anti-dsDNA, anti-ssDNA, Complement (C3, C4)
DV2-HBV-04 Study Period: June 21, 2005-Jan 4, 2007	Phase 3, multicenter, double-blind, randomized, parallel group, active-control study in healthy adult subjects 40-70 years of age conducted South Korea, Philippines, and Singapore.	Heplisav: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant (not the to-be-marketed formulation) Schedule: 0, 8, 24 weeks IM (placebo at 4 weeks) N=207	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks IM (placebo at 8 weeks) N=213	Solicited AEs 7 days post-injection(s) AEs Study Week 28 SAEs Study Week 50 Serum chemistry, hematology, Urinalysis
DV2-HBV-05 Study Period: June 22, 2004-Aug 24, 2005	Phase 2 multicenter, double-blind, randomized, parallel group, active-control study in healthy subjects 40-70 years of age conducted in Singapore.	Heplisav: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant Schedule: 0, 8, 24 weeks IM (placebo at 4 weeks) N=48	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks IM (placebo at 8 weeks) N=48	Solicited AEs 7 days following each injection AEs Study Week 24 SAEs Study Week 50 Serum chemistry, hematology, ANA, anti-dsDNA

	Study Design	Heplisav Dose/Schedule/N	Active Comparator Dose/Schedule/N	Key Endpoint(s)
DV2-HBV-08 Study Period: July 14, 2005-Sept 6, 2006	Phase 1 single-center, double-blind, randomized, parallel group study in healthy subjects 18-39 years of age conducted in Canada	HEPLISAV: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant Schedule: 0, 4 weeks (placebo at 8 weeks), N=18 0, 8 weeks (placebo at 4 weeks), N=23 Heplisav: 10 mcg HBsAg/1500 mcg 1018 ISS adjuvant Schedule: 0, 4 weeks (placebo at 8 weeks), N=20	None	Solicited AEs 7 days following each injection AEs Study Week 12, SAEs Study Week 32 Serum chemistry, hematology, urinalysis, ANA
DV2-HBV-14 Study Period: June 6, 2007-March 6, 2008	Phase 2, multicenter, open label, single-arm study in healthy subjects 11-55 year of age conducted in the U.S.	Heplisav: 20 mcg HBsAg/3000 mcg 1018 adjuvant (proposed formulation) Schedule: 0, 4 weeks IM N=207	None	Solicited reactions 7 days following each injection AEs/SAEs Study Week 28
DV2-HBV-22 Study Period: Nov 11, 2013-Dec 9, 2014	Single-center, open-label, single group trial in healthy adults 50 – 70 years of age in the U.S.	Heplisav: 20 mcg HBsAg/3000 mcg 1018 adjuvant (proposed formulation) Schedule: 0, 4 weeks IM N = 25	None	AEs Study Week 12, SAEs/AESIs Study Week 56

SPR: Seroprotection Rate: anti-HbsAg level ≥ 10 mIU/mL
Study Period defined as date of enrollment of first study subject to the date of safety evaluation for the last study subject.
Source: BLA STN 125428.0.42, Summary of Clinical Efficacy, Table 2.7.3-2, pp. 15-16; BLA STN 125428/0.42, Summary of Clinical Safety, Table 2.7.4-1, pp. 16-20.

5.0 Pivotal Clinical Immunogenicity and Safety Studies Conducted with Heplisav

Immunogenicity results for Studies DV2-HBV-10 and -16 were reviewed and presented to VRBPAC in 2012. The effectiveness of Heplisav was established in these studies and therefore, does not require further discussion at the July 2017 VRBPAC meeting, although the revised immunogenicity data are included in this briefing document for completeness. Additional information regarding the case of Tolosa-Hunt Syndrome in a subject in Study DV2-HBV-16 is included as an update for the July 2017 VRBPAC.

5.1 Study DV2-HBV-10:

A Phase 3 Safety and Efficacy Study to Compare Immune Responses following Injection with Either Two Doses of Heplisav or Three Doses of Engerix-B

5.1.1 Study Design

This phase 3 study was a subject and observer-blind, randomized, controlled study of approximately 2400 subjects, 11-55 years of age (ages 18-55 in Germany) conducted at 21 sites in Canada and Germany. Subjects were randomized 3:1 to receive either Heplisav or Engerix-B vaccine. Enrollment of subjects was stratified by age (11 to 39

years of age and 40 to 55 years of age). Subjects randomized to Engerix-B received three 1.0 mL (20 mcg) injections of Engerix-B, the FDA-approved dose for adults not on dialysis. Subjects randomized to Heplisav received two injections of Heplisav vaccine at Weeks 0 and 4 and saline placebo at Week 24. Thus, all subjects received a total of three injections (active vaccine or matching placebo), given on Day 0, Week 4, and Week 24. The duration of the study was 28 weeks.

5.1.2 Study Objectives

The primary immunogenicity objective was to compare the proportion of subjects who exhibit seroprotective antibody levels at Week 12 following vaccination with Heplisav at 0 and 1 month to the proportion of subjects who exhibit seroprotective antibody levels when measured at Week 28 following vaccination with the active comparator, Engerix-B, at 0, 1, and 6 months. The primary safety objective of this study was to demonstrate safety and tolerability of vaccination with Heplisav when administered to adolescent and adult subjects.

5.1.3 Study Population

The study population comprised HBV seronegative male and female subjects 11-55 years of age who were serum negative for HBsAg (defined as an anti-HsBAg antibody level < 5 mIU/mL), anti-HBsAg antibody and anti-HBcAg antibody and who had never received any prior HBV vaccine (one or more doses). Subjects who were at high risk for recent exposure to HBV, HCV or HIV (e.g., current intravenous (IV) drug use, unprotected sex with known HBV, HCV or HIV positive partner) were excluded from the study.

5.1.4 Endpoints and Criteria for Study Success

The primary immunogenicity endpoint was the SPR after the final active injection. The primary immunogenicity analysis determined the difference in SPR between the Engerix-B group at Week 28 and Heplisav group at Week 12. If the upper limit of the 2-sided 95% CI was below the pre-specified non-inferiority criterion of +10%, Heplisav was determined to be non-inferior to Engerix-B.

5.1.5 Populations Analyzed

The primary immunogenicity analysis population was the Per-Protocol (PP) Population defined as subjects who met the eligibility criteria, did not violate the protocol in a substantial manner, received all protocol-specified study injections, had anti-HBsAg measurements and all injections within the specified day ranges, and had an anti-HBsAg measurement at the time defined by the protocol. This population was used for the primary immunogenicity analysis.

Safety was evaluated using the ‘safety population’, defined as enrolled subjects who received at least one study injection and had any post-baseline safety data. Subjects were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data. All 2415 vaccinated adult subjects were included in the safety analysis population (n=1809 in Heplisav and n=606 in the Engerix-B groups).

5.1.6 Subject Disposition

A total of 2910 subjects were screened for this study and 2428 enrolled. Thirteen subjects (0.5%) were adolescents (< 18 years), of whom 11 were assigned to the Heplisav group and two subjects were assigned to Engerix-B. The remaining 2415 subjects were adults, including 1809 subjects assigned to Heplisav and 606 subjects assigned to Engerix-B. Although this phase 3 study was originally designed to evaluate safety and immunogenicity in subjects aged 11 to 55 years, only 13 (0.5%) of the 2428 subjects enrolled in the study were younger than 18 years. Accordingly, the results of this study focused on adult subjects only (18 through 55 years).

Approximately 97% of all adult subjects completed the study. The most common reason for subject discontinuation was 'lost to follow-up', reported by 1.7% of subjects in each group. Additional reported reasons for discontinuation were adverse events (AEs), subject noncompliance, and subject withdrawal of consent.

5.1.7 Demographics and Baseline Characteristics

Demographic and baseline characteristics were similar between the two treatment groups, with no statistically significant differences found. Within each group, almost all subjects were white or non-Hispanic/Latino, the mean age was approximately 40 years, and the percentage of females was slightly higher than that of males. More than 99% of subjects in each treatment group had an anti-HBsAg level below 5 mIU/mL at baseline. The majority of enrolled study subjects (63-64% for both treatment groups) were non-smokers.

5.1.8 Immunogenicity Results

Primary Immunogenicity Endpoint

Based on the revised immunogenicity data submitted in the March 2016 Complete Response for reasons previously stated, the estimated difference in SPR between the Engerix-B and Heplisav groups and associated 95% CI was -13.7% (CI: -17.5, -10.4). The upper limit of the CI was -10.4%, which was below the pre-specified non-inferiority criterion of +10%, establishing that the SPR at the Week 12 time point for Heplisav was non-inferior to that of Engerix-B at Week 28, thereby meeting the pre-specified criterion for non-inferiority. The numerical change in SPR for the primary immunogenicity analysis was negligible, using the revised per protocol population numbers and did not change conclusions for Study DV2-HBV-10.

5.1.9 Safety Results (Study DV2-HBV-10)

Safety and tolerability were evaluated until Week 28 on the basis of the following parameters: solicited post-injection local and systemic AEs, unsolicited AEs, SAEs, clinical laboratory results, including ANA and anti-dsDNA, and oral temperature. Descriptive statistical analyses (count and percentage) were provided for all clinical parameters. Solicited systemic and local AEs (days 0-6), systemic AEs and treatment related local AEs occurring in ≥1% of subjects in any group (days 0-28) and temperature elevations ≥ 100.4 degrees Fahrenheit (day 0-6) were provided. ANA and anti-dsDNA were measured at baseline and at Week 28.

Overall, more subjects receiving Heplisav reported local pain (dose 1: 39% vs. 34%, dose 2: 35% vs. 25%), redness (dose 1: 4% vs. 0.5%, dose 2: 3% vs. 1%), and swelling (dose 1: 2% vs. 1%, dose 2: 2% vs. 0.5%) after the first or second dose than subjects receiving Engerix-B. The majority of events were reported as mild in intensity. The incidence and severity of systemic solicited AEs (fatigue, headache, and malaise) were similar between treatment groups.

Overall, unsolicited AEs occurred with similar incidence among subjects in each treatment group. A larger proportion of subjects in the Engerix-B arm experienced a severe unsolicited AE (87 [14.4%]) compared to the Heplisav arm (192 [10.6%]).

Deaths
No deaths were reported for the 28 week duration of the study.

Serious Adverse Events (SAEs)
All SAEs occurred in subjects 18 years of age and older. Twenty-eight (1.5%) of subjects in the Heplisav arm and 13 (2.1%) of subjects in the Engerix-B arm experienced at least one SAE. Overall, the incidence of SAEs was similar between treatment groups and did not raise safety concerns.

Autoimmune Adverse Events
Immune system disorders occurred with similar incidence among subjects in each treatment group (Heplisav 16 [0.9%], Engerix-B 7 [1.2%]). Musculoskeletal and connective tissue disorders occurred with similar incidence and severity in each group (Heplisav total 267 [14.8%], Engerix-B total 85 [14.0%]).

In the Heplisav group, three new-onset autoimmune adverse events were reported: c-ANCA (cytoplasmic ANCA) positive vasculitis (granulomatosis with polyangiitis [GPA], formerly Wegener's granulomatosis), Guillain-Barré syndrome, and Basedow's disease (Grave's disease). In the Engerix-B group, two subjects reported autoimmune adverse events: p-ANCA (perinuclear ANCA) positive vasculitis and Basedow's disease. The following additional adverse events that are potentially immune-mediated were identified by a retrospective analysis: lichen planus (n=1) in the Heplisav group and Bell's palsy (n=1) and Raynaud's phenomenon (n=1) in the Engerix-B group. In addition, an event of rheumatoid arthritis (RA) and an event of systemic lupus erythematosus (SLE) in two Heplisav subjects were reported as exacerbations of pre-existing disease. The three rare autoimmune diseases reported in this study are described here.

c-ANCA positive vasculitis (granulomatosis with polyangiitis, formerly Wegener's granulomatosis) (Heplisav Group)
A 55-year-old woman with a medical history of menopause experienced severe widespread urticaria 18 days after the first study injection which was attributed to the consumption of herring. Eleven days after the second study injection, the subject presented with vocal hoarseness. Approximately 8 weeks later, the subject reported symptoms of sinusitis. She reported never having had similar episodes before. She required septal surgery and paranasal sinus drainage. Approximately 7 months after her first vaccination, she was hospitalized for recurrent sinusitis. During this hospitalization she developed a pericardial effusion, pulmonary infiltrates, bilateral pleural effusions and proteinuria. Due to this constellation of symptoms, a serologic

workup ensued and an ELISA test was positive for c-ANCA (titer of 1:128, positive for proteinase-3 [PR-3]). The c-ANCA test was repeated at two outside reference laboratories with comparable results. A diagnosis of Wegener's granulomatosis was made and she was started on corticosteroids and cyclophosphamide. The subject had both anti-dsDNA and ANA levels within the normal range throughout the study.

The subject's Wegener's granulomatosis was determined by the investigator to be clinically stable 4 months after diagnosis. The investigator assessed the event as serious, severe, and 'possibly related' to study treatment.

Retrospective analysis of the subject's banked serum demonstrated negative ANCA to anti-PR3 at baseline, which was weakly positive four weeks after dose one and prior to dose 2, positive 12 weeks after dose 1, and strongly positive 23 and 28 weeks after dose one.

Guillain-Barré syndrome (Heplisav Group)
A 36-year-old woman with a medical history of splenectomy in 1985 received two study injections and an inactivated influenza vaccine injection 105 days after her second study injection. No complaints or reactogenicity events were noted during this period.

Five days after receiving the influenza vaccine injection, the subject was hospitalized complaining of progressive weakness that progressed to respiratory failure. A diagnosis of Guillain-Barré Syndrome was made. The subject's hospitalization was prolonged by the diagnosis of a follicular variant of papillary carcinoma (thyroid) and bilateral pulmonary embolism. While hospitalized, she was treated with anticoagulants, antibiotics, immunoglobulins, and plasmapheresis, resulting in noticeable improvement.

The subject's Guillain-Barré Syndrome was assessed by the investigator as being severe and 'probably not related' to study treatment but, instead, related to the influenza vaccine the subject received 5 days prior to symptom onset. The subject was discontinued from the study due to Guillain-Barré Syndrome.

p-ANCA positive vasculitis (Engerix-B Group)
A 44-year-old woman with a medical history that included mixed connective tissue disease and osteoarthritis, experienced fever approximately three months after the second study injection and was treated for presumed pneumonia. She returned to the hospital 127 days following her second study injection with severe dyspnea, hemoptysis, and pleuritic pain. She required intubation and mechanical ventilation. 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. Further investigation later disclosed a medical history (approximately 10 years prior) of mixed connective tissue disease (MCTD) that was diagnosed and treated with prednisone and chloroquine for over 2 years. She also had pre-existing

features of scleroderma. This medical history of MCTD was not disclosed by the subject at the time of study enrollment. A retrospective evaluation of specimens collected at screening revealed that the subject had anti-dsDNA levels within normal range, while her ANA levels were elevated (> 1:5120).

Autoimmune laboratory assessments

Antinuclear antibody (ANA) and anti-double stranded deoxyribonucleic acid (dsDNA) were assessed in subjects at baseline and Week 28. No clinically significant differences were identified between treatment groups.

Study Conclusion: Seroprotection rates following two doses of Heplisav were non-inferior to seroprotection rates after three doses of Engerix B. No clear safety concerns arose from the review of the safety data submitted for Study DV2-HBV-10. Similar rates of adverse events were observed in both study groups. One case of c-ANCA-positive GPA (Wegener's granulomatosis) occurred in a Heplisav recipient and one case of p-ANCA positive vasculitis occurred in an Engerix-B recipient who had pre-existing autoimmune disease. Independently, the development of granulomatosis with polyangiitis in temporal association with the receipt of Heplisav is notable. Additionally, the two cases of vasculitis in this study may not be comparable given that the subject in the Engerix-B arm had a history of autoimmune disease. However, the 3:1 randomization ratio, the single occurrence of this disease in this study, and the 28 week follow-up period of this study make interpretation of the incidence of a rare disease difficult.

5.2 Study DV2-HBV-16

An observer-blinded, randomized, parallel-group, multi-center phase 3 study comparing the safety and immunogenicity of Heplisav to Licensed Vaccine (Engerix-B) among Healthy Adults 40 to 70 years of Age

5.2.1 Study Design

The study was a subject- and observer-blinded, randomized, controlled study of approximately 2000 adult subjects, 40 to 70 years of age.

Similar to Study DV2-HBV-10, the Applicant revised the per protocol population for Study DV2-HBV-16, based on an audit conducted by the Applicant in 2014. Safety population numbers were not affected by this audit. Revised data for the primary immunogenicity endpoints are included in this briefing document.

The overall allocation ratio of Heplisav to Engerix-B was 4:1. For the primary objective of noninferiority, the allocation ratio of the three consistency lots to Engerix-B was 3:1. Randomization was stratified by age: 40 to 49 years, 50 to 59 years, and 60 to 70 years, and by study site.

Subjects randomized to Engerix-B received three injections of Engerix-B. Subjects randomized to Heplisav received two injections of Heplisav vaccine at Weeks 0 and 4 and saline placebo at Week 24. Thus, all subjects received a total of three injections (active vaccine or matching placebo), given on Day 0, Week 4 (1 month), and Week 24 (6 months). This dosing regimen and schedule was identical to that of the pivotal phase 3

study, DV2-HBV-10. Upon completion of Week 0, subjects 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-HBsAg serum concentrations. The duration of the study was 56 weeks.

5.2.2 Study Objectives

The co-primary immunogenicity objectives of this phase 3 study were: 1) to demonstrate lot consistency through clinical evaluation of three consecutively manufactured lots of Heplisav, and 2) to compare the proportion of subjects who exhibit a seroprotective immune response when measured at Week 12 following vaccination with Heplisav at 0 and 1 month to the proportion of subjects who exhibit SPRs when measured at Week 32 following vaccination with Engerix-B, at 0, 4, and 24 weeks. The primary safety objective of this study was to demonstrate safety and tolerability of vaccination with Heplisav when administered to subjects 40 to 70 years of age and to compare the safety profile to that of Engerix-B for this age group.

5.2.3 Study Population

The study enrolled HBV seronegative, low HBV-risk, male and female subjects 40-70 years of age who were serum negative for HBsAg, anti-HBsAg antibody and anti-HBcAg antibody and who had never received any prior HBV vaccine.

5.2.4 Endpoints and Criteria for Study Success

A summary of primary immunogenicity endpoints is presented in Table 2:

Table 2. Immunogenicity Testing (Study DV2-HBV-16)

Hypothesis	Study Parameter
Primary	Non-inferiority of SPR, measured at 8 weeks after the last active dose of Heplisav (combined lots) vs. Engerix-B
Primary	Lot-to-lot consistency measured by GMC at 4 weeks after last active dose among 3 consecutively manufactured Heplisav lots (008, 009, 010).

Source: *BLA 125428, DV2-HBV-16, Statistical Analysis Plan, 2. Study Objectives Page 8 of 38, Section 4.5. Immunogenicity Evaluation, pages 13-18 of 38*

Lot-to-lot consistency was established if all three CIs for the pairwise ratios of GMCs were embedded in the interval between 2/3 (0.667) and 1.5.

Heplisav was declared non-inferior to Engerix-B with respect to SPR if the lower limit of the 95% CIs of the difference in seroprotection rates (Heplisav seroprotection rate at Week 12 minus the Engerix-B seroprotection rate at Week 32) was greater than -10%.

5.2.5 Populations Analyzed

Three per protocol populations were used for the immunogenicity analysis in Study DV2-HBV-16, one for the noninferiority immunogenicity analysis, one for the lot consistency immunogenicity analysis, and one for the bridging study analysis (consistency of immune responses between lot TDG006 and the three combined consistency lots). The bridging population is not germane to evaluation of immunogenicity for the purposes of the July 2017 VRBPAC. The non-inferiority and lot consistency per protocol populations were defined as follows:

- Noninferiority Per Protocol Population: randomized subjects who received one of the three consistency lots of Heplisav or Engerix-B, received all three study injections as randomized and within the study visit windows, had no major protocol deviations, and had anti-HBsAg measurements and all injections within the specified day ranges (primary immunogenicity analysis population).

- Lot Consistency Per Protocol Population: all subjects randomized to one of three consistency lots of Heplisav who received the first two study injections within the study visit windows, had no major protocol deviations, and had anti-HBsAg levels obtained within study visit windows at baseline and Week 8.

The safety population included all subjects who received at least one study injection, excluding subjects who had no on-study safety data.

5.2.6 Subject Disposition

A total of 2269 subjects (92.5% of the randomized population) completed the study and 183 subjects (7.5%) discontinued the study early (before Week 52). The percentage of subjects completing the study was similar across all treatment groups. The most common reasons for early study discontinuation were lost to follow-up (3.8%), consent withdrawn (2.3%), and 'other' reasons (0.7%). Treatment compliance of the randomized population with the three-dose regimen remained high throughout the study. Compliance was similar across all treatment groups, with 94.3% of Heplisav consistency lot groups, 92.0% of the TDG006 group, and 94.4% of Engerix-B group subjects receiving all three injections.

5.2.7 Demographics and Baseline Characteristics

Demographic and baseline characteristics were similar between the Heplisav (all lots) and Engerix-B groups, with no statistically significant differences found. Within each group, almost all subjects were white or non-Hispanic/Latino, the mean age was approximately 54 years, and the percentage of females was slightly higher than that of males. The breakdown by age stratum was similar between the study groups, with slightly more subjects in the 50 through 59 year subgroup than in the age 40 through 49 and age 60 to 70 age subgroups. More than 96% of subjects in each treatment group had an anti-HBsAg level below 5 mIU/mL, at baseline. The majority of enrolled study subjects were non-smokers (79% for both treatment groups), non-diabetic (91-92%), and non-obese (BMI $\leq$ 30 kg/m^2 in 56-67% for both treatment groups).

5.2.8 Immunogenicity Results

Primary Immunogenicity Endpoints

Immunogenicity criteria for demonstration of lot consistency were met when measured 8 weeks after the last vaccination of Heplisav (Week 12).

For the comparison of SPRs at 8 weeks after the last active dose of study treatment between Heplisav (Week 12) and Engerix-B (Week 32) for the revised per protocol population, noninferiority was demonstrated between the two treatment arms. The SPR in the Heplisav group was 90.1% and that of the Engerix-B group was 70.5%; the

estimated difference between these rates was 19.6% (Heplisav- Engerix-B; 95% CI 14.7%, 24.8%). Because the lower limit of the 95% CI (14.7%) was greater than -10%, the SPR for the Heplisav group at Week 12 met the pre-specified non-inferiority SPR criterion for the Engerix-B group at Week 32. The revised per protocol population did not significantly alter the non-inferiority results between Heplisav and Engerix-B and did not change conclusions for the noninferiority comparison.

5.2.9 Safety results

Safety monitoring for Study DV2-HBV-16 was conducted in a similar manner as in Study DV2-HBV-10, with the exception that an algorithm was prospectively designed to capture potentially autoimmune adverse events. The safety population included 2449 subjects (Heplisav: n=1968; Engerix-B: n=481).
/
The reporting period for non-serious AEs was the time period from the first injection (Week 0) until 4 weeks after the third injection (Week 28). The reporting period for SAEs and AESIs was from the first injection (Week 0) to 28 weeks after the third injection (Week 52). Potentially autoimmune events were referred to a Safety Evaluation and Adjudication Committee (SEAC) for review.

Solicited adverse events:
Solicited adverse events included local pain, redness and swelling, fatigue, headache, malaise, myalgia, and elevated oral temperature. More subjects receiving Heplisav reported injection site redness and pain than did subjects receiving Engerix-B, though the majority of reactions were mild in intensity. The incidence and severity of malaise, headache, myalgia, and fatigue were similar among treatment groups for both active doses. The vast majority of subjects did not report fever after vaccination, and fever intensity was similar among treatment groups. Most solicited systemic adverse events were graded as mild or moderate in intensity.

Unsolicited Adverse Events:
Overall, the proportions of subjects experiencing any AE were similar among treatment groups. There were more active injections in the Engerix-B group and therefore more AEs reported after active injections in this treatment arm than in other arms. Adverse events rated as grade 3 or higher occurred with a slightly lower incidence in the Heplisav consistency lots (4.5%) than in the Engerix-B arm (5.8%).

The majority of unsolicited adverse events were deemed unrelated to the study vaccine by the investigator. More AEs led to discontinuation of treatment in the Heplisav lots (consistency lots total: 0.9%) than in the Engerix-B arm (0.4%).

Deaths
Two deaths were reported in study DV2-HBV-16, one in a Heplisav recipient and one in an Engerix-B recipient:

1. A report of pulmonary embolus which occurred (b) (6) days after the second study injection of Heplisav, in a 46 year old active white male with no relevant past medical history; including no history of a coagulation disorder, preceding trauma, or other pre-disposing cause for hypercoagulability (Subject 22-003). The investigator assessed the

event as not related to study treatment, but no autopsy information was available on this subject.

2. A report of fatal myocardial infarction in a 64 year old black or African American male with a history of gout, hypertension, gastroesophageal reflux and bilateral knee osteoarthritis (Subject 92-638) which occurred (b) (6) days after the second study injection of Engerix-B. The investigator assessed the cardiac arrest as not related to the study treatment.

Serious adverse events

Non-fatal SAEs occurred with similar frequency in the Heplisav consistency lots (3.4%) and the Engerix-B group (4.8%).

Autoimmune Adverse Events

A list of autoimmune and potentially immune-mediated conditions was pre-specified and events considered to be possibly autoimmune were reviewed and evaluated by a Safety Evaluation and Adjudication Committee (SEAC). Nine potential autoimmune adverse events were reported: hypothyroidism (n=5), VIIth cranial nerve palsy (n=1), erythema nodosum (n=1), vitiligo (n=1) and microscopic colitis (n=1). Seven of these events were confirmed by a treating specialist's evaluation to be potentially autoimmune in nature: hypothyroidism (n=4), VIIth cranial nerve palsy (n=1), erythema nodosum (n=1), and vitiligo (n=1). All of these events occurred in subjects in the Heplisav consistency lot group (7/1439, 0.5%), were mild to moderate in severity, and were considered non-serious.

The SEAC adjudication, confirmed three cases of new-onset autoimmune adverse events: hypothyroidism (n=2) and vitiligo (n=1). The events of VIIth cranial nerve palsy and erythema nodosum were not considered by the SEAC to be autoimmune events. The event of erythema nodosum was considered to be related to vaccination. The other cases were determined to be pre-existing through testing of baseline blood samples.

Review of the initial BLA submission in 2012 identified one additional subject with a potentially immune-mediated adverse event that was not initially referred to the SEAC for adjudication. The subject was diagnosed with cavernous sinus syndrome, which was considered by treating physicians to possibly be Tolosa-Hunt syndrome. Additional information was requested in the February 2013 CR letter and was submitted to the FDA in March 2013. Four expert consultations were obtained by FDA to determine the diagnosis and relationship to the vaccine, which was pending at the time the CR Letter was issued. A brief summary of the case and results of the expert consultants appears here.

Tolosa-Hunt Syndrome

A 69-year-old male Heplisav recipient with multiple medical issues developed "amblyopia" approximately six months after the second injection of Heplisav, followed by severe headaches, later associated with diplopia. He was also noted to have severe ptosis and left cranial nerve VI palsy. The subject's symptoms were acutely responsive to each of several courses of steroids with symptoms returning upon discontinuation. A diagnostic evaluation, which included imaging, was negative. More than nine months

following the second study injection, the subject was diagnosed with Tolosa-Hunt syndrome, a painful ophthalmoplegia caused by a non-specific granulomatous inflammation of the cavernous sinus of unknown etiology with potential vasculitic or other autoimmune etiology. Anti-neutrophil cytoplasmic antibody (ANCA) testing is often negative. Following resolution of the event, the treating neurologist changed the diagnosis from Tolosa-Hunt syndrome to cavernous sinus syndrome. The investigator assessed the event of cavernous sinus syndrome as severe in intensity and not related to study treatment.

Four FDA specialist consultants assessed the case as Tolosa-Hunt syndrome, each of them noting the response to steroids and reasonable exclusion of alternate etiologies. Of the three consultants that commented, two did not believe that there was evidence of overlap between THS and GPA. One consultant noted that there can be overlap, but that the case of THS reported in DV2-HBV-16 did not display features the consultant would expect if it were GPA. Of the three consultants that commented, none endorsed a causal association between the vaccine and the adverse event.

Autoimmune laboratory assessments

ANA and anti-dsDNA were assessed in subjects at baseline and Week 56 or at the time of early discontinuation. No clinically significant differences were identified between treatment groups.

Study Conclusion: Immunogenicity data supporting lot consistency was shown, and Heplisav was non-inferior to Engerix B with respect to SPR rates in this second pivotal study. The numerical change in the two primary immunogenicity analyses using the revised per protocol populations was negligible.

The overall rates of solicited and unsolicited AEs, SAEs and AESIs were similar among the treatment arms. While the incidence of autoimmune events was low, all autoimmune AEs occurred in Heplisav recipients. The occurrence of Tolosa-Hunt syndrome, a condition caused by presumed granulomatous inflammation, following Heplisav administration is notable. Given the randomization ratio employed in this study and the low background incidence of many autoimmune diseases, the clinical significance of the difference in the incidence of autoimmune disease between groups is unclear. However, it is acknowledged that the ability to reliably evaluate uncommon specific autoimmune events is limited due to the size of the study.

5.3 Study DV2-HBV-23

A Phase 3, Observer-Blinded, Randomized, Active-Controlled (Engerix-B), Multicenter Trial of the Safety and Immunogenicity of Heplisav in Adults 18 to 70 Years of Age.

5.3.1 Study Design

This phase 3 study was a subject and observer-blind, randomized, active-controlled study of approximately 8250 subjects, 18 - 70 years of age conducted at 40 sites in the US. Subjects were randomized 2:1 to receive either Heplisav or Engerix-B vaccine. The Applicant planned to enroll at least 413 subjects with type 2 diabetes mellitus, defined as having a clinical diagnosis of type 2 diabetes mellitus and taking at least an oral or non-insulin injectable hypoglycemic agent and/or insulin. Because immunogenicity and

benefit of Heplisav was established in previous studies, FDA's analysis and the VRBPAC discussion will focus on safety data from this study. Enrollment of subjects was stratified by site, age (18 – 39 and 40 – 70 years of age), and type 2 diabetes mellitus status. Subjects randomized to Engerix-B received three 1.0 mL (20 mcg) injections of Engerix-B, the FDA-approved dose for adults not on dialysis. Subjects randomized to Heplisav received two 0.5 mL (20 mcg antigen/3000 mcg adjuvant) injections at Weeks 0 and 4 and saline placebo at Week 24. Thus, all subjects received a total of three injections (active vaccine or matching placebo), given on Day 0, Week 4, and Week 24. The duration of the study was 56 weeks.

5.3.2 Study Objectives

The primary safety objective of this study was to demonstrate overall safety of Heplisav with respect to clinically significant adverse events.

FDA reviewed the immunogenicity endpoint of the non-inferiority of the SPR at Week 24 in Heplisav recipients compared with the SPR at Week 28 in Engerix-B recipients in all per protocol subjects (secondary endpoint) in Study DV2-HBV23, in order to confirm that results were consistent with Studies DV2-HBV-10 and -16.

5.3.3 Study Population

The study population comprised male and female subjects 18 – 70 years of age who were serum negative for HBsAg, anti-HBsAg antibody, and anti-HBcAg antibody and who had never received any prior HBV vaccine. Subjects who were HIV antibody positive or who had an autoimmune disorder were excluded from the study.

5.3.4 Endpoints

The primary safety endpoints were proportion of subjects with the following: new-onset medically-attended adverse events (MAEs), SAEs or deaths, AESIs, and adverse events of special interest or autoimmune adverse events (AIAEs). Secondary safety endpoints were proportion of subjects with the following: new-onset GPA or THS, new-onset thrombotic events, new-onset abnormal thrombotic screens in the laboratory sub-study, and new-onset abnormal renal blood or urine tests in the laboratory sub-study.

5.3.5 Populations Analyzed

The Safety Population (SP) was defined as: all subjects who received at least one injection of study drug, excluding subjects who had no on-study safety data. All subjects treated were included in the SP. The SP was the primary analysis population for all safety analyses.

The Per Protocol (PP) population was defined as: all randomized subjects who received all study injections, had no major protocol deviations, and had anti-HBs levels obtained within the protocol-defined study visit window at Week 28. The PP population was the primary analysis populations for all immunogenicity analyses.

5.3.6 Subject Disposition

A total of 8374 subjects were randomized into the study; 5587 subjects were administered Heplisav and 2781 subjects received Engerix-B. Approximately 94% of all subjects completed study treatment (received three doses) and 92% completed the study

(had Week 56 visit). The most common reason for subject discontinuation was 'lost to follow-up', reported by 5.6% of subjects. Other reported reasons for discontinuation were withdrawal of consent, pregnancy, other, and death.

5.3.7 Demographics and Baseline Characteristics

Demographic and baseline characteristics were similar between the two treatment groups, with no statistically significant differences found. Subjects were 71% white, 26% black, and 1% Asian; subjects were 91% non-Hispanic/Latino. The mean age was approximately 50 years, and the percentage of males was slightly higher than that of females for the Heplisav arm.

Baseline characteristics and history of medical conditions that may be indicative of increased cardiovascular risk factors were similar between the two treatment groups and are summarized in Table 3.

Table 3. Number and proportion of subjects with medical history and baseline characteristics indicating increased risk for cardiovascular disease, SafetyPopulation, DV2-HBV-23

Condition or characteristic	Heplisav N=5587 n (%)	Engerix-B N=2781 n (%)
Type 2 Diabetes*	762 (13.6)	381 (13.7)
Hypertension†	2021 (36.2)	978 (35.2)
Hyperlipidemia‡	1757 (31.4)	879 (31.6)
Sex and Age: Male > 45 years	1879 (33.6)	919 (33.0)
Sex and Age: Female > 55 years	1028 (18.4)	537 (19.3)
Smoking within 1 year	1843 (33.0)	909 (32.7)
Obesity: BMI ≥ 30	2724 (48.8)	1285 (46.2)
At least one baseline medical diagnosis of cardiac ischemia§	211 (3.8)	99 (3.6)

Source: Adapted from 125428/0.42, Module 2.7.4, Summary of Clinical Safety, Table 2.7.4-27, pp. 84-86
* Defined as subjects flagged by the Applicant as diabetic – subjects with a clinical diagnosis of diabetes and taking a hypoglycemic agent
† Reviewer-generated analysis using dataset ADMH, defined as subjects with at least one medical history preferred term of Accelerated hypertension, Diastolic hypertension, Essential hypertension, Hypertension, Hypertensive heart disease, Labile hypertension, Malignant hypertension, Systolic hypertension, Secondary hypertension
‡ Defined as subjects with at least one medical history preferred term for Dyslipidemia SMQ narrow
§ Defined as subjects with at least one medical history preferred term within the narrow SMQs of Myocardial Infarction and Other Ischemic Heart Disease

5.3.8 Immunogenicity Results

The SPR response in Heplisav recipients at Week 24 was non-inferior to the SPR response in Engerix-B recipients at Week 28 for all per protocol subjects, consistent with the results of Studies DV2-HBV-10 and -16.

5.3.9 Safety results

Solicited adverse events were not collected during the study. Safety was evaluated through Week 56 by the following parameters: medically-attended AEs (MAEs), SAEs, and AESIs. Similar to Study DV2-HBV-16, autoimmune events were prospectively defined and captured. Clinical laboratory results were assessed on a subset of subjects and are described below.

The safety population included 8368 subjects (Heplisav n = 5587, Engerix-B n = 2781).

Medically-attended Adverse Events
The rate of MAEs reported from vaccination through the Week 56 study visit was approximately 46% in both study groups. The most common MAEs (>1%) in either treatment group are presented in Table 4 below.

Table 4. Number and percent of subjects reporting common (>1% in either trial arm) medically attended adverse events from vaccination through Week 56 by trial arm, Safety Population, Study DV2-HBV-23

Preferred Term	Heplisav N = 5587 n (%)	Engerix-B N = 2781 n (%)
Upper respiratory tract infection	192 (3.44%)	92 (3.31%)
Bronchitis	176 (3.15%)	102 (3.67%)
Sinusitis	149 (2.67%)	84 (3.02%)
Hypertension	133 (2.38%)	59 (2.12%)
Urinary tract infection	132 (2.36%)	64 (2.30%)
Back pain	116 (2.08%)	54 (1.94%)
Arthralgia	98 (1.75%)	54 (1.94%)
Osteoarthritis	77 (1.38%)	32 (1.15%)
Pain in extremity	72 (1.29%)	28 (1.01%)
Type 2 diabetes mellitus	67 (1.20%)	37 (1.33%)
Cough	62 (1.11%)	37 (1.33%)
Acute sinusitis	59 (1.06%)	37 (1.33%)
Musculoskeletal pain	45 (0.8%)	30 (1.1%)

Source: Adapted from BLA STN 125428/0.42, DV2-HBV-23 CSR, Table 12-3, p. 80
N number of subjects in each treatment group
n number of subjects reporting event

The following MAEs occurred in at least 0.5% of either treatment group and at a rate of at least twice the other treatment group: Herpes zoster (38 Heplisav subjects, 0.68%; 9 Engerix-B subjects, 0.32%), Tooth infection (17 Heplisav subjects, 0.3%; 17 Engerix-B subjects, 0.61%), and Exostosis (6 Heplisav subjects, 0.11%; 14 Engerix-B subjects, 0.5%). Events of venous thromboembolism, including PE and DVT occurred with similar frequency between treatment groups.

Deaths
There were 32 deaths in study DV2-HBV-23, 25 in the Heplisav group (0.45%) and seven in the Engerix-B group (0.25%). Cause of death, timing, and investigator assessment of relationship are presented in Table 5 below.

Table 5. Fatal adverse events, Safety Population, Study DV2-HBV-23

Age	Sex	Cause of Death	Last Active Dose	AE Start (Days Since Last Active Dose)	Date of Death (Days Since Last Active Dose)	Related per investigator
Heplisav					(b) (6)	
Cardiac						
50	M	Acute coronary syndrome*	1	7		N
69	M	Acute myocardial infarction*	2	57		N
57	M	Hypertensive heart disease	2	63		N
62	M	Hypertensive heart disease*	2	212		N
58	F	Hypertensive heart disease	2	225		N
70	F	Cardiac arrest	2	243		N
47	M	Myocardial infarction	2	287		N
55	F	Cardio-respiratory arrest	2	298		N
General						
61	F	Death – Unknown cause	2	59		N
51	F	Death – Unknown cause	2	354		N
Hepatobiliary						
68	M	Hepatic cirrhosis	2	27		N
Infectious						
56	M	Hepatitis C	2	35		N
Injury and Poisoning						
58	F	Victim of homicide†	1	1		N
49	M	Toxicity to various agents†	2	3		N
38	M	Toxicity to various agents†	2	36		N
62	M	Overdose†	2	88		N
44	M	Toxicity to various agents†	2	159		N
49	M	Toxicity to various agents†	2	160		N
42	F	Gunshot wound†	2	283		N
49	M	Accident†	2	286		N
Neoplasm						
49	M	Lung cancer metastatic	2	244		N
43	F	Small cell lung cancer metastatic	2	300		N
Nervous system						
46	F	Hypoxic-ischemic encephalopathy†	2	191		N
Respiratory						
67	M	Acute respiratory failure	2	15‡		N
61	M	Acute respiratory distress syndrome§	2	120		N
Engerix-B						
Cardiac						
52	M	Myocardial infarction	1	12		N
48	M	Hypertensive heart disease§	3	27		N
69	M	Cardio-respiratory arrest	3	88		N
Injury and Poisoning						
44	M	Craniocerebral injury†	1	17		N

Age	Sex	Cause of Death	Last Active Dose	AE Start (Days Since Last Active Dose)	Date of Death (Days Since Last Active Dose)	Related per investigator
55	M	Toxicity to various agents†	2	99	(b) (6)	N
33	F	Head injury†	3	162		N
Neoplasm						
67	M	Pancreatic carcinoma metastatic	3	179		N

Source: Adapted from BLA STN 125428/0.42 CSR DV2-HBV-23, Table 12-3, p. 96
AE: adverse event
* Subject found dead. No autopsy performed.
† Events assessed by the Applicant and reviewer to be due to illicit drug overdose or injury.
§ Alcohol and drugs contributed.

Nine deaths in the Heplisav group and three deaths in the Engerix-B group were determined by the Applicant and the clinical reviewer to be due to illicit drug overdose or injury based upon the narratives provided, and are noted in the table above. Excluding these deaths, 16 subjects in the Heplisav group (0.29%) and four subjects in the Engerix-B group (0.14%) experienced a fatal adverse event. Within one month of vaccination, there was one non-injury, non-poisoning death in the Heplisav group, due to acute coronary syndrome, and two in the Engerix-B group, due to myocardial infarction and hypertensive heart disease. There were five non-injury, non-poisoning deaths within 90 days in the Heplisav group and three in the Engerix-B group.

SAEs

Overall, SAEs were reported in 345 Heplisav subjects (6.2%) and 148 Engerix-B subjects (5.3%). Non-fatal SAEs occurred with similar frequency in the Heplisav and the Engerix-B group with 325 subjects (5.8%) in the Heplisav group reporting 491 SAEs, 142 (5.1%) subjects in the Engerix-B reporting 212 SAEs. Overall, the most common organ systems represented by SAEs were infections and infestations (Heplisav 1.3%, Engerix-B 1.2%), cardiac disorders (Heplisav 0.9%, Engerix-B 0.5%), gastrointestinal disorders (Heplisav 0.7%, Engerix-B 0.5%), nervous system disorders (Heplisav 0.7%, Engerix-B 0.6%), respiratory, thoracic, and mediastinal disorders (Heplisav 0.6%, Engerix-B 0.4%), and neoplasms (Heplisav 0.6%, Engerix-B 0.5%).

The most commonly reported SAEs, including fatal events, for the Heplisav group from vaccination through Week 56 are presented in Table 6 below.

Table 6. Number and percentage of subjects reporting the most commonly reported treatment-emergent serious adverse events (> 0.1% in either trial arm) from vaccination through Week 56 by trial arm, Safety Population, Study DV2-HBV-23

Preferred Term	Heplisav n (%)	Engerix-B n (%)
Pneumonia	15 (0.27)	8 (0.29)
Acute myocardial infarction	14 (0.25)	1 (0.04)
Non-cardiac chest pain	9 (0.16)	7 (0.25)
Chronic obstructive pulmonary disease	9 (0.16)	3 (0.11)
Cellulitis	7 (0.13)	4 (0.14)
Osteoarthritis	7 (0.13)	3 (0.11)

Preferred Term	Heplisav n (%)	Engerix-B n (%)
Cerebrovascular accident	7 (0.13)	3 (0.11)
Atrial fibrillation	6 (0.11)	3 (0.11)
Cardiac failure congestive	6 (0.11)	3 (0.11)
Coronary artery disease	6 (0.11)	2 (0.07)
Small intestinal obstruction	6 (0.11)	2 (0.07)
Acute respiratory failure	6 (0.11)	1 (0.04)
Hypertension	5 (0.09)	3 (0.11)
Cholelithiasis	4 (0.07)	4 (0.14)
Renal failure acute	4 (0.07)	3 (0.11)
Deep vein thrombosis	4 (0.07)	3 (0.11)
Prostate cancer	3 (0.05)	4 (0.14)
Syncope	2 (0.04)	4 (0.14)
Dehydration	1 (0.02)	3 (0.11)

Source: Adapted from BLA STN 125428/0.042, CSR DV2-HBV-23, Table 12-14, p. 97.
N number of subjects in each treatment group
n number of subjects reporting event

As noted above, rates of cardiac SAEs were more frequent in the Heplisav group compared to the Engerix-B group (Heplisav 0.9%, Engerix-B 0.5%). This difference in frequency was most notable in the preferred term of acute myocardial infarction (AMI), which was reported in 14 subjects in the Heplisav group (0.25%) and one subject in the Engerix-B group (0.04%). Rates of non-serious MAEs in the organ system of cardiac disorders were similar between treatment groups (Heplisav 1.22%, Engerix-B 1.19%). Because of the differences noted, further evaluation was performed by the Applicant and the FDA, which is summarized here.

An overview of all cardiac SAEs is shown in Table 7 below with preferred terms within the standard MedDRA query (SMQ) narrow for myocardial infarction shaded.

Table 7. Number and proportion of subjects with treatment-emergent serious adverse events in the system organ class of cardiac disorders by treatment group, Safety Population, Study DV2-HBV-23

Preferred Term	Heplisav N = 5587 n (%)	Engerix-B N = 2781 n (%)
Acute coronary syndrome	1 (0.02)	0
Acute myocardial infarction	14 (0.25)	1 (0.04)
Angina pectoris	2 (0.04)	1 (0.04)
Angina unstable	1 (0.02)	0
Atrial fibrillation	6 (0.11)	3 (0.11)
Atrial flutter	2 (0.04)	1 (0.04)
Bradycardia	2 (0.04)	0
Cardiac arrest	3 (0.05)	0
Cardiac failure	4 (0.04)	0
Cardiac failure acute	1 (0.02)	0
Cardiac failure congestive	9 (0.11)	3 (0.11)
Cardiac ventricular thrombosis	1 (0.02)	1 (0.04)
Cardiogenic shock	1 (0.02)	0
Cardiomyopathy	0	1 (0.04)

Preferred Term	Heplisav N = 5587 n (%)	Engerix-B N = 2781 n (%)
Cardio-respiratory arrest	1 (0.02)	1 (0.04)
Coronary artery disease	6 (0.11)	2 (0.07)
Coronary artery occlusion	1 (0.02)	1 (0.04)
Coronary artery stenosis	2 (0.04)	0
Hypertensive heart disease	4 (0.07)	1 (0.04)
Myocardial infarction	2 (0.04)	1 (0.04)
Myocardial ischemia	1 (0.02)	0
Pulseless electrical activity	1 (0.02)	0
Supraventricular tachycardia	1 (0.02)	0
Ventricular fibrillation	1 (0.02)	0
Ventricular tachycardia	2 (0.04)	0
Total Subjects with at least 1 Cardiac SAE	**51 (0.91)**	**15 (0.54)**

Source: Adapted from BLA STN 125428/0.42, CSR DV2-HBV-23, Table 12-16, p. 105.
N number of subjects in each treatment group
n number of subjects reporting event
Shaded rows represent events in the SMQ narrow for MI

Nineteen Heplisav subjects (0.3%) and three Engerix-B subjects (0.1%) reported events in the SMQ narrow for MI.

There were three additional subjects who reported non-serious MAEs in the SMQ narrow for MI and who are not included in the table above. A 64 year-old man who received Heplisav was diagnosed with a silent MI that was noted incidentally by adenosine nuclear stress test and EKG 112 days following the first injection of Heplisav, although the timing of the actual MI in relationship to vaccination is unknown. Two events of troponin increased were reported in two subjects in the Engerix-B group in the setting of another SAE (urosepsis and diabetes mellitus inadequate control). These subjects are not considered in the analysis below.

Table 8 below is a clinical reviewer-generated summary of the 22 subjects reporting an SAE with a preferred term in the SMQ narrow for MI in DV2-HBV-23, the timing of the SAEs and the subject's risk factors for coronary disease. All subjects reporting events identified as MI had at least one risk factor for cardiovascular disease and/or prior known cardiovascular disease. Within one week of the last active vaccination, one subject in the Heplisav group and none in the Engerix-B group reported an MI. Within one month, three subjects in the Heplisav group and one in the Engerix-B group reported an MI. Within three months, nine subjects in the Heplisav group and one in the Engerix-B group reported an MI. The remainder of MI events was reported more than three months after the last active injection. Please see Section 6.2.2 for further analyses of timing of MI adverse events.

Table 8. Timing of myocardial infarction following vaccination and baseline risk factors of subjects reporting myocardial infarction, by treatment group, Safety Population, DV2-HBV-23

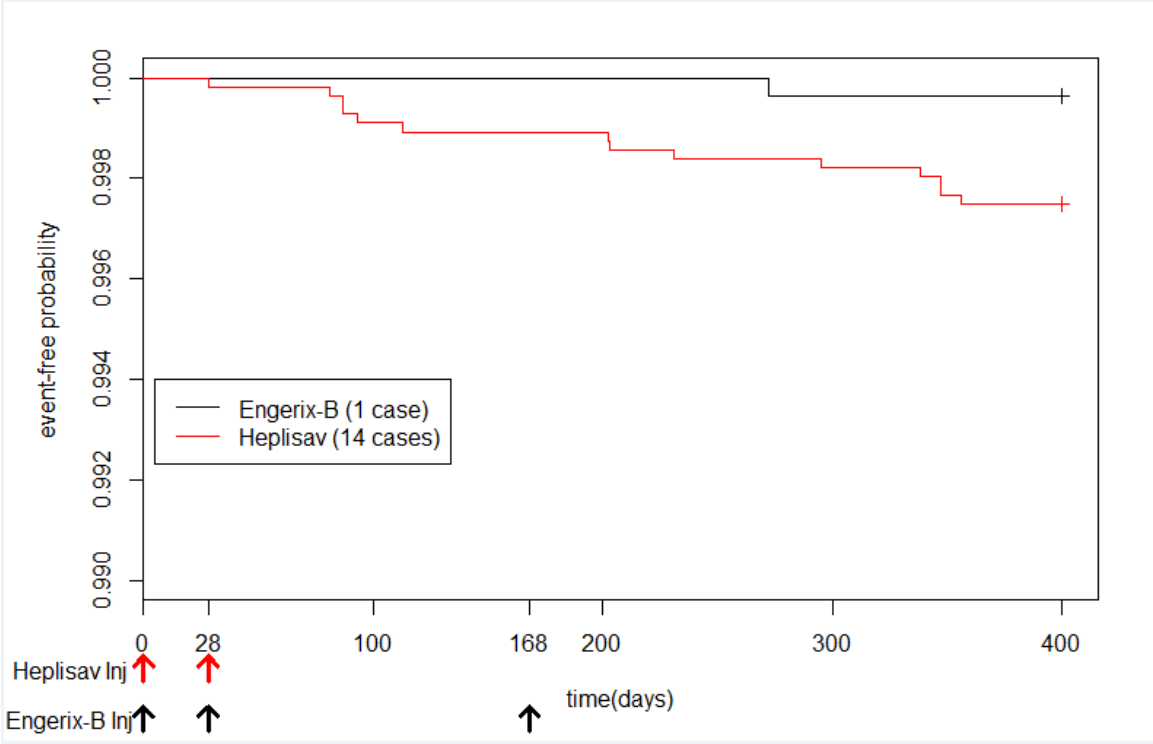
Treatment Group and Preferred Term	Study Day of MI event	Day of MI event relative to most recent active dose	Most recent active dose #	Age	Sex	Prior Ischemic Heart Disease	DM	HTN	DL	Current or former smoker	Obesity
Heplisav											
AMI	28	3	2	61	F	?		+	+		
ACS†	8	8	1	50	M	+		+			
Coronary artery occlusion	14	14	1	64	F		+	+	+		
MI	81	53	2	68	F	?			+	+	
AMI†	85	58	2	69	M			+	+	+	
AMI	87	62	2	64	M			+	+	+	
AMI	93	64	2	53	M		+	+	+		+
AMI	87	64	2	65	M	?	+**	+		+	
AMI	113	85	2	68	M	+		+	+		+
Angina Unstable*	123	96	2	56	M			+	+	+	+
AMI	202	174	2	39	F			+		+	
AMI	203	175	2	46	M			+	+		+
AMI	231	208	2	69	F				+		+
MI†	320	288	2	47	M		+				
AMI	295	295	1	52	M			+			
AMI	338	309	2	68	M		+	+	+	+	+
AMI	347	319	2	62	M	+		+	+		+
AMI	347	319	2	63	F		+	+			+
AMI	356	329	2	60	M			+	+		
Engerix-B											
MI†	13	13	1	52	M	+				+	
AMI	272	115	3	65	M	+	+	+	+		+
Coronary artery occlusion	371	203	3	54	M	+			+		

Source: Reviewer-generated analysis from 125428/0.42, Module 5.3.5.1, datasets ADSL, ADAE, and ADMH and 125428/0.65; Module 5.3.5.3, Integrated Summary of Safety.
Day 1 is day of administration. An event start day relative to the most recent dose of x is x-1 days following the most recent dose.
Risk factors were determined by datasets ADSL and ADMH, or noted in narrative.
AMI: acute myocardial infarction, MI: myocardial infarction, CAD: coronary artery disease, DM: diabetes mellitus, HTN: hypertension, DL: dyslipidemia
+ Subject has risk factor
? Not clear from narrative and datasets if diagnosis of ischemic heart disease occurred prior to enrollment
† Fatal event
* Subject had a cardiac catheterization showing no coronary artery disease
** Subject had no baseline diagnosis of diabetes, but an elevated hemoglobin A1C within 3 months of first vaccination, suggesting pre-existing diabetes
Events shaded represent events that were adjudicated by the Applicant's analysis as events of cardiac death or MI

The Applicant conducted an analysis of major adverse cardiovascular events that were reported in the three pivotal trials. Please see the Integrated Summary of Safety below (Section 6) for a description of this and other evaluations of cardiovascular events in the pivotal trials. Events adjudicated by the Applicant's external blinded consultants as events of cardiac deaths or MI are shaded in Table 8 above. FDA obtained three cardiology consults to aid in the evaluation of the differences in cardiovascular events between treatment groups. The consult documents are in Appendix 10.1.

Figure 1 presents an FDA analysis of the timing of SAEs that were adjudicated by the Applicant's consultants as MI from the time of first vaccination in DV2-HBV-23. The graph shows that, with regard to adjudicated MIs, the trial arms diverge approximately three months after the first vaccination (two months following the second vaccination) and the difference persists throughout the study period.

Figure 1. Kaplan-Meier curve for adjudicated myocardial infarction events from time of first injection in DV2-HBV-23



Source: FDA analysis 125428/0.42, Module 5.3.5.1, dataset ADAE and 125428/0.65; Module 5.3.5.3, Integrated Summary of Safety.
Events of MI are included. Events of cardiovascular death not adjudicated as MI are not included.
Arrows show timing of injections.

Adverse Events of Special Interest

AESIs were pre-specified by a list of conditions FDA considers potentially immune-mediated. Adverse events that were potentially AESIs were referred to a specialist and to the SEAC for review and adjudication. The SEAC adjudicated cases as autoimmune or not autoimmune, and if autoimmune, adjudicated whether the event was new in onset and the relationship to vaccination. Some events included in the AESI list were not considered by the SEAC to be autoimmune (e.g. cranial nerve palsies, in particular VIIth cranial nerve palsy [Bell's palsy]), but may be potentially immune-mediated and are included here in the counts of AESIs when appropriate.

Sixty-one subjects reported at least one potential adverse event of special interest (AESI) that was referred to the SEAC for adjudication. Thirty-nine Heplisav subjects (0.7%) reported 41 potential AESIs and 22 Engerix-B (0.8%) subjects reported 24 potential AESIs.

The SEAC adjudicated four events in four subjects in the Heplisav group as new-onset autoimmune events – alopecia areata, ulcerative colitis, polymyalgia rheumatica, and hypothyroidism. The event of hypothyroidism was assessed by the SEAC as due to papillary thyroid carcinoma. Five events of VIIth cranial nerve palsy in the Heplisav group and one in the Engerix-B group were not considered by the SEAC to be autoimmune events. One event of VIth nerve palsy in the Heplisav group was adjudicated by the SEAC and the treating specialist as secondary to diabetes and not autoimmune. One event of diplopia in a subject in the Heplisav group who also reported Bell's palsy was diagnosed as IIIrd cranial nerve palsy and adjudicated by the SEAC and the treating specialist as secondary to diabetes and not autoimmune.

Five additional events in four subjects who received Heplisav were adjudicated as new-onset events, but the diagnosis was not confirmed by the SEAC, and thus, they are not included here in the counts of AESIs (rheumatoid arthritis, Takayasu's arteritis, VIth nerve palsy, and Sjogren's syndrome and Raynaud's phenomenon in the same subject). FDA obtained two expert consultations regarding the subject who reported Takayasu's arteritis. Both consultants agreed the event was likely Takayasu's arteritis, but that it was a chronic, pre-existing condition. In addition, one subject with a history of recurrent bilateral ankle cellulitis prior to vaccination received Heplisav and reported a rash 69 days following her second vaccination, which was diagnosed as granulomatous dermatitis of her forearms by biopsy. The subject's dermatopathologist recommended evaluation for sarcoidosis, which was unable to be obtained. The SEAC adjudicated this event as not autoimmune, also noting the possibility of symptoms occurring prior to vaccination and the limited response to steroids. This event is included in the reviewer's count of AESIs, as it is potentially immune-mediated and the forearm rash appeared to be new-onset.

In summary, the reviewer concludes that there was sufficient evidence of 12 new-onset AESIs in 11 subjects in the Heplisav group (VIIth cranial nerve palsy in five subjects, VIth cranial nerve palsy, IIIrd cranial nerve palsy, alopecia areata, ulcerative colitis, polymyalgia rheumatica, hypothyroidism, and granulomatous dermatitis) and one new-onset AESI in the Engerix-B group (Bell's palsy). No events were assessed by the SEAC as related to study vaccination. Three events in the Heplisav group were assessed as having alternative plausible causes (hypothyroidism, VIth cranial nerve palsy, and IIIrd cranial nerve palsy). Nine subjects in the Heplisav group and one subject in the Engerix-B group reported confirmed new-onset AESIs without alternative plausible causes.

<u>Laboratory assessments of renal function and thrombophilia</u>

Approximately 300 subjects at two study sites were enrolled in the laboratory sub-study, 207 in the Heplisav group and 102 in the Engerix-B group.

Renal function was assessed by serum creatinine and urinalysis, including creatinine, urine microalbumin, urine microalbumin/creatinine ratio, and microscopy. No clinically significant differences between treatment groups were identified.

Due to a numerical imbalance in pulmonary embolism between trial arms noted in the integrated safety analysis in the initial BLA submission, thrombophilia was assessed by testing subjects for genetic risk factors (Protein C, Protein S, antithrombin III, Factor V Leiden) at baseline and for PT, PTT, and antiphospholipid antibodies (anti-cardiolipin

IgG/IgM, anti-beta2 glycoprotein 1 IgG/IgM, and lupus anticoagulant screen/confirmatory) at baseline and Weeks 4, 8, 24, and 56. Differences between treatment groups are noted here.

New-onset abnormalities in antiphospholipid antibodies of anti-cardiolipin IgG and IgM and anti-beta2 glycoprotein 1 IgG were uncommon and similar in both groups. For new-onset anti-beta2 glycoprotein 1 IgM, there were 19 subjects (9.2%) in the Heplisav group and two subjects (2.0%) in the Engerix-B group who had normal antibody levels at baseline and had at least one elevated level at Weeks 8, 24 or 56. Of subjects with values for Week 8 and normal values at baseline, there were 16 subjects in the Heplisav group (8.3%) with elevated anti-beta2 glycoprotein 1 IgM levels at Week 8 (5 subjects > 40 units) compared to one subject in the Engerix-B group (1.1%, none > 40 units). One additional subject in the Heplisav group had no baseline value, but a normal value at Day 10 and Week 4, and an elevated value at Week 8 (53 units). At other time points, the percentage of subjects with abnormal anti-beta2 glycoprotein 1 IgM was similar between groups.

Similar to the trend observed with anti-beta2 glycoprotein 1 IgM, there were more subjects in the Heplisav group with normal baseline lupus anticoagulant screen testing and elevated levels at Week 8 (n = 30, 19.9% of subjects with normal baseline levels), compared to Engerix-B (n = 5 , 6.4% of subjects with normal baseline levels). This trend was not observed with the lupus anticoagulant confirmatory test. Nine subjects, all in the Heplisav group, were noted to have more than one antiphospholipid antibody test (anti-beta2 glycoprotein 1 IgM and lupus anticoagulant screen) change from normal to elevated following vaccination.

The clinical significance of an abnormal test in the setting of no or low suspicion of antiphospholipid syndrome is unknown. Subjects who reported VTE also had laboratory assessments for thrombophilia performed following identification of the adverse event. Of subjects who reported VTE and had laboratory assessment of thrombophilia performed (7 of 11 Heplisav subjects and 6 of 7 Engerix-B subjects), no subjects were identified with anti-beta2 glycoprotein 1 or cardiolipin IgM or IgG abnormalities following VTE.

Study Conclusions: Although the immunogenicity of Heplisav was established in Studies DV2-HBV-10 and -16, immunogenicity in all per protocol subjects was reviewed in Study DV2-HBV-23 to confirm that non-inferiority criteria for the SPR were met for Heplisav, when compared to Engerix-B. Immunogenicity results of this study were consistent, numerically and statistically, with those seen in studies DV2-HBV-10 and -16.

Overall, the rate of all MAEs and SAEs reported in the 56-week study period were similar between the Heplisav and Engerix-B groups. Imbalances between trial arms in the frequency of deaths, myocardial infarctions, and herpes zoster were observed. After excluding deaths that were due to overdose or injury, 0.29% of Heplisav and 0.14% of Engerix-B recipients experienced fatal SAEs. Based on the standard Medical Dictionary for Regulatory Activities (MedDRA) query for MI (including the preferred terms acute myocardial infarction, myocardial infarction, coronary artery occlusion, acute coronary syndrome, and angina unstable), 19 Heplisav subjects (0.3%) and three Engerix-B

subjects (0.1%) reported events of MI. All subjects who reported SAEs of MI had cardiovascular risk factors. A discrete risk window was not identified, but proportionally more subjects in the Heplisav group reported events of MI within three months after the last active injection. While the number of cardiovascular events is small, the relative risk in the Heplisav group is approximately three times that of the Engerix-B group. A comparison of cardiovascular AEs between groups was not prospectively specified, potentially leading to under ascertainment of events. Additionally, there are issues of multiplicity and alpha error inflation in post hoc safety analyses, further complicating interpretation of the results. However, one is more concerned with false negatives in safety analyses, at least initially.

Venous thromboembolic adverse events occurred with similar frequency between the two treatment groups. In a laboratory sub-study, slightly more Heplisav subjects reported normal baseline and elevated Week 8 anti-beta2 glycoprotein 1 IgM and lupus anticoagulant screen test levels compared to Engerix-B subjects. The clinical significance of this finding is unclear.

Nine subjects in the Heplisav group (0.2%) reported new onset AESIs without an alternative plausible cause (VIIth cranial nerve palsy in five subjects, alopecia areata, ulcerative colitis, polymyalgia rheumatica, and granulomatous dermatitis). One subject in the Engerix-B group (0.03%) reported a confirmed new-onset AESI (VIIth cranial nerve palsy). No events were assessed by the SEAC as related to study vaccination. Given the randomization ratio and the low background rate of autoimmune events, the significance of the difference in the frequency of potentially immune-mediated AEs in the context of this study is not clear.

6.0 Integrated Summary of Safety: Key Points

6.1 Demographic Data

In the Integrated Summary of Safety (ISS), the safety population included adult subjects who received at least one dose of Heplisav or Engerix-B and had any post-baseline safety assessment. The ISS included the following three integrated study populations to examine SAEs reported in the specified time periods:

- 6-month Primary Safety Population (PSP): Pivotal trials that monitored subjects for at least 6 months (DV2-HBV-10, DV2-HBV-16, DV2-HBV-23), SAEs reported within 28 weeks of first vaccination were evaluated. (Heplisav N=9365, Engerix-B N=3867)
- 1-year PSP: Pivotal trials that monitored subjects for one year (DV2-HBV-16, DV2-HBV-23), all SAEs reported were evaluated. (Heplisav N=7555, Engerix-B N=3867)
- Modified Total Safety Population (mTSP): Studies which utilized the final formulation of Heplisav (DV2-HBV-10, DV2-HBV-14, DV2-HBV-16, DV2-HBV-22, and DV2-HBV-23), SAEs reported within 28 weeks of first vaccination were evaluated. (Heplisav N=9597, Engerix-B, N=3867)

In the mTSP, slightly more females than males received both Heplisav (50.8% females) and Engerix-B (51.2% females). The mean age was 49 years (standard deviation 12). Most subjects were of white race (77.6% in both arms combined), and non-Hispanic

ethnicity (92.6% in both arms combined). The demographic characteristics of subjects receiving Heplisav and Engerix-B do not suggest that selection bias based on age, sex, race or Hispanic ethnicity was introduced. Due to the different administration schedules for Heplisav and Engerix-B, subjects in the 6-month PSP and mTSP were followed for either 6 months following the last dose of Heplisav or 4 weeks following the last dose of Engerix-B. Subjects in the one-year PSP were followed for one-year following the last dose of Heplisav or 6 months following the last dose of Engerix-B. However, subjects in both arms were followed for the same length of time after the first vaccination.

As one of the Applicant's primary objectives of DV2-HBV-23 was to assess non-inferiority of Heplisav compared to Engerix-B in subjects with Type 2 diabetes, subjects enrolled in this study had different baseline characteristics than those enrolled in other Heplisav trials. Table 9 below shows the baseline characteristics suggestive of increased cardiovascular risk of subjects in DV2-HBV-23, DV2-HBV-16, and other studies that used the final formulation of Heplisav. Subjects enrolled in DV2-HBV-23, reported more diabetes, hypertension, smoking, and history of cardiac ischemic disease than reported by subjects enrolled in other trials. Because of these differences in baseline cardiovascular risks between study populations and varying timing of monitoring of SAEs, pooling of trials may result in dampening of the ability to detect potential safety signals in the overall population and lead to erroneous conclusions regarding the safety of the vaccine. Therefore, safety is evaluated for studies individually as well as pooled. Differences between the treatment arms within individual studies in baseline characteristics and medical conditions indicative of increased cardiovascular risk are minimal.

Table 9. Number and proportion of subjects with medical history and baseline characteristics indicating increased risk for cardiovascular disease, Safety Population for DV2-HBV-23, Safety Population for DV2-HBV-16, and Safety Population for all other studies utilizing the proposed formulation of Heplisav (DV2-HBV-10, -14, and -22)

Condition or characteristic	DV2-HBV-23 Heplisav N=5587 n (%)	DV2-HBV-23 Engerix-B N=2781 n (%)	DV2-HBV-16 Heplisav N=1968 n (%)	DV2-HBV-16 Engerix-B N=481 n (%)	DV2-HBV-10, -14, and -22* Heplisav N = 2042 n (%)	DV2-HBV-10, -14, and -22* Engerix-B N = 605 n (%)
At least one baseline medical diagnosis of cardiac ischemia†	211 (3.8)	99 (3.6)	50 (2.5)*	15 (3.1)*	13 (0.6%)	2 (0.3%)
Type 2 Diabetes‡	762 (13.6)	381 (13.7)	158 (8.0)	33 (6.9)	48 (2.4)	11 (1.8)
Hypertension§	2021 (36.2)	978 (35.2)	579 (29.4)	143 (29.7)	239 (11.7)	57 (9.4)
Hyperlipidemia¶	1757 (31.4)	879 (31.6)	587 (29.8)	152 (31.6)	181 (8.9)	47 (7.8)
Sex and Age: Male ≥ 46 years	1879 (33.6)	919 (33.0)	776 (39.4)*	195 (40.5)*	330 (16.2)	76 (12.6)
Sex and Age: Female ≥ 56 years	1028 (18.4)	537 (19.3)	451 (22.9)*	92 (19.1)*	8 (0.4)	0
Smoking within 1 year	1843 (33.0)	909 (32.7)	431 (21.9)	118 (24.5)	703 (34.4)	224 (37.0)
Obesity: BMI ≥ 30	2724 (48.8)	1285 (46.2)	863 (43.9)	205 (42.6)	542 (26.5)	167 (27.6)

Source: Adapted from 125428/0.42, Module 2.7.4, Summary of Clinical Safety, Table 2.7.4-27, pp. 84-86 and reviewer-generated analysis from 125428/0.42, Module 5.3.5.3 datasets ADSL and ADMH of the integrated studies.
Thirteen subjects less than 18 years of age, who were enrolled in DV2-HBV-10, are not included.
N number of subjects in each treatment group

n number of subjects reporting medical history item or characteristic
* Reviewer-generated from 125428/0.42, Module 5.3.5.3 datasets ADSL and ADMH of integrated studies
† Defined as subjects with at least one medical history preferred term within the narrow SMQs of Myocardial Infarction and Other Ischemic Heart Disease
‡ Defined as, in DV2-HBV-23, subjects identified as diabetic in the Diabetes History case report form; in DV2-HBV-16 and -10, subjects with a medical history term of diabetes and taking a drug with a WHO Drug ATC2 code of "DRUGS USED IN DIABETES"; in DV2-HBV-14 and -22, subjects with a medical history term of diabetes
§ Reviewer-generated analysis using dataset ADMH, defined as subjects with at least one medical history preferred term of Accelerated hypertension, Diastolic hypertension, Essential hypertension, Hypertension, Hypertensive heart disease, Labile hypertension, Malignant hypertension, Systolic hypertension, Secondary hypertension
¶ Defined as subjects with at least one medical history preferred term for Dyslipidemia SMQ narrow, including preferred terms Blood Cholesterol Increased, Blood Triglycerides Increased, Dyslipidemia, High Density Lipoprotein Decreased, Hypercholesterolemia, Hyperlipidemia, Hypertriglyceridemia, and Lipids Increased.

6.2 Adverse Events

6.2.1 Deaths

There were two deaths in study DV2-HBV-16 (Section 5.2.9), one in each treatment group (Heplisav 0.05%, Engerix-B 0.2%). There were 32 deaths in study DV2-HBV-23, 25 in the Heplisav group (0.45%) and seven in the Engerix-B group (0.25%) (Section 5.3.9). There were no deaths in any other studies. Table 10, below, summarizes the deaths reported across studies. Cardiovascular death was evaluated as part of the major adverse cardiovascular events analysis discussed in Section 6.2.2.

Table 10. Deaths and deaths due to causes other than accident, injury, or overdose, Integrated Safety Populations

	6 mo PSP Heplisav N = 9365 n (%)	6 mo PSP Engerix-B N = 3867 n (%)	1 yr PSP Heplisav N = 7555 n (%)	1 yr PSP Engerix-B N = 3262 n (%)	mTSP Heplisav N = 9597 n (%)	mTSP Engerix-B N = 3867 n (%)
Deaths	15 (0.16)	5 (0.13)	26 (0.34)	8 (0.25)	15 (0.16)	5 (0.13)
Deaths not clearly due to overdose or injury	9 (0.10)	3 (0.08)	17 (0.23)	5 (0.15)	9 (0.09)	3 (0.08)

Source: Reviewer-generated analysis from BLA STN 125428/0.42, Module 5.3.5.3, integrated dataset ADAE.
mo month
PSP primary safety population
mTSP modified total safety population
N number of subjects in each treatment group
n number of subjects reporting event

6.2.2 Serious Adverse Events

SAEs and non-fatal SAEs occurred at similar rates in the Heplisav and Engerix-B treatment groups in the integrated safety populations and are displayed in Table 11 below.

Table 11. Number and percentage of subjects with serious adverse events by treatment group, Integrated Safety Populations

Event	6 mo PSP Heplisav N = 9365 n (%)	6 mo PSP Engerix-B N = 3867 n (%)	1 yr PSP Heplisav N = 7555 n (%)	1 yr PSP Engerix-B N = 3262 n (%)	mTSP Heplisav N = 9597 n (%)	mTSP Engerix-B N = 3867 n (%)
At least one SAE	271 (2.89)	114 (2.95)	421 (5.57)	171 (5.24)	273 (2.84)	114 (2.95)
At least one non-fatal SAE	260 (2.78)	109 (2.82)	400 (5.29)	164 (5.03)	262 (2.73)	109 (2.82)

Source: Reviewer-generated analyses from BLA STN 125428/0.42, Module 5.3.5.3, ADAE integrated dataset.
mo month
PSP primary safety population
mTSP modified total safety population

N number of subjects in each treatment group
n number of subjects reporting event
SAE serious adverse event

The differences between trial arms in cardiovascular events noted in DV2-HBV-23 are discussed in Section 5.3.9. An imbalance unfavorable to Heplisav was not observed in other studies. Table 12 below presents a summary of deaths and MIs identified in studies of Heplisav other than DV2-HBV-23. In addition to the fatal events and SAEs of MI identified in Study DV2-HBV-16, there were two events, one in each trial arm, of MI that were identified in the supportive studies DV2-HBV-04 and -05. Both studies were double-blind, randomized trials conducted in Asia that enrolled adults 40 – 70 years of age, randomized 1:1 to receive an earlier formulation of Heplisav (different antigen strain, same dose of antigen and adjuvant) at Weeks 0, 8, and 24 or Engerix-B at Weeks 0, 4, and 24. In both studies, SAEs were collected through Week 50.

Table 12. Summary of deaths and myocardial infarction reported in Heplisav studies in the initial BLA submission, Safety Populations, DV2-HBV-0001, -02, -03, -04, -05, -08, -10, -14, and -16

Study	Age	Sex	MedDRA Preferred Term	Study Day	Last Active Dose	Day of event relative to most recent active dose*
Heplisav, N=4437						
DV2-HBV-16	45	M	Pulmonary embolism†	75	2	46
DV2-HBV-16	58	M	Acute myocardial infarction	22	1	22
DV2-HBV-16	63	F	Acute myocardial infarction	44	2	15
DV2-HBV-05§	52	M	Acute myocardial infarction	275	3	121
Engerix-B, N=1421						
DV2-HBV-16	64	M	Cardiac failure†‡	73	2	43
DV2-HBV-16	60	M	Acute myocardial infarction and Unstable angina	39	2	11
DV2-HBV-04§	43	F	Unstable angina	182	3	14

Source: Reviewer generated summary based upon 125428/0.65; Module 5.3.5.3, Integrated Summary of Safety and 125428/0.42, Module 5.3.5.3, dataset ADAE for the integrated studies
* Day 1 is day of administration. An event start day relative to the most recent dose of x is x-1 days following the most recent dose.
§ Study utilized a previous formulation of Heplisav
† Fatal event
‡ Following a myocardial infarction

The Applicant also conducted a multivariate logistic regression analysis for the pivotal trials with MI events (by preferred terms in the SMQ narrow for MI) as the dependent variable, and age, sex, race, hypertension, BMI, diabetes mellitus, smoking, history of MI or stroke, and treatment group as the independent variables. This analysis indicated that hypertension (Odds Ratio [OR] = 3.78; 95% CI: 1.44, 9.91) and age (OR = 1.07 per one year increase; 95% CI: 1.02, 1.13) were statistically significant independent predictors of MI. Treatment group was not a significant independent predictor of events identified by the MI SMQ (OR = 2.21; 95% CI: 0.76, 6.45). Other known risk factors for cardiovascular disease were not significant independent predictors in this model as well. Limitations to this analysis include a small number of events leading to limited power to draw robust conclusions, post-hoc assessment of MI may contribute to incomplete ascertainment of events, issues with pooling data across trials with different lengths of follow-up and baseline population characteristics, no distinction between first and recurrent events, omission of some covariates (dyslipidemia), and use of binary variables instead of continuous variables.

In order to further assess the cardiovascular events that were reported in the pivotal trials, the Applicant conducted a major adverse cardiovascular events (MACE) analysis consisting of a composite three-point outcome of 1) cardiovascular death, 2) non-fatal MI, and 3) stroke. This analysis included independent and blinded post-hoc adjudication by The Applicant's external consultants of all potential MACE events, categorizing events as 1) a MACE event, 2) not a MACE event, or 3) insufficient information to make a determination. The results of the subjects identified as reporting an adjudicated MACE outcome in the three pivotal trials are presented in the table below. This table also includes additional columns for the MACE events identified in studies DV2-HBV-16 and -23, excluding -10. Studies DV2-HBV-16 and -23 were the pivotal trials that monitored SAEs for approximately one year following vaccination. DV2-HBV-10 followed subjects for 28 weeks following the first vaccination. The table presented here includes 95% exact confidence intervals, which FDA statisticians consider appropriate for evaluating rare events, such as the MACE outcomes in this study.

Table 13. Applicant-identified, treatment-emergent, serious three-point adjudicated major adverse cardiovascular events by treatment group, DV2-HBV-16, DV2-HBV-23, -16 and -23 combined, and the pivotal studies combined (DV2-HBV-10, -16, and -23) (Total Safety Populations)

Adjudicated MACE Outcome	DV2-HBV-23 Heplisav N=5587 n (%)	DV2-HBV-23 Engerix-B N=2781 n (%)	DV2-HBV-23 Relative Risk (95% CI)[a] (95% CI)[b]	DV2-HBV-16 Heplisav N=1968 n (%)	DV2-HBV-16 Engerix-B N=481 n (%)	DV2-HBV-16 Relative Risk (95% CI)[a] (95% CI)[b]	DV2-HBV-16 and -23 Heplisav N = 7555 n (%)	DV2-HBV-16 and -23 Engerix-B N = 3262 n (%)	DV2-HBV-16 and -23 Relative Risk (95% CI)[a] (95% CI)[b]	DV2-HBV-10, -16 and -23 Heplisav N = 9365 n (%)	DV2-HBV-10, -16 and -23 Engerix-B N = 3867 n (%)	DV2-HBV-10, -16 and -23 Relative Risk (95% CI)[a] (95% CI)[b]
Composite 3-point MACE events	28 (0.50)	6 (0.22)	2.32 (0.96, 5.60) (0.98, 7.52)	3 (0.15)	2 (0.42)	0.37 (0.06, 2.19) (0.06, 3.69)	31 (0.41)	8 (0.25)	1.67 (0.77, 3.64) (0.78, 6.36)	31 (0.33)	8 (0.21)	1.6 (0.74, 3.48) (0.75, 6.08)
Cardiovascular death*	3 (0.05)	1 (0.04)	1.49 (0.16, 14.35) (0.15, 38.32)	1 (0.05)	1 (0.21)	0.24 (0.02, 3.9) (0.01, 8.20)	4 (0.05)	2 (0.06)	0.86 (0.16, 4.71) (0.15, 6.54)	4 (0.04)	2 (0.05)	0.83 (0.15, 4.51) (0.15, 6.26)
Non-fatal Myocardial infarction†	14 (0.25)	1 (0.04)	6.97 (0.92, 52.97) (1.00, 184.9)	2 (0.10)	1 (0.21)	0.49 (0.04, 5.38) (0.04,13.31)	16 (0.21)	2 (0.06)	3.45 (0.79, 15.01) (0.88, 35.33)	16 (0.17)	2 (0.05)	3.30 (0.76, 14.36) (0.84, 33.80)
Non-fatal Stroke‡	11 (0.20)	4 (0.14)	1.37 (0.44, 4.30) (0.44, 7.46)	0	0	-	11 (0.15)	4 (0.12)	1.19 (0.38, 3.73) (0.38, 6.48)	11 (0.12)	4 (0.10)	1.14 (0.36, 3.56) (0.37, 6.19)

Source: Adapted from 125428/0.65, Module 2.7.4, Evaluation of acute myocardial infarction and major adverse cardiovascular events in the Phase 3 Heplisav clinical trials, Table 3-3, p. 16
Thirteen subjects less than 18 years of age, who were enrolled in DV2-HBV-10, are not included.
N number of subjects in each treatment group
n number of subjects reporting adverse event
CI confidence interval
MACE major adverse cardiovascular events
a Asymptotic confidence interval
b Exact confidence interval
* Cardiovascular cause of death comprises the following preferred terms: Death from cardiovascular cause includes death due to Acute Coronary Syndrome, Acute Myocardial Infarction, Acute Respiratory Failure, Cardiac Arrest, Cardiac Failure, Cardio-respiratory Arrest, Death, Hypertensive Heart Disease, Myocardial Infarction, or Pulmonary Embolism.
† Myocardial infarction includes deaths due to myocardial infarction and comprises the following preferred terms: Myocardial infarction includes Acute Coronary Syndrome, Acute Myocardial Infarction, Coronary Artery Embolism, Coronary Artery Thrombosis, Coronary Bypass Thrombosis, Myocardial infarction, Post Procedural Myocardial Infarction, or Silent Myocardial Infarction.

‡ ‡ Stroke includes deaths due to stroke and comprises the following preferred terms: Stroke includes Basal Ganglia Stroke, Brain Stem Stroke, Cerebrovascular Accident, Hemorrhagic Stroke, Hemorrhagic Transformation Stroke, Stroke in Evolution, Basal Ganglia Infarction, Basal Ganglia Stroke, Brain Stem Embolism, Brain Stem Infarction, Brain Stem Stroke, Cerebellar Embolism, Cerebellar Infarction, Cerebral Artery Embolism, Cerebral infarction, Cerebrovascular Accident, Embolic Cerebral Stroke, Embolic Stroke, Ischemic Cerebral infarction, Ischemic Stroke, Lacunar Infarction, Lacunar Stroke, Thalamic Infarction, Thrombotic Cerebral Infarction, or Thrombotic Stroke.

The Applicant compared the rates and numbers of adjudicated major cardiovascular events observed in the three Phase 3 trials to expected rates obtained by age, sex, and race adjusted estimates from population-based data and to expected rates obtained by risk prediction models that account for cardiovascular risk factors in the study populations. The Applicant concludes that the observed number of major cardiovascular events in Heplisav recipients is similar to, or lower than expected and that the observed number of major cardiovascular events in Engerix-B recipients is lower than expected, and thus, the imbalance in events coded to the preferred term AMI appears to be due to a lower than expected number of events in the Engerix-B group as opposed to an excess of events in the Heplisav group. Limitations of this analysis include possible under-ascertainment of events due to post-hoc analysis, potential issues with comparability between the study population and overall population, and lack of testing for certain risk factors, such as cholesterol, in DV2-HBV-23.

The FDA statisticians performed additional analyses of cardiovascular events, using Bayesian analysis methods. These results will be presented during the VRBPAC meeting.

The Applicant also presented an analysis of causality based upon seven Bradford Hill criteria, in which they conclude that none of the criteria support causality (temporality, strength/effect size, consistency, coherence, specificity, biologic plausibility, and analogy). While an evaluation using the Bradford-Hill criteria are reasonable to explore causality, particularly in observational studies, differences noted in DV2-HBV-23 were observed in a randomized, controlled trial.

6.2.3 Adverse Events of Special Interest

In studies that utilized a SEAC for prospective adjudication of AESIs (DV2-HBV-16 and -23), new-onset AESIs without alternative plausible causes were reported in 15 Heplisav subjects (0.20%) and one Engerix-B subject (0.03%) (RR = 6.48, 95% exact CI 1.00, 172.90). Events reported in the Heplisav groups were VIIth cranial nerve palsy (n=6), hypothyroidism (n=2), alopecia areata (n=1), erythema nodosum (n=1), granulomatous dermatitis (n=1), Tolosa-Hunt syndrome (n=1), polymyalgia rheumatica (n=1), ulcerative colitis (n=1), and vitiligo (n=1)). One subject in the Engerix-B group (0.03%) reported a confirmed new-onset AESI (VIIth cranial nerve palsy).

In studies that did not utilize a SEAC for prospective adjudication of AESIs, the Applicant identified AESIs by a retrospective analysis by preferred term. Six subjects in the Heplisav groups (0.2%) and five subjects in the Engerix-B groups (0.5%) reported new-onset diagnoses of events of possible AESIs. In Study DV2-HBV-10, the following adverse events that are autoimmune or potentially immune-mediated, were identified in one subject each: c-ANCA positive vasculitis (GPA), Guillain-Barré, Basedow's disease, and lichen planus in the Heplisav group, and p-ANCA positive vasculitis (in a subject with pre-existing mixed connective tissue disorder), Basedow's disease, Bell's palsy, and Raynaud's phenomenon in the Engerix-B group. In addition, an event of rheumatoid arthritis and an event of systemic lupus erythematosus in two Heplisav subjects were reported as exacerbations of pre-existing disease. In Study DV2-HBV-04, VIIth cranial nerve palsy and uveitis were identified in two subjects the Heplisav group and Rheumatoid arthritis was identified in one subject in the Engerix-B group. In Study

DV2-HBV-0001, an event of Rheumatoid arthritis in a Heplisav subject was determined to be an exacerbation of pre-existing disease.

6.2.4 ANA Results

ANA testing was performed as a protocol-specified assessment in all trials except DV2-HBV-04. ANA results from HBV0001 were excluded from analysis because they were not reported as titers. These data confirm the data from the two pivotal studies previously presented and demonstrate that there does not appear to be an increased risk of converting from an ANA titer of <1:160 to a higher titer for Heplisav recipients as compared to Engerix-B recipients.

6.2.5 Anti-dsDNA Assessment

Anti-dsDNA testing was performed as a protocol-specified assessment in all trials except DV2-HBV-04 and DV2-HBV-08. The majority of subjects maintained a negative anti-dsDNA test throughout their participation in the study in which they were enrolled. As was seen in the two pivotal studies, a similar and small proportion of Heplisav and Engerix-B recipients had negative anti-dsDNA results at baseline and positive results post-treatment.

6.2.6 Anti-Neutrophil Cytoplasmic Antibody (ANCA) Assessment

Anti-neutrophil cytoplasmic antibody (ANCA) assessments were retrospectively performed for Studies DV2-HBV-10 and Study DV2-HBV-14. In summary, other than the two subjects noted in Study DV2-HBV-10 with ANCA-positive vasculitides (GPA in the Heplisav group, p-ANCA-positive vasculitis in the Engerix-B group) no subjects had positive screening and confirmatory tests for ANCAs.

Integrated Summary of Safety Conclusion: With the previous review cycle, review of the local and systemic reactogenicity data, and testing for ANA, anti-dsDNA, and c-ANCA, did not detect clinically relevant differences in safety outcomes among Heplisav-immunized subjects, when compared to Engerix-B-immunized subjects. In the integrated summary of safety, differences between treatment groups in adjudicated events of myocardial infarction and the three-point composite MACE outcome appear smaller than in study DV2-HBV-23 alone. However, pooling of studies is limited by differences in population baseline risk and monitoring time between studies.

In studies that utilized expert committee adjudication for AESIs, more subjects in the Heplisav groups reported AESIs than in the Engerix-B group. Events were small in number and included multiple organ systems and disease processes. Two subjects in the Heplisav groups reported what appear to be two pathologically distinct new-onset granulomatous or presumed granulomatous vasculitic inflammatory diseases.

7.0 Pharmacovigilance Plan

The Applicant has proposed to conduct a retrospective observational study among hepatitis B vaccinees ages 18 years or older enrolled in Kaiser Permanente Northern California to compare (1) the rates of pre-specified immune-mediated events in Heplisav recipients with the rates in concurrent recipients of other hepatitis B vaccines; (2) the rates of 3-point Major Adverse Cardiovascular Events (MACE) in Heplisav recipients using self-controlled risk interval methods; and (3) the rates of medical events other than immune-mediated or MACE in Heplisav recipients using self-controlled risk interval

methods. Participants would be followed for a total of 13 months following first dose administration. The Applicant indicated in the last version of the Pharmacovigilance plan that assuming an accrual rate of 8,000 subjects per year and a 50:50 allocation ratio, they would be able to include a total of 40,000 subjects (20,000 per arm) in 5 years and provide results on year 8. As per the Applicant, a sample size of 20,000 subjects per group would provide approximately 87% power to detect a 2.5-fold increase in the incidence of auto-immune diseases (one-sided test, α=0.025) if the background rate is 1 per 1,000 persons-year, and would provide approximately 90% power to detect a 2-fold increase in MACE outcomes assuming a background incidence rate of 5 per 1,000 persons-years. In addition to this post-marketing study, the Applicant has proposed routine pharmacovigilance and a pregnancy registry.

In regard to the investigation of autoimmune events, although the study design seems acceptable to FDA, the study power would only permit to study the occurrence of the most frequent events (or all pre-specified immune-mediated events together as proposed by the Applicant).

FDA informed the Applicant that, based on the case distribution observed in the DV2-HBV-23 study (with cases distributed throughout the entire follow-up period), a self-controlled risk interval approach was not appropriate to assess risk of MACE outcomes following Heplisav vaccination, and asked for further details on an alternative approach. The Applicant agreed on investigating the risk of MACE using a cohort design (head-to-head comparison) including frequency matching, stratification, or propensity scores to account for potential differences among the two cohorts.

Regarding the analyses to evaluate medical events other than immune-mediated or MACE in Heplisav recipients using self-controlled risk interval methods, the Applicant clarified that they are planning to evaluate all emergency room and hospital events occurring after vaccination. Nonetheless, as pointed out by FDA, based on the case distribution observed in the DV2-HBV-23 study, this method is not appropriate either to examine events such as herpes zoster. The Applicant agreed on examining herpes zoster using a cohort design.

Review of the planned post-marketing study and discussions with the Applicant are ongoing.

8.0 VRBPAC Meeting

The questions to the Committee will be sequentially on safety and the pharmacovigilance plan, with focus on the adequacy of the pre-licensure safety data to support licensure of Heplisav and the proposed pharmacovigilance plan for the proposed indication of active immunization against all subtypes of hepatitis B virus infection in adults 18 years of age and older.

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10.0 Appendix

10.1 Cardiology Consults

Consult 1

Questions for the consultant

1. In the "Evaluation of Acute Myocardial Infarction and Major Adverse Cardiovascular Events in the Phase 3 Heplisav Clinical Trials," the Applicant uses the following tools to assess cardiovascular risk: 1) identification of reported events of AMI in the safety database and multivariate logistic regression analysis to assess risk factors associated with MI in Study DV2- HBV-23, 2) a three-point MACE analysis to identify serious cardiovascular events in the three Phase 3 studies, 3) comparison of observed to expected number and rate of cardiovascular events in studies DV2-HBV-16 and -23, and 4) discussion of the Bradford Hill criteria for assessment of causation applied to the three-point MACE analysis. Are these the appropriate tools to use to evaluate the cardiovascular risk following Heplisav? Are there any additional tools you would use to assess cardiovascular risk associated with Heplisav?

Response:

- The tools listed, as well as the applicant's analysis of absolute risk and risk difference, seem reasonable in evaluating cardiac risk.

- In general, comparing rates of observed cardiovascular events in the study population to expected event rates in the overall population raises the issue of comparability. However, on its face, the sponsor's argument that MI and cardiovascular death rates in the Engerix-B group appear lower than predicted seems plausible.

2. Please comment on whether the appropriate cardiovascular outcomes have been selected for inclusion in the analyses. Specifically, we have the following questions:

- In order to identify subjects with myocardial infarction, are SAEs with preferred terms in the MedDRA SMQ narrow for myocardial infarction the most appropriate criteria?
- What, if any, additional preferred terms, or other criteria, would you recommend using to identify subjects with probable myocardial ischemic events?

Response:

- The applicant's SMQ search for myocardial infarction seems appropriate as they included terms such as "acute coronary syndrome."

- Since the event capture appears to have been driven by adverse events, it is possible that events (such as silent MI) were missed.

- Is the three-point MACE analysis (death due to cardiovascular cause, first non-fatal myocardial infarction, and first non-fatal stroke) the most appropriate to evaluate risk

in this situation? Would you recommend other types of cardiovascular events (for example, heart failure) be used to assess cardiovascular risk for this vaccine? Did the Applicant use the appropriate preferred terms to identify potential major adverse cardiovascular events?

Response:

- The three-point MACE analysis has been commonly used as a composite endpoint in cardiovascular outcome trials and it seems reasonable to analyze this composite outcome in a safety analysis.

- The applicant appears to have used appropriate preferred terms to identify potential MACE events.

- Depending on the underlying concern (i.e., accelerated atherosclerosis), you might consider additional analyses regarding: need for urgent revascularization, unstable angina, angina, transient ischemic attack.

- One can get to heart failure through some myocarditis syndrome without ischemic events of MI, but there is no evidence that is happening here. Heart failure can be a late consequence of MI, generally multiple MIs, but if it were related to MIs, one would expect to see the MI signal strongly first. Excluding it from the main assessment thus seems reasonable.

- In the MACE analysis, for study DV2-HBV-23, the Applicant's consultants, C5Research, adjudicated 4 cardiovascular deaths (3 Heplisav, 1 Engerix-B) and 15 MIs (14 Heplisav, 1 Engerix-B). If one defines cardiovascular death to also include subjects with an unclear cause of death who were last seen more than 24 hours previously, 10 subjects total may be considered to have died due to a cardiovascular cause (9 Heplisav, 1 Engerix-B). If one defines MI to also include subjects who underwent urgent coronary artery revascularization or bypass graft with no evidence of necrosis presented in the narrative, 17 subjects total may be considered to have reported MI (15 Heplisav, 2 Engerix-B). Please provide your assessment of the criteria used to identify major cardiovascular events.

Response: This question raises the issue of determining cause-specific mortality and definitions of MI, which are more difficult in the post-hoc, unblinded setting. Depending on the available data, it might be useful to you to apply the cardiovascular definitions outlined in the paper: Hicks KA et. al. Standardized definitions for cardiovascular and stroke end point events in clinical trials (available at: https://www.cdisc.org/system/files/all/reference_material/application/pdf/Draft%20Definitions%20for%20CDISC%20July%203,%202014.pdf) as a guideline. In general, we would include subjects with sudden death or unknown cause of death as cardiovascular deaths; as stated, it is unclear why cardiac arrest events were determined to be "noncardiovascular deaths." In fact, sudden death can be a first presentation of a myocardial infarction. Our comments in this review will pertain to the available analyses.

3. If the multivariate logistic regression analysis is an appropriate analysis, were the appropriate risk factors included in the model? Are there any additional risk factors that you would include in the model (for example dyslipidemia)?

Response: The applicant's findings are consistent with the literature. According to the World Heart Federation, the leading CVD risk factors are: hypertension, followed by tobacco, elevated blood glucose, physical inactivity and obesity. While dyslipidemia is a known risk factor and can be included in the model, the risk is likely modified by factors such as LDL level and statin use.

4. Do you have any concerns with the three-point MACE analysis and the comparison of observed to expected major adverse cardiovascular events?

Response:

- The three-point MACE analysis has been used as an endpoint in many previous cardiovascular outcomes studies. Such endpoints and analyses are ideally defined and conducted in a blinded, prospective manner.

- Additional analyses can be done (e.g., MACE plus urgent revascularizations, heart failure) but their value may depend, in part, on the data collected.

- Since the MACE events seem to depend on adverse event capture, it is possible that some events were missed or miscoded. Since HBV-23 is a large, randomized, blinded study, we would hope that any missed or miscoded events occurred at random or at a low rate and do not affect the overall results.

- The comparison of observed to expected events has limitations, such as the comparability across populations and whether the applicant's risk model is applicable to the study population. The applicant has also acknowledged limitations of the risk models, including: 1. Conversion of the 10-year event risk to a 1-year risk under the assumption of constant risk; 2. Assumptions of cholesterol and LDL levels, since the data were not collected in all study subjects. However, even under conservative assumptions (e.g., ignoring presence of diabetes and assuming ideal lipids), the expected events still appear higher than observed in the Engerix-B group; on its face, the applicant's argument (i.e., events in the comparator group appear lower than expected) seems plausible.

5. Based upon the three-point MACE analysis, the Applicant concludes that "the primary reason for the observed imbalance in myocardial infarctions in HBV-23 appears to be that fewer than expected events occurred in the Engerix-B group rather than more than expected in the Heplisav group." Please comment.

Response: See above. With the limitations of cross-population comparisons and models, this argument appears plausible.

6. What is your assessment of the Applicant's discussion of the Bradford Hill criteria and the conclusions they draw? In particular, please comment on the Applicant's

conclusions that 1) the evidence does not support the premise that Heplisav mimics an acute infection causing increased risk of plaque rupture, 2) there is no clear evidence supporting an increase in thromboembolic events or myocardial oxygen supply demand mismatch associated with Heplisav, and 3) dose level and frequency of Heplisav is far below levels demonstrated in a mouse model to enhance atherosclerosis (Attachment 4, pp. 28-33).

Response:

- While the Hill criteria are general principles that may be useful in assessing causality, this reviewer disagrees with several conclusions made by the applicant.
    - Under "biological plausibility," the applicant advances the hypothesis that Heplisav mimics acute infection in initiating a systemic inflammatory response sufficient to trigger destabilization of a coronary plaque, and such an association would predict that events occur in close temporal proximity to an injection. We do not know that this is the case—but do not observe another biologically plausible mechanism for the observed imbalance in MI.
- You should discuss the preclinical data and safety margin of Heplisav with reviewers with expertise in animal toxicology and safety pharmacology.

7. What is your assessment of the cardiovascular risk associated with Heplisav? What, if any, problems have you identified with the Applicant's conclusions with regard to the analyses they have presented?

- There are a number of factors that make us think that this is not likely to be a reliable safety signal.

i. An imbalance of MI that was not statistically significant was observed in study HBV-23. This imbalance was not observed in previous smaller studies; however, HBV-23 study population included a higher percentage of subjects with higher cardiovascular risk.

ii. Analyses of adjudicated, confirmed stroke, cardiovascular death and MACE events in HBV-23 showed similar directionality (e.g., RR> 1.0), but none of the analyses showed a statistically significant difference between the two treatments. The cardiovascular death events were few and the RR was not robust.

iii. The imbalance in cardiac events did not occur shortly after the first or second dose of vaccine; according to the Kaplan-Meier curve for MACE events, the two groups appear to separate only after 100 days. Thus, we agree with the applicant that there is not a close temporal relationship between vaccine administration and cardiovascular events. This timing is particularly incompatible with attribution to the adjuvant.

iv. Non-clinical and clinical studies failed to reveal a plausible mechanism for MI. The risk of MI could result from accelerated atherosclerosis, sustained increase in blood pressure, or some prothrombotic state. None of these is in evidence.

v. The sponsor's assessment that the event rate in the control arm is spuriously low is plausible. It is also plausible that the observed between-group difference is spurious.

- Based upon the low likelihood that there is a real safety signal here, and the low absolute risk that these data suggest, we would label the finding in section 6 only and consider ways to monitor this risk post-marketing through some passive surveillance system.

Consult 2

Questions for the consultant

1. In the "Evaluation of Acute Myocardial Infarction and Major Adverse Cardiovascular Events in the Phase 3 Heplisav Clinical Trials," the Applicant uses the following tools to assess cardiovascular risk: 1) identification of reported events of AMI in the safety database and multivariate logistic regression analysis to assess risk factors associated with MI in Study DV2- HBV-23, 2) a three-point MACE analysis to identify serious cardiovascular events in the three Phase 3 studies, 3) comparison of observed to expected number and rate of cardiovascular events in studies DV2-HBV-16 and -23, and 4) discussion of the Bradford Hill criteria for assessment of causation applied to the three-point MACE analysis. Are these the appropriate tools to use to evaluate the cardiovascular risk following Heplisav? Are there any additional tools you would use to assess cardiovascular risk associated with Heplisav?

Response: *In the aggregated RCT experience with Heplisav, an excess of cardiac events, notably death or myocardial infarction, was noted in the experimental treatment group compared with an active control. While none of the trials were prospectively designed to examine ischemic cardiac events, the sponsors have done an appropriate job trying to understand and place into context the observation of excess ischemic events. Unfortunately, because the question was not prospectively designed to capture this information, there was not systematic ascertainment of suspected cardiac events and the materials to support blinded (and before database unlocking) adjudication of these events. Using an adjusted analysis to understand the contribution of treatment assignment to cardiac outcomes is a reasonable approach. Focusing the post hoc adjudication exercise on a three-component composite endpoint of death, MI or stroke is reasonable and consistent with the approach taken with many contemporary randomized trials examining therapies for chronic ischemic heart disease and diabetes. Heart failure, unstable angina requiring hospitalization and revascularization procedures are often times included in various composites but the three-component composite is most frequently used and contains the most important ischemic events. The analyses that compare observed to expected cardiac event rates and conclude that the active control group experienced lower than expected cardiac event rates is limited in its usefulness. Study 23 was a randomized comparison and should allow appropriate direct comparison between the treatment groups although cautions are warranted given that the endpoints were not prospectively defined nor endpoint information systematically collected. Similarly, the use of the Bradford-Hill criteria to assess causation, while interesting, has less usefulness given that the observation of excess cardiac events emerged from a randomized comparison and not from non-randomized datasets. Further insights into possible cardiac risk associated with Heplisav requires randomized comparisons and/or large post market observational studies with appropriate collection of suspected events, ECGs, biomarkers and other records needed for event adjudication.*

2. Please comment on whether the appropriate cardiovascular outcomes have been selected for inclusion in the analyses. Specifically, we have the following questions:

a) In order to identify subjects with myocardial infarction, are SAEs with preferred terms in the MedDRA SMQ narrow for myocardial infarction the most appropriate criteria? What, if any, additional preferred terms, or other criteria, would you recommend using to identify subjects with probable myocardial ischemic events?

Response: *The SAEs identified are reasonable terms to seek detection of suspected myocardial infarctions. Would have been helpful to add coronary revascularization events (PCI or CABG) and heart failure as terms to increase sensitivity (while recognizing that adjudication needed for specificity).*

b) Is the three-point MACE analysis (death due to cardiovascular cause, first non-fatal myocardial infarction, and first non-fatal stroke) the most appropriate to evaluate risk in this situation? Would you recommend other types of cardiovascular events (for example, heart failure) be used to assess cardiovascular risk for this vaccine? Did the Applicant use the appropriate preferred terms to identify potential major adverse cardiovascular events?

Response: *The three-component composite is a reasonable one given that many/most contemporary trials in both chronic and acute ischemic heart disease use this composite in assessing efficacy of treatments. It would be reasonable to include some assessment of heart failure as an accepted measure of cardiac safety, as has been done in trials with hypoglycemic agents and NSAIDs.*

c) In the MACE analysis, for study DV2-HBV-23, the Applicant's consultants, C5Research, adjudicated 4 cardiovascular deaths (3 Heplisav, 1 Engerix-B) and 15 MIs (14 Heplisav, 1 Engerix-B). If one defines cardiovascular death to also include subjects with an unclear cause of death who were last seen more than 24 hours previously, 10 subjects total may be considered to have died due to a cardiovascular cause (9 Heplisav, 1 Engerix-B). If one defines MI to also include subjects who underwent urgent coronary artery revascularization or bypass graft with no evidence of necrosis presented in the narrative, 17 subjects total may be considered to have reported MI (15 Heplisav, 2 Engerix-B). Please provide your assessment of the criteria used to identify major cardiovascular events.

Response: *The FDA perspective on this that includes broadening definitions and the inclusion of other terms (such as revascularization procedures) is completely reasonable as a way to increase the sensitivity around any cardiac safety signal. This approach is consistent with contemporary trials that aim to cast a broad net and capture all possible related cardiac ischemic events. The sponsor, using their methodology, have chosen to increase specificity and to de-emphasize sensitivity. In an assessment of cardiac safety, an emphasis on sensitivity (broad approach to capturing possible events) is likely preferred in spirit of public health protection.*

3. If the multivariate logistic regression analysis is an appropriate analysis, were the appropriate risk factors included in the model? Are there any additional risk factors that you would include in the model (for example dyslipidemia)?

Response: *Given that the trial plan did not pre-specify a formal planned comparison of ischemic cardiac events between the treatment, there are a number of limitations in the comparison, including the multiplicity issue. Multivariate logistic regression is a reasonable way to compare the treatments for ischemic cardiac risk. The variables included in the model are appropriate ones and consistent with much contemporary cardiovascular research.*

4. Do you have any concerns with the three-point MACE analysis and the comparison of observed to expected major adverse cardiovascular events?

Response: *As previously stated, the use of the three-component composite is quite reasonable and consistent with many contemporary cardiovascular trials. Given that the current program(s) is addressing the issue of cardiac safety (rather than efficacy), adding other components such as hospitalization for cardiac causes would be quite reasonable as well. Because Study 23 is a randomized trial and of a sufficient sample size to assure a reasonable balance between the treatment groups, the most appropriate comparison is between the vaccine therapies. The expected versus observed analyses are interesting and lend some insight into the overall event rate but should not supersede the randomized comparisons.*

5. Based upon the three-point MACE analysis, the Applicant concludes that "the primary reason for the observed imbalance in myocardial infarctions in HBV-23 appears to be that fewer than expected events occurred in the Engerix-B group rather than more than expected in the Heplisav group." Please comment.

Response: *Study 23 was a large RCT that looks to have appropriately balanced groups that allow a direct comparison of the treatment groups. The expected versus observed analyses are interesting but less so than the comparison based on randomization. Other observational datasets may well generate different event rates.*

6. What is your assessment of the Applicant's discussion of the Bradford Hill criteria and the conclusions they draw? In particular, please comment on the Applicant's conclusions that 1) the evidence does not support the premise that Heplisav mimics an acute infection causing increased risk of plaque rupture, 2) there is no clear evidence supporting an increase in thromboembolic events or myocardial oxygen supply demand mismatch associated with Heplisav, and 3) dose level and frequency of Heplisav is far below levels demonstrated in a mouse model to enhance atherosclerosis (Attachment 4, pp. 28-33).

Response: *The Bradford Hill criteria can be useful for providing insight into an observation and possible causation. Most often, the criteria are used in assessing the strength of evidence in epidemiological research when treatment (or exposure) comparisons do not have the benefit of being a randomized comparison. In the example given in these data, one might suppose alternative biological hypotheses that would be opposite offered up by the sponsor. The reality is that the biological suppositions are hypotheses and not facts. Additionally, the mechanistic issue is not likely to be progression of atherosclerosis over such a short period of observation but rather some*

biological mechanism that contributes to plaque instability and/or heightened response to thrombosis.

7. What is your assessment of the cardiovascular risk associated with Heplisav? What, if any, problems have you identified with the Applicant's conclusions with regard to the analyses they have presented?

Response: *The sponsor has observed an imbalance of ischemic cardiac events (mostly myocardial infarction) associated with use of its vaccine compared with an active control vaccine in a large randomized clinical trial. The trial was not prospectively designed to optimally identify suspected ischemic events, to have appropriately collected supporting materials on these events nor to prospectively adjudicate suspected events. The trial did however enroll a group of patients at increased cardiac events based on entry cardiac risk factor profiles. The sponsor has performed a very reasonable series of analyses intended to "explain" or to minimize this infrequent, but troubling, difference in cardiac risk. The observation is consistent across several cardiac events, including unexplained death and myocardial infarction. In Study 23, the comparison of the MACE composite does not meet conventional statistical significance. The sponsor cannot/does not fully eliminate the notion that this is a "real" observation worth further investigation. I agree.*

Consult 3

Questions for the consultant

1. In the "Evaluation of Acute Myocardial Infarction and Major Adverse Cardiovascular Events in the Phase 3 Heplisav Clinical Trials," the Applicant uses the following tools to assess cardiovascular risk: 1) identification of reported events of AMI in the safety database and multivariate logistic regression analysis to assess risk factors associated with MI in Study DV2- HBV-23, 2) a three-point MACE analysis to identify serious cardiovascular events in the three Phase 3 studies, 3) comparison of observed to expected number and rate of cardiovascular events in studies DV2-HBV-16 and -23, and 4) discussion of the Bradford Hill criteria for assessment of causation applied to the three-point MACE analysis. Are these the appropriate tools to use to evaluate the cardiovascular risk following Heplisav? Are there any additional tools you would use to assess cardiovascular risk associated with Heplisav?

Response: The Applicant has conducted an appropriate set of analyses. The most useful findings provided by the Applicant are (a) re-assessment of MACE outcomes in the phase 3 studies, and (b) the comparison of observed and expected event rates with Heplisav.

With regard to the analysis of MACE outcomes, an independent adjudication by C5Research confirmed the numerical imbalance in cardiovascular events between Heplisav and Engerix-B, which was driven almost entirely by MI events in the HBV-23 trial. This was true despite the fact that adjudication reduced the number of cardiovascular deaths from 16 to 6, MI from 22 to 18, and stroke from 16 to 15. The relative excess in MI events was similar before (19 vs 3) and after (16 vs 2) the independent adjudication. This analysis provides some confidence that the cardiovascular findings were not the result of "overcalling" MI events. It remains possible that some MI's were missed, but it is unlikely that such misclassification would affect the arms differentially.

The Applicant argues that MI rates in individuals randomized to Engerix-B in HBV-23 were lower than expected, which accounts for the excess risk observed in the Heplisav arm. Several analyses were performed to support this argument. First, the expected number of MI's were calculated using age- (by decade), sex-, and race-specific incidence rates generated using ARIC surveillance data and published in the AHA 2016 Statistical Update. This is the most "nonspecific" of the estimates presented, as it doesn't account for risk factor differences and it is limited to the 4 communities that enroll ARIC participants.

Next, they used the AHA/ACC Pooled Cohort Equations to estimate expected rates of hard atherosclerotic cardiovascular disease (comparable to the 3-point MACE). This approach does incorporate information about baseline risk, although 2 variables in the Pooled Cohort Equations, total cholesterol and HDL, were not collected in HBV-23. The Applicant addressed this limitation by testing 2-scenarios: inserting predicted cholesterol and substituting "clinical optimal" cholesterol into the equation. Lastly, they used the Framingham Risk Score to estimate rates of hard coronary heart disease (myocardial infarction or coronary death) in this population. Similar assumptions were made to

account for the missing cholesterol data. The AHA/ACC and Framingham models are intended only for individuals without prior cardiovascular disease, which appears to be the case for the vast majority of participants enrolled in HBV-23.

Despite the disparate comparison methodologies and endpoints, there is a consistent pattern of lower than expected coronary event rates in the Engerix-B participants in HBV-23. There is no clear explanation for this finding. It is unlikely that Engerix-B is cardioprotective, suggesting that the finding is either due to chance or to incomplete ascertainment of MI events in HBV-23. If chance is the explanation, then the apparent excess in MI risk associated with Heplisav is likely to be due to chance as well. On the other hand, if MI events were consistently under-documented in HBV-23, then the higher risk with Heplisav would still be a concern, because the missed diagnoses should be distributed among both arms. As noted above, the independent adjudication does not address this problem, because only positive diagnoses were adjudicated.

The multivariable analysis to assess risk factors for MI in the PSP sample does not provide any evidence to support the Applicant's argument. Indeed, the fact that age and hypertension were the only significant predictors of MI in their model highlights the lack of statistical power and the concern regarding incomplete ascertainment of MI events. This is because other variables in the model, such as smoking and prior MI/stroke, are known to be strong predictors of incident MI.

Lastly, the Applicant's use of the Bradford Hill criteria is only somewhat informative. As the Applicant notes, the temporal delay in the accumulation of excess MI events after Heplisav administration is difficult to explain on the basis of any known biology. On the other hand, there is still much that is not understood regarding the interaction of atherothrombotic events, inflammation, and immunity. While the Bradford Hill criteria provide a framework for organizing several lines of evidence, in my opinion the criteria cannot be used to exclude treatment-related risk.

In summary, several points raised by the Applicant in the response letter are reasonable, and the analyses are largely appropriate. That said, an important limitation of their analysis is the uncertainty regarding the completeness of ascertainment of MI events, which might explain some of the discrepancies between observed and expected risk. This limitation is inherent to the fact that HBV-23 was not designed to look at cardiovascular risk. I suspect that a broader search of terms related to myocardial infarction or ischemia (see question #2) would not yield significant additional insight regarding the numerical imbalance in MI events. There are no obvious ways to address this limitation using the current dataset, which highlights the potential utility of collecting prospective data with regard to cardiovascular risk.

2. Please comment on whether the appropriate cardiovascular outcomes have been selected for inclusion in the analyses. Specifically, we have the following questions:

   a) In order to identify subjects with myocardial infarction, are SAEs with preferred terms in the MedDRA SMQ narrow for myocardial infarction the most appropriate criteria? What, if any, additional preferred terms, or other criteria, would you recommend using to identify subjects with probable myocardial ischemic events?

b) Is the three-point MACE analysis (death due to cardiovascular cause, first non-fatal myocardial infarction, and first non-fatal stroke) the most appropriate to evaluate risk in this situation? Would you recommend other types of cardiovascular events (for example, heart failure) be used to assess cardiovascular risk for this vaccine? Did the Applicant use the appropriate preferred terms to identify potential major adverse cardiovascular events?

c) In the MACE analysis, for study DV2-HBV-23, the Applicant's consultants, C5Research, adjudicated 4 cardiovascular deaths (3 Heplisav, 1 Engerix-B) and 15 MIs (14 Heplisav, 1 Engerix-B). If one defines cardiovascular death to also include subjects with an unclear cause of death who were last seen more than 24 hours previously, 10 subjects total may be considered to have died due to a cardiovascular cause (9 Heplisav, 1 Engerix-B). If one defines MI to also include subjects who underwent urgent coronary artery revascularization or bypass graft with no evidence of necrosis presented in the narrative, 17 subjects total may be considered to have reported MI (15 Heplisav, 2 Engerix-B). Please provide your assessment of the criteria used to identify major cardiovascular events.

Response: The focus on terms in the myocardial infarction SMQ is reasonable, and probably favors specificity over sensitivity. Table 3-2 shows that for a subset of these terms, the clearest imbalance exists for acute MI. Many of the other terms in the SMQ for MI or ischemic heart disease are less specific and/or relate to symptoms, biochemical abnormalities, or procedural outcomes. Thus, a broader set of search terms would not necessarily provide new insight.

The 3-point MACE analysis appears appropriate. Other events such as heart failure are often not atherosclerotic in origin, so it is reasonable to omit them from the current MACE outcome. Although heart failure could be looked at separately, diagnostic criteria are more variable, and a robust analysis would require its own adjudication.

While coronary revascularization (CABG, PCI) is sometimes included in the MACE outcome, a number of non-biological factors may influence use of revascularization. Also, with the use of contemporary troponin assays, "urgent" revascularization without biochemical evidence of necrosis is less common than in the past. Not surprisingly, the inclusion of urgent revascularization only adds 1 case per arm.

Similarly, I think it is reasonable to omit "unknown cause of death" from the cardiovascular death outcome. It has been the practice in most long-term observational studies not to assume that all unknown events are cardiovascular in origin, in part because the inclusion of unknown events does not strengthen associations with accepted cardiovascular risk factors.

3. If the multivariate logistic regression analysis is an appropriate analysis, were the appropriate risk factors included in the model? Are there any additional risk factors that you would include in the model (for example dyslipidemia)?

Response: I have concerns about the multivariable logistic regression First, there is insufficient statistical power to draw robust conclusions, given the small number of events. This is supported by the fact that known risk factors such as smoking are not significant in the model. Second, it is best to develop separate models for first and recurrent events, as the predictors are not identical. Third, the model omits covariates such as dyslipidemia. Although BMI may serve as a surrogate for dyslipidemia in primary prevention populations, this does not hold in secondary prevention populations. Lastly, for cardiovascular risk models, it is also preferable to model risk factors with continuous variables when possible (systolic blood pressure, total cholesterol, HDL cholesterol) rather than binary variables (hypertension, dyslipidemia).

4. Do you have any concerns with the three-point MACE analysis and the comparison of observed to expected major adverse cardiovascular events?

Response: Several concerns about the MACE analysis and comparison of observed-to-expected events are noted in the response to Comment #1. I believe that the analyses are reasonable overall based on the data available to the Applicant.

5. Based upon the three-point MACE analysis, the Applicant concludes that "the primary reason for the observed imbalance in myocardial infarctions in HBV-23 appears to be that fewer than expected events occurred in the Engerix-B group rather than more than expected in the Heplisav group." Please comment.

Response: It does appear that there is a consistent pattern of lower than expected event rates in the Engerix-B arm in HBV-23. Nonetheless, it is worthwhile to consider potential sources of error in the estimation of expected event rates and/or actual event rates. Challenges in estimating expected event rates include missing covariate data in HBV-23 (e.g. lipids), the mixed study sample (primary/secondary prevention), and differences in endpoint definitions between the trials and the registry/observational datasets.

A potentially larger concern is the possibility of under-ascertainment of MI events in HBV-23, since MI was not prospectively identified as an endpoint of interest. This would explain the lower than expected events in the "control" arm (Engerix-B) and the inability of several known cardiovascular risk factors to predict MI's in HBV-23.

6. What is your assessment of the Applicant's discussion of the Bradford Hill criteria and the conclusions they draw? In particular, please comment on the Applicant's conclusions that 1) the evidence does not support the premise that Heplisav mimics an acute infection causing increased risk of plaque rupture, 2) there is no clear evidence supporting an increase in thromboembolic events or myocardial oxygen supply demand mismatch associated with Heplisav, and 3) dose level and frequency of Heplisav is far below levels demonstrated in a mouse model to enhance atherosclerosis (Attachment 4, pp. 28-33).

Response: I agree with the Applicant that the temporal relation between Heplisav administration and MI events in HBV-23 does not fit a model of acute exposure causing plaque rupture. Also, the occurrence of other thrombotic events does not appear increased. These observations fit with the finding that higher doses of adjuvant exposure

are required in animal models to incite an acute inflammatory response. On the other hand, it is difficult to fully exclude the possibility that lower levels of exposure could promote chronic atherosclerotic plaque formation based on animal data alone, as animal models of atherosclerosis have well-known limitations.

7. What is your assessment of the cardiovascular risk associated with Heplisav? What, if any, problems have you identified with the Applicant's conclusions with regard to the analyses they have presented?

Response: The numerical imbalance in MI events between Heplisav and Engerix-B is moderately concerning. While the finding could be attributable to chance, I cannot confidently say that there is no increased cardiovascular risk with Heplisav. Thus, I believe that further evaluation is warranted. The Applicant's analyses are a reasonable first step, but their conclusions largely hinge on the low ratio of observed to expected events with Engerix-B in the phase 3 trials. That analysis has several limitations, as described above, and it is difficult to place more weight on a comparison with externally-derived event rates (observed vs expected) than on the internal comparison (between study arms).