

BLA Clinical Review Memorandum

Application Type	Complete Response (CR) to Original Application
STN	125428
CBER Received Date	16 March 2016
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Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
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Review Completion Date / Stamped Date	11 November 2016/7 April 2017
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Applicant	Dynavax Technologies Corporation
Established Name	Hepatitis B Vaccine (Recombinant), Adjuvanted
(Proposed) Trade Name	HEPLISAV
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Each 0.5 mL dose contains 20 mcg of recombinant yeast cell-derived hepatitis B virus surface antigen (HBsAg) and 3000 mcg Dynavax's proprietary adjuvant, 1018
Dosage Form(s) and Route(s) of Administration	Solution for Intramuscular Injection
Dosing Regimen	Two 0.5 mL doses administered four weeks apart
Indication(s) and Intended Population(s)	Immunization against infection caused by all known subtypes of hepatitis B virus in adults age 18 years of age and older
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
AESI	adverse event of special interest
AMI	acute myocardial infarction
ANCA	anti-neutrophil cytoplasmic antibody
BIMO	Bioresearch Monitoring Program
BLA	Biologics License Application
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMC	Chemistry, manufacturing, and controls
COPD	chronic obstructive pulmonary disease
CpG	cytosine phosphoguanine
CR	complete response
CRF	case report form
CSR	clinical study report
dL	deciliter
DNA	deoxyribonucleic acid
EMA	European Medicines Agency
FDA	Food and Drug Administration
GPA	granulomatosis with polyangiitis
GMC	geometric mean concentration
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
hr	hour
Ig	immunoglobulin
IM	intramuscular
IND	Investigational New Drug application
IR	information request
ISS	Integrated summary of safety
L	liter
LCPP	lot consistency per protocol
LMP	last menstrual period
mcg	micrograms
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	modified intent-to-treat
mIU	milli-international units
mL	milliliter
mM	millimole
ODN	oligodeoxynucleotide
PP	per protocol
PREA	Pediatric Research Equity Act
PT	preferred term

QC	quality control
rHBsAg	recombinant hepatitis B surface antigen
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SEAC	Safety Evaluation and Adjudication Committee
SPR	seroprotection rate
STN	submission tracking number
THS	Tolosa-Hunt Syndrome
TLR	toll-like receptor
TSH	thyroid stimulating hormone
US	United States
VRBPAC	Vaccines and Related Biological Products Advisory Committee
µIU	micro-international units

1. Executive Summary

Dynavax submitted Biologics License Application (BLA) STN 125428/0 to the Food and Drug Administration (FDA) on 26 April 2012 to support its application to license a recombinant hepatitis B virus vaccine adjuvanted with a novel cytosine phosphoguanine enriched oligodeoxynucleotide phosphorothioate immunostimulatory sequence (1018 immunostimulatory sequence) with the proposed trade name Heplisav. The vaccine is intended for active immunization against all subtypes of hepatitis B virus infection in adults 18-70 years of age.

Because of the novel nature of the adjuvant, a Vaccines and Related Products Advisory Committee (VRBPAC) was held to discuss the product's safety and immunogenicity on 15 November 2012. The committee voiced concerns about the small size of the safety database submitted in support of licensure and recommended that additional safety information be obtained in a larger population.

On 22 February 2013, FDA issued a Complete Response (CR) Letter. In addition to a number of non-clinical concerns, three clinical items precluded approval at that time: 1) the inadequate size of the safety database; 2) the need for additional information regarding a number of specific adverse events; and 3) the need for information regarding a case of possible Tolosa-Hunt syndrome in a Heplisav recipient in Study DV2-HBV-16. Additionally, the Bioresearch Monitoring (BIMO) reviewer identified concerns which precluded approval at that time and were based on inspection findings from Study DV2-HBV-16.

Following the CR Letter, the Applicant conducted an additional study to increase the size of the total safety database, Study DV2-HBV-23. A secondary, unpowered endpoint of this study was the proportion of subjects diagnosed with granulomatosis with polyangiitis (GPA) and Tolosa-Hunt syndrome (THS). The Applicant included this secondary endpoint because two Heplisav recipients were diagnosed with these potential granulomatous vasculitides in previous studies: one subject with GPA (formerly "Wegener's granulomatosis" and so diagnosed at the time the study was conducted) in Study DV2-HBV-10 and the possible case of Tolosa-Hunt syndrome in Study DV2-HBV-16 noted above.

The Applicant submitted a complete response on 16 March 2016, including the Clinical Study Report (CSR) and supporting documents from the additional safety study, DV2-HBV-23, and additional information intended to address the other two clinical CR Letter items. Additionally, the March 2016 submission included revised CSRs for Studies DV2-HBV-10 and DV2-HBV-16. The Applicant determined these revisions were necessary to correct errors in the DV2-HBV-10 and DV2-HBV-16 CSRs submitted previously to the Biologics License Application (BLA) in 2012. The Applicant stated that it detected these errors during audits performed after another regulatory agency's inspections had identified concerns with data quality in a study not submitted to the BLA. However, the Applicant did not include datasets for Studies DV2-HBV-10 and DV2-HBV-16 to support the revised CSRs. This deficiency resulted in a Major Amendment.

The errors in the CSRs for DV2-HBV-10 and DV2-HBV-16 were primarily concerning subjects erroneously included or excluded from the per protocol (PP) immunogenicity populations of each study. The safety population for neither study changed as a result of the audit. Thus, FDA's review of the revised CSRs for Study DV2-HBV-10 and -16 focused exclusively on the revised immunogenicity data. This review does, however, address outstanding safety questions at the time of the last review, including the possible diagnosis of Tolosa-Hunt Syndrome in a subject who received Heplisav in Study DV2-HBV-16. Prior to the current submission, the FDA solicited outside consultations from several experts regarding the diagnosis and possible relationship to Heplisav. All four consultants assessed the event as Tolosa-Hunt syndrome, each of them noting the subject's response to steroids and reasonable exclusion of alternate etiologies. None of the consultants endorsed a definitive causal association between the vaccine and the adverse event.

During review of the revised immunogenicity data in Studies DV2-HBV-10 and -16, FDA identified additional subject accounting discrepancies, separate from those initially identified by the Applicant in the Complete Response. Despite a number of communications with the Applicant during the review cycle, including Information Requests (IRs) and teleconferences, persistent inconsistencies in the information submitted require significant re-evaluation and correction before any further review of these data can ensue.

Study DV2-HBV-23 was reviewed for immunogenicity in all per protocol immunogenicity subjects, for the sole purpose of confirming what Studies DV2-HBV-10 and -16 had shown, when originally reviewed by FDA in 2013. The immunogenicity analysis for all PP non-inferiority subjects in Study DV2-HBV-23 was a secondary endpoint and differed slightly from that of Studies DV2-HBV-10 and -16 in timing of the measurement of the immune response: the SPR for Heplisav at Week 24 was compared to the SPR of Engerix-B at Week 28.

On 2 November 2016, the clinical review team learned from discussions with the BIMO reviewer that inspections of select Study DV2-HBV-23 sites 122/222 identified data inconsistencies in a subset of randomly selected subjects. These subjects were found to have major protocol deviations and were incorrectly labeled as PP subjects. Due to the BIMO inspection findings, the validity of immunogenicity findings of Study DV2-HBV-23 is in question at present. Thus, currently, no final conclusions may be made regarding the immunogenicity results for Heplisav.

The Safety Population in DV2-HBV-23 consisted of 8368 subjects, 5587 who received at least one dose of Heplisav and 2781 who received at least one dose of Engerix-B. Subjects in this study reported more baseline medical conditions and risk factors for coronary artery disease than those enrolled in previous studies utilizing the proposed formulation (for example, prior diagnosis of cardiac ischemic disease: 3.7% DV2-HBV-23, 1.6% other studies; type 2 diabetes mellitus: 13.7% DV2-HBV-23, 4.9% other studies; smoking: 33% DV2-HBV-23, 29% other studies; obesity: 48% DV2-HBV-23, 35% other studies). However, medical conditions and cardiac risk factors were balanced between study groups in DV2-HBV-23 (prior diagnosis of cardiac ischemic disease: 3.8% Heplisav, 3.6% Engerix-B; type 2 diabetes mellitus: 13.6% Heplisav, 13.7% Engerix-B; smoking: 33% Heplisav, 33% Engerix-B; obesity: 49% Heplisav, 46% Engerix-B).

Safety endpoints of medically attended adverse events (MAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) were monitored through Week 56, one-year following the second and final dose of Heplisav. Solicited adverse events and unsolicited adverse events that were not medically attended were not collected and are not addressed directly in this review. A laboratory sub-study was also conducted to evaluate renal function and factors pre-disposing to thrombophilia following vaccination with Heplisav.

Overall, the rates of all MAEs (46.0% Heplisav, 46.2% Engerix-B) and SAEs (6.2% Heplisav, 5.3% Engerix-B) reported in the 56-week study period were similar between the Heplisav and Engerix-B groups. Potentially clinically significant imbalances were noted in deaths and acute myocardial infarction. After excluding deaths that were clearly due to illicit drug overdose or injury, an imbalance remained (0.29% Heplisav, 0.14% Engerix-B). There was not a close temporal relationship between most of the deaths and Heplisav; thirteen of 16 deaths not due to overdose or injury occurred beyond one month following the last dose of Heplisav. However, the difference between groups remains concerning given the study was randomized. Using standardized queries, events that are likely to represent events of acute cardiac ischemia were reported in 0.34% of Heplisav recipients and 0.11% of Engerix-B recipients. However, the clinical reviewer is unable to fully assess the significance of this imbalance as insufficient information was submitted regarding all cardiac SAEs. This information, and other clinical information, was requested from the Applicant in an information request (IR) 9 September 2016. The need for thorough review of this information in order to accurately assess the vaccine's risk benefit profile precludes approval by 15 December 2016, the action due date.

Smaller imbalances were noted in the following MAEs, the clinical significance of which are unknown: herpes zoster (0.7% Heplisav, 0.3% Engerix-B), atrial fibrillation (0.29% Heplisav, 0.11% Engerix-B), and renal failure (0.21% Heplisav, 0.11% Engerix-B for chronic and 0.32% Heplisav, 0.22% Engerix-B for acute). No differences between study groups were noted in pulmonary embolism or other venous thromboembolic events (0.21% Heplisav, 0.25% Engerix-B).

Due to a theoretical concern that novel adjuvants could be associated with autoimmunity and the previously reported events of vasculitis, any potential AESIs in Study DV2-HBV-23 were referred to a Safety Evaluation and Adjudication Committee (SEAC) for assessment of accurate diagnosis, timing of onset, and relationship to study vaccine. A

similar number of subjects in each treatment group reported potential AESIs that were referred to the SEAC for evaluation (0.70% Heplisav, 0.79% Engerix-B). No new-onset vasculitic AESIs were identified during the 56-week study period. Based upon the clinical reviewer's understanding of the SEAC's assessments, 10 subjects in the Heplisav group (0.18%) and one subject in the Engerix-B group (0.04%) reported a new-onset event with a diagnosis that qualified as an adverse event of special interest (AESI) confirmed by the SEAC. The SEAC determined that none of the events were related to study vaccination and that three of the events in the Heplisav group were clearly due to another cause. Six of the AESIs were Bell's palsy, reported in five subjects in the Heplisav group and one subject in the Engerix-B group. There was one additional event of granulomatous dermatitis in the Heplisav arm. Treating physicians recommended an evaluation for sarcoidosis, which was not performed. Further information regarding this subject was submitted by the Applicant in response to the 9 September 2016 IR.

The laboratory sub-study was conducted in 309 subjects enrolled at two sites. 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. Assessments of renal function, including urine microalbumin, in Heplisav recipients were reassuring. 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. The significance of one abnormal antiphospholipid antibody level and its possible role, if any, in imbalances of events noted in this study is unclear.

The integrated summary of safety (ISS) conducted by FDA focused on SAEs and AESIs, as these safety outcomes were collected in DV2-HBV-23, the major trial submitted in response to the complete response, and overlapped with previous trials. The FDA ISS was based on three different populations and differed from the populations presented by the Applicant because of concerns integrating studies with different lengths of follow-up, different safety endpoints (adverse events versus MAEs), and employing different formulations of the vaccine. No new safety issues were identified in FDA's integrated analysis. SAEs in the cardiac system organ class were slightly less frequent in subjects who received Heplisav (0.30 – 0.31%) compared to Engerix-B (0.41%) in the six-month ISS populations, but more frequent in subjects receiving Heplisav (0.77%) compared to Engerix-B (0.58%) in the one-year ISS population. However, when considering events that are likely to be acute cardiac ischemic events, a smaller imbalance than that observed in Study DV2-HBV-23 was seen in all three FDA safety populations (Heplisav 0.12 – 0.13%, Engerix-B 0.8 % in the six-month safety populations, Heplisav 0.28%, Engerix-B 0.18% in the one-year safety populations). In the two studies that utilized review of potential AESIs by an expert panel, both demonstrated that a small number of new-onset confirmed AESIs were reported almost exclusively in the Heplisav groups. Per SEAC adjudication and including the subject with Tolosa-Hunt syndrome, in DV2-HBV-16 and -23, 14 subjects who received Heplisav (0.19%) and one subject who received Engerix-B (0.03%) reported new-onset AESIs. This does not include two additional subjects in the Heplisav group with suspected, but unconfirmed AESIs: narcolepsy in DV2-HBV-16 and granulomatous dermatitis in DV2-HBV-23. The assessment of cardiac imbalances will be deferred due to additional information that was requested on 9 September 2016. The Applicant will be asked to provide an integrated analysis of safety based upon the safety populations the FDA has identified.

In conclusion, the information submitted with the complete response and subsequent IR responses prior to 9 September 2016, is not adequate to recommend approval of Heplisav at this time. Review of information submitted after 23 September 2016 will proceed beyond the action due date in order to accurately assess the potential safety signals that have been identified and to verify immunogenicity results.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The Applicant did not provide a summary of safety based upon demographic characteristics in DV2-HBV-23. This analysis will be requested and reviewed at a later date. The Applicant did provide an integrated analysis of safety outcomes based upon their safety populations. However, the integration of safety data in these populations is problematic for the reasons stated above. Consequently, we will ask for an analysis of safety based on integrated safety populations that the FDA has identified.

2. Clinical and Regulatory Background

Product: Heplisav (rHBsAg-1018 immunostimulatory sequence)

- 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. The 1018 immunostimulatory sequence used in Heplisav is a 22-mer oligonucleotide with the sequence:

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

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

Dosage and Administration: Each 0.5 mL dose contains 20 mcg rHBsAg and 3000 mcg 1018 immunostimulatory sequence adjuvant. The dosing regimen is two 0.5 mL doses administered four weeks apart.

2.1 Disease or Health-Related Condition(s) Studied

Hepatitis B virus (HBV) infects more than two billion persons worldwide, and 350-400 million persons are chronic carriers. Each year chronic HBV causes 0.5 to 1.0 million deaths from end-stage liver disease and hepatocellular carcinoma. In the U.S., universal childhood vaccination has been recommended since 1992. Subsequently, the incidence of HBV infection has substantially decreased from 8.5 per 100,000 (1990) to 0.9 per 100,000 (2014).¹ Prevalence remains high at 800,000 to 1.4 million, and chronic HBV infection causes 2,000-4,000 deaths annually. The Centers for Disease Control and Prevention (CDC) estimated that there were 18,100 acute HBV infections in 2014 with highest rates reported for persons aged 30-39 years (2.2 cases per 100,000) and lowest rates reported in children and adolescents aged ≤ 19 years (0.02 per 100,000). Chronic hepatitis B was reported at an incidence of 7.1 cases per 100,000 in 2014,¹ with the largest number of case reports submitted by New York State (18.2% of chronic hepatitis B cases in the US in 2014). Among the cases for which place of birth was known (n=665), those born outside the U.S. accounted for the greatest number of chronic hepatitis B cases (71.3%).

Transmission of HBV is by percutaneous and mucosal exposure to infectious blood or body fluids. In the U.S. transmission is primarily sexual. Injection drug use accounts for approximately 26% of new HBV infections.¹ Nosocomial transmission between patients and from patients to health care workers, including hemodialysis and oncology units, has become rare, declining more than 95% since implementation of routine vaccination and standard precautions for blood-borne pathogens.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Two licensed vaccines, both made from yeast-derived recombinant antigen adsorbed to aluminum compounds are currently available for the prevention of HBV in adults in the U.S., Engerix-B (GlaxoSmithKline) and Recombivax HB (Merck). There is also one combination vaccine for adults, Twinrix (GlaxoSmithKline), which includes a hepatitis A vaccine component. Engerix-B and Recombivax HB are both approved for use in adults and adolescents as a three-dose series to be administered at months 0, 1 to 2, and 6 to 12. 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. 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 infection² and prospective observational studies,^{3,4} 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.⁴

Breakthrough infections (detected by presence of anti-hepatitis B core (HBc) antibodies or HBV deoxyribonucleic acid (DNA)) have occurred in immunized people, but these infections typically are transient and asymptomatic. Chronic HBV infection in immunized people has been documented in dialysis patients whose anti-hepatitis B surface antigen (HBsAg) antibody concentrations fell below 10 mIU/mL. For adults on dialysis, formulations of Engerix-B and Recombivax HB containing 40 mcg per dose administered in a 3 or 4 dose series 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.⁵

2.3 Safety and Efficacy of Pharmacologically Related Products

Currently, there are no approved vaccine products containing this 1018 immunostimulatory sequence novel adjuvant.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

This product is not approved anywhere else in the world. A marketing authorization application was submitted to the European Medicines Agency (EMA) in 2012 intended to support an indication for immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 through 70 years of age and in patients with chronic kidney disease. In 2014, Dynavax officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wished to withdraw its application. According to the EMA website.⁶

“The Committee considered that the way in which the study in patients with kidney disease had been carried out and documented was not satisfactory. This followed an inspection of some of the sites involved in the study, to ensure proper standards for medicines studies (Good Clinical Practice) had been followed. The nature of the findings from the inspection also raised questions about the other main studies. Therefore, there were serious uncertainties at that point about the reliability of the data submitted in support of the application. Furthermore, the number of patients in whom the safety of the medicine had been tested was insufficient to rule out an unacceptable level of risk for less common but serious side effects.”

Therefore, at the time of the withdrawal, the CHMP was of the opinion that the medicine could not have been approved based on the data presented by the company.

In its EMA withdrawal letter, Dynavax stated it could not provide the additional safety data required by the CHMP within the allowed timeframe.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

26 April 2012: Submission of BLA STN 125428/0.

15 November 2012: Vaccines and Related Products Advisory Committee (VRBPAC) stated concerns with the size of the safety database, as well as underrepresentation of Asian subjects enrolled in the trials.

22 February 2013: The Food and Drug Administration (FDA) issued a Complete Response Letter based on submissions to STN 125428/0, with the exception of amendments dated 29 December 2012, 16 January 2013, 1 February 2013, and 7 February 2013. In addition to a number of non-clinical concerns, clinical items precluding approval at that time included the inadequate size of the safety database, the need for additional information regarding a number of adverse events and a possible case of Tolosa-Hunt syndrome in one HepLisav recipient in Study DV2-HBV-16. Two CR items were generated from the Bioresearch Monitoring (BIMO) reviewer as a result of inspection findings from Study DV2-HBV-16.

16 March 2016: Applicant submitted a Complete Response. In addition to the Clinical Study Report (CSR) and supporting documents from the required safety study, DV2-HBV-23, the submission included revised CSRs for Studies DV2-HBV-10 and DV2-HBV-16. The Applicant determined these revisions were necessary due to errors it detected during audits performed after another regulatory agency's inspections had identified concerns with data quality in a study not submitted to the BLA. However, the submission lacked revised datasets for Studies DV2-HBV-10 and DV2-HBV-16.

8 April 2016: Applicant submitted datasets for Studies DV2-HBV-10 and DV2-HBV-16 at FDA's request, received on 11 April 2016.

18 April 2016: FDA notified the Applicant that the datasets constituted a Major Amendment because they contained a substantial amount of new data not previously

submitted to, or reviewed by the Agency, thus adding an additional three months to the review clock. Therefore, the action due date was revised to 15 December 2016.

27 May 2016: Applicant responded to a FDA Information Request (IR) regarding revised immunogenicity data for Studies DV2-HBV-10 and DV2-HBV-16 and included newly revised subject disposition datasets for these two studies, as well as a tabular summary of subjects whose disposition changed based on the audit.

12 July 2016: Applicant responded to a FDA IR again seeking clarity regarding subject disposition in Studies DV2-HBV-10 and DV2-HBV-16 with tabular summaries and datasets.

3 August 2016: FDA discussed inconsistencies in the data submitted regarding subject disposition in Studies DV2-HBV-10 and DV2-HBV-16 in a teleconference with the Applicant.

9 September 2016: FDA issued IR regarding need for additional information to support assessment of safety in Study DV2-HBV-23, as well as information needed to support evaluation of immunogenicity assessments and subject disposition for Studies DV2-HBV-10 and DV2-HBV-16.

30 September 2016: Teleconference with Applicant regarding organization of datasets to be submitted for Studies DV2-HBV-10 and DV2-HBV-16 in response to IR. Applicant informed FDA that for study DV2-HBV-16 the final disposition of subjects, whether included or merely eligible for inclusion, in the lot consistency per protocol (LCPP) analysis is not clearly indicated in the corresponding ADSL dataset, and therefore FDA could not determine the accurate number of subjects in the LCPP analysis from the dataset. The Applicant agreed to clearly designate subject disposition by adding additional variables to the revised master dataset to be submitted in response to the 9 September 2016 IR.

2.6 Other Relevant Background Information

Not applicable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission provided in the 16 March 2016 CR did not include datasets for Studies DV2-HBV-10 and DV2-HBV-16 to support the revised CSRs. This deficiency resulted in a Major Amendment. The Applicant did not submit a complete listing of subjects newly excluded and newly included into the per protocol population for Studies DV2-HBV-10 and -16. During the review process, the immunogenicity reviewer noted additional subject accounting discrepancies.

The Applicant additionally failed to clarify in each of the revised CSRs that a subset of subjects in Studies DV2-HBV-10 and -16 were newly included into the per protocol population as a result of the Applicant's audit of these studies. Neither revised CSR mentioned that the number of subjects newly excluded from the per protocol population actually represented the net number of subjects excluded, that was based on the total number of subjects newly excluded and the number of subjects newly included. The first

IR response dated 27 April 2016 represents the first document submitted by the Applicant which clarified that the Applicant had indeed also revised the number of subjects who were newly included in the per protocol populations for Studies DV2-HBV-10, and -16.

Prior to this submission, the Applicant and the FDA agreed that the Applicant could submit only select serious adverse event (SAE) narratives from DV2-HBV-23, for deaths, AESIs, and any SAEs that were not clearly attributable to another cause. At the time of this discussion, the FDA was unaware of additional safety concerns, in cardiac SAEs, that were identified by the Safety reviewer during this review. Narratives and case report forms (CRFs) for all cardiac SAEs and additional SAEs of interest were submitted in response to a September 9, 2016 IR; due to the volume of the response, the information will not be reviewed this cycle. Narratives and information on additional specific events identified will be requested of the Applicant, as well.

The following is a list of additional errors, inconsistencies, or discrepancies noted in the information submitted for HBV-23:

- Hyperlinks inserted throughout the submission are not functional. Some supportive documents were not located where one would expect.

Reviewer comment: *The Applicant will be asked to ensure that all hyperlinks are correct and functional.*

- In DV2-HBV-23, 762 subjects who received at least one dose of Heplisav and 381 subjects who received at least one dose of Engerix-B were reported (flagged) to be diabetic, defined as a clinical diagnosis of diabetes and taking a hypoglycemic agent. A reviewer-generated analysis using the dataset ADMH found of subjects flagged as diabetics, 172 Heplisav subjects and 93 Engerix-B subjects did not have any history of diabetes or diabetic-related condition recorded in the dataset ADMH. Furthermore, 114 Heplisav subjects and 43 Engerix-B subjects were not flagged as diabetics, but are likely to have diabetes based on a medical history of diabetes or a diabetic complication. The primary immunogenicity endpoint was evaluated based on the flagged diabetic population, those who met the criteria for the per protocol population.

Reviewer comment: *The FDA advised the Applicant under the Investigational New Drug application (IND) that the design of Study DV2-HBV-23 was insufficient to meet its stated primary objective of evaluating immune response in diabetics and therefore considers the Applicant's analyses invalid. However, the information above is included because, while both treatment groups seem to be affected similarly, these discrepancies suggest incomplete data collection and quality control in Study DV2-HBV-23.*

- Start dates for AESIs listed in the dataset ADAE, for which detailed narratives were reviewed, appear to be inconsistently applied. Start dates could represent the date of symptom onset, the date of initial clinical laboratory evaluation, the date of physician final diagnosis including the date a physician reviewed labs that were previously drawn when those laboratory results determined diagnosis, the first date of the study when the Applicant tested pre-vaccination blood draw to determine an event was pre-existing, or some other date.

Reviewer comment: While some variation is expected depending on the nature of the event or diagnosis, similar types of events appeared to have different types of start dates. Some AESIs that were determined to be pre-existing based upon symptomatology and investigator assessment have a post-treatment start date and are flagged as treatment emergent. In the opinion of the clinical reviewer, the start dates of AESIs are sometimes unreliable. The extent to which this occurs for SAEs and other MAEs and its impact on the safety review is unknown. The Applicant's response to FDA's 9 September 2016 IR asking them how investigators were instructed to report start dates will be reviewed at a later time point.

- Several entries in the dataset ADAE appear to be the same event listed multiple times when an event progressed from non-serious to serious (for example, subject 118-229 chest pain and angina pectoris). Event terms are the same or similar and the stop date for one event is the same as the start date for the other event.

Reviewer comment: If the same event is listed in multiple entries, the clinical reviewer is unable to determine the number of events per subject. The Applicant was asked to provide a list of adverse events that appear in the datasets as two separate events but are described as the same actual event in the 9 September 2016 IR. Their response will be evaluated following this review.

- Dataset ADAE also contained two errors in start date years, which were not noted by the Applicant. The same dataset contained four apparent errors in misclassification of the venous thromboembolism flag, not all of which were identified by the Applicant in their CSR.

Reviewer comment: While these errors are not felt to represent systemic problems, they could indicate poor quality control. Correct start dates were submitted in 125428/0.54 in response to an IR sent 28 June 2016.

The absence of datasets for Studies DV2-HBV-10 and -16 resulted in a Major Amendment being issued on 18 April 2016. The incomplete and/or inconsistent data cited for other outstanding issues (listed above) resulted in subsequent IR letters to the Applicant, issued 8 April 2016, 27 May 2016, and 9 September 2016.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The number of inconsistencies and discrepancies found during the immunogenicity and safety review of each of the studies provided in this CR (revised Studies DV2-HBV-10, -16, and Study DV2-HBV-23) bring into question the overall quality of the data submitted in this application.

With respect to revised Studies DV2-HBV-10 and -16, a tabular listing of subjects newly excluded from the per protocol populations was not submitted in the CR, even though the purpose of the revised CSRs was to provide accurate subject accounting, based on inappropriate inclusion or exclusion of subjects into the per protocol (PP) populations in these two respective studies. Subsequent IR letters issued to the Applicant resulted in IR responses which failed to provide accurate accounting of newly excluded and newly

included subjects for both Studies DV2-HBV-10 and -16. Using the subject accounting information provided in the Applicant's second IR response dated 12 July 2016, the clinical reviewer was able to account for the number of newly excluded and newly included per protocol population subjects for Study DV2-HBV-10, and the statistical reviewer was able to verify these subjects using the SAS dataset. Because the Applicant's IR responses were unable to address subject accounting discrepancies for Study DV2-HBV-16, additional clarification was sought by FDA.

A subsequent teleconference with the Applicant on 3 August 2016 revealed mislabeling by the Applicant of subjects' non-inferiority and lot consistency per protocol status that would require correction in the .xpt files by the Applicant. A follow-up teleconference on 30 September 2016 also revealed that the Applicant had denoted 'study eligible' subjects as being the same as the 'per protocol population' even though the specific criteria for inclusion into, and definitions for the two populations are different, as provided by the Applicant in the original and revised CSR for Study DV2-HBV-16. The newly excluded and newly included 'per protocol' subjects provided in the tabular listings for Study DV2-HBV-16 in the two IR responses submitted by the Applicant on 27 April 2016 and 12 July 2016 also included 'study eligible' subjects which resulted in uninterpretable subject accounting data. When queried, the Applicant stated that the data for Study DV2-HBV-10 did not include this error. However, FDA will need to verify the data from this study based on the response to the 9 September 2016 IR and informed by the 30 September 2016 teleconference.

Verification of the immunogenicity data for Studies DV2-HBV-10 and -16 was complicated by the Applicant's inclusion of newly excluded subjects only, in the revised .xpt files for Study DV2-HBV-10 and -16. Immunogenicity data for the newly included subjects should have been but was not included. The statistical reviewer was not able to verify immunogenicity data for either of these studies and was only able to derive a revised immunogenicity analysis for the primary immunogenicity endpoints of Studies DV2-HBV-10 and -16 using a dataset compiled with newly excluded subjects.

Pending review of the requested master datasets and listing of newly excluded and newly included per protocol subjects for Study DV2-HBV-16, which the Applicant states it has now ensured are correct, the recurrent nature of inconsistencies seen in subject accounting, despite multiple efforts to obtain clarification from the Applicant, and the finding of overtly mislabeled subjects, despite a previous study audit, raise concerns about data integrity and overall quality of this submission. The clinical reviewer believes that the inaccuracies detected do not represent isolated events. The pervasive nature of the events appears underscored by BIMO's inspection findings for Study DV2-HBV-23, which suggest similar data inconsistencies occurred with respect to determination of the per protocol immunogenicity population. These findings require further evaluation before conclusions about the immunogenicity of Heplisav can be made by the clinical review team.

As stated in section 3.1, narratives and CRFs for all cardiac SAEs reported in DV-HBV-23 were not submitted in the March 16, 2016 response to the CR letter, although the Applicant noted an imbalance in acute myocardial infarction in their CSR. This imbalance, and an imbalance in deaths reported between the two study groups, was not specifically discussed with the FDA prior to submission of the response to the CR letter. The Applicant communicated to FDA that it did not need a Type C Meeting prior to

submitting the current documents, during which handling of these findings could have been discussed.

3.3 Financial Disclosures

Investigators with financial conflicts of interest for Studies DV2-HBV-10 and -16 were previously addressed in the original clinical review of this application dated 26 February 2013.

With regard to study DV2-HBV-23, the Applicant provided FDA Form 3455 and a list of 41 investigators and no more than 585 sub-investigators. Some sub-investigators were associated with more than one site and were listed at all sites. With regard to study DV2-HBV-22, the Applicant identified one investigator and nine sub-investigators. The Applicant stated there were no investigators with disclosable financial interests as per 21 Code of Federal Regulations (CFR) 54.2.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Pending at the time this clinical review was completed. Please refer to the FDA Chemistry, manufacturing, and controls (CMC) reviewer's memo.

4.2 Assay Validation

Pending at the time this clinical review was completed. Please refer to the FDA assay reviewer's memo.

4.3 Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology/toxicology for the combined recombinant hepatitis B antigen and 1018 immunostimulatory sequence adjuvant and for the 1018 immunostimulatory sequence adjuvant alone were previously reviewed in the original application for BLA STN 125428/0000. There have been no manufacturing changes to the product to warrant additional pharmacologic/toxicologic evaluation. Please refer to the reviews of Dr. Steven Kunder dated 21 February 2013 and Dr. Claudia Wrzesinski dated 23 January 2013 for pharmacology/toxicology reviews of Heplisav (rHBsAg plus 1018 immunostimulatory sequence) and the 1018 immunostimulatory sequence adjuvant alone, respectively.

4.4 Clinical Pharmacology

Clinical pharmacology was previously discussed in the original clinical review of Heplisav dated 26 February 2013. Please refer to Sections 4.4 and 4.4.1 in that review for further information.

4.4.1 Mechanism of Action

Heplisav consists of rHBsAg and a synthetic cytosine phosphoguanine oligodeoxynucleotide (CpG ODN) adjuvant, 1018 immunostimulatory sequence, which is comprised of cytosine and guanine enriched unmethylated single strand DNA sequences. Unmethylated CpG sequences are recognized as foreign by the innate immune system through interaction with toll-like receptor 9 (TLR9), present on dendritic cells and B cells. Activation of TLR9 receptors stimulates a T helper 1 (Th1) immune response, with secretion of proinflammatory cytokines that activate macrophages,

monocytes, and natural killer cells. 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.

In summary, Heplisav is proposed to act by using an adjuvant that activates TLR9 in plasmacytoid dendritic cells which, combined with HBsAg, leads to production of HBsAg-specific antibodies.

4.4.2 Human Pharmacodynamics

Human pharmacodynamics and the rationale for dose selection of the 1018 immunostimulatory sequence for further clinical development and for the candidate vaccine formulation was previously addressed in the original clinical review dated 26 February 2013.

4.4.3 Human Pharmacokinetics

Not applicable.

4.5 Statistical

Pending at the time this clinical review was completed. Please refer to Dr. Chowdhury's review memo.

4.6 Pharmacovigilance

Pending at the time this clinical review was completed. Please refer to Dr. Said's review memo.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Dr. Alexandra Worobec reviewed revised immunogenicity data from Studies DV2-HBV-10 and DV2-HBV-16. Because of incomplete data submitted in the revised CSRs and revised supporting datasets (.xpt files), Dr. Worobec is not able to verify the revised immunogenicity results of Studies DV2-HBV-10 and -16. Immunogenicity of Heplisav in the total subject population was evaluated in Study DV2-HBV-23 to ascertain that the SPR in this population was non-inferior to the active comparator, Engerix-B and did not show a quantitatively significantly different immune response from that seen in Studies DV2-HBV-10 and -16. However, currently, immunogenicity results from these three studies are not yet confirmed. Dr. Darcie Everett reviewed safety data from Study DV2-HBV-23 as well as an integrated analysis in which the Applicant incorporated safety data from all of the studies evaluating Heplisav. The FDA analysis integrated Studies DV2-HBV-23, -10, -16, -14, and -22, studies in which subjects received the final formulation and dosing regimen of the candidate vaccine. Only the safety data from study DV2-HBV-23 was reviewed individually in Section 6 during this review cycle. HBV-22 was not included in the clinical review of the initial BLA submission and not reviewed individually during this review cycle because it was a small, uncontrolled supportive study. All other studies were included in the clinical review of the original BLA submission. Please refer to Dr. Lorie Smith's review for details.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following sections of 125428/0.42 were assigned to and reviewed by the Clinical Reviewers:

- 1.2 Cover Letters
- 1.3.4 Financial Certification and Disclosure
- 1.9.1 Request for Waiver of Pediatric Studies
- 1.11.3 Clinical Information Amendment
- 2.5 Clinical Overview
- 2.7 Clinical Summary
- 5.2 Tabular Listing of all Clinical Studies
- 5.3.5.1 Study Reports of Controlled Clinical Studies Pertaining to the Claimed Indication
- 5.3.5.3 Reports of Analyses of Data from More than One Study
- 5.4 Literature References

The following amendments received following the 16 March 2016 submission were reviewed by the Clinical Reviewers:

- 125428/0.54 Module 5.3.5.1
- 125428/0.45 Module 5.3.5.1
- 125428/0.49 Module 5.3.5.1

The following additional amendments prior to the 16 March 2016 submission were submitted incrementally in response to the CR letter and reviewed:

- 125428/0.34 Module 5.3.5.1 Safety information for individual subjects for DV2-HBV-10 and -16
- 125428/0.35 Module 5.3.5.1

5.3 Table of Studies/Clinical Trials

Table 1. Summary of the studies using the proposed formulation of Heplisav for the immunogenicity and safety analyses in this review

Study Name	Study Design	Heplisav Dose/Schedule/N	Comparator Dose/Schedule/N	Key Endpoints
DV2-HBV-10 Pivotal NCT00435812	Phase 3, observer-blind, randomized, active-controlled, parallel group, multicenter study in healthy subjects 11-55 years of age conducted in Canada and Germany	Heplisav: 20 mcg HBsAg/3000 mcg 1018 adjuvant Schedule: 0, 4 weeks IM (placebo at 24 weeks) N=1809	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks IM N=606	Primary Endpoint: SPR at Week 12 for Heplisav and Week 28 for Engerix-B Major Safety Endpoints: Solicited reactions 7 days following each injection, AEs/SAEs Study Week 28

Study Name	Study Design	Heplisav Dose/Schedule/N	Comparator Dose/Schedule/N	Key Endpoints
DV2-HBV-16 Pivotal NCT01005407	Phase 3, observer-blind, randomized, active-controlled, parallel group, multicenter study in healthy adult subjects 40-70 years of age conducted in Canada and Germany	Heplisav: 20 mcg HBsAg/3000 mcg 1018 adjuvant Schedule: 0, 4 weeks IM (placebo at 24 weeks) N=1969	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks IM 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 Major Safety Endpoints: Solicited reactions 7 days following each injection, AEs Study Week 28, SAEs/AESIs Study Week 52
DV2-HBV-23 Pivotal NCT02117934	Phase 3, observer-blind, randomized, active-controlled, parallel group, multicenter study in adults 18-70 years of age conducted in US	Heplisav: 20 mcg HBsAg/3000 mcg 1018 adjuvant Schedule: 0, 4 weeks IM (placebo at 24 weeks) N = 4537	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks IM N = 2289	Secondary Efficacy Endpoint: SPR at Week 24 for Heplisav and Week 28 for Engerix-B Major Safety Endpoints: MAEs/SAEs/AESIs Study Week 56
DV2-HBV-14 NCT00511095	Phase 2, multicenter, open label, single-arm study in healthy subjects 11-55 years of age conducted in the U.S.	Heplisav: 20 mcg HBsAg/3000 mcg 1018 adjuvant Schedule: 0, 4 weeks IM N=207	None	Major Safety Endpoints: Solicited reactions 7 days following each injection, AEs/SAEs Study Week 28
DV2-HBV-22 NCT01999699	Single-center, open-label, single group trial in healthy subjects	Heplisav: 20 mcg HBsAg/3000 mcg 1018 adjuvant Schedule: 0, 4 weeks IM N = 25	None	Major Safety Endpoints: AEs Study Week 12, SAEs/AESIs Study Week 56

Source: Adapted from STN 125428/0.42, module 5.2 Tabular Listing of All Clinical Studies and module 2.7.4 Summary of Clinical Safety, Table 2.7.4-1, p. 16 – 20

N: number of subjects in the per protocol population

Mcg: micrograms
HBsAg: hepatitis B surface antigen
IM: intramuscular
SPR: seroprotection rate
AE: adverse event
SAE: serious adverse event
GMC: geometric mean concentration
AESI: adverse event of special interest
MAE: medically-attended adverse event

5.4 Consultations

5.4.1 Advisory Committee Meeting

No Advisory Committee Meeting was held to address the current submission. Please refer to the original clinical review and VRBPAC transcript for an in depth discussion of the VRBPAC meeting held on 15 November 2012. The immunogenicity and safety data were presented at the time of the original BLA review to the VRBPAC on 15 November 2012. At the conclusion of this meeting, the committee raised concerns that the safety database was insufficient to recommend approval of Heplisav. VRBPAC members voted 13:1 that the data submitted in the BLA adequately demonstrated Heplisav immunogenicity. However, the Committee voted 8:5, with one abstention, that inadequate safety data were available to recommend approval of Heplisav. The VRBPAC also noted that the studies did not evaluate the vaccine in a racially heterogeneous population of subjects who were most likely to benefit from this vaccine, that the studies performed were not adequately balanced in terms of the racial and ethnic groups studied, and that concomitant administration studies were not done.⁷

5.4.2 External Consults/Collaborations

Review of the initial BLA submission in 2012 identified one subject with a potential granulomatous vasculitis adverse event of special interest (AESI). The subject was diagnosed with possible Tolosa-Hunt syndrome, reported as cavernous sinus syndrome, in Study DV2-HBV-16. Additional information was requested in CR letter item #3 and was submitted in STN 125428/0.33, received 18 March 2013. Expert consultation was sought 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. Please see the Appendix for the consultations.

Subject 40-616 was a 69-year-old male Heplisav recipient, with multiple medical issues, who 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. None of the consultants endorsed a definitive causal association between the vaccine and the adverse event.

Reviewer comment: *This case is considered by the clinical reviewer to be a new-onset AESI, the second rare granulomatous vasculitis identified within the safety database.*

In addition, in this review cycle, two experts were consulted regarding the case of Takayasu's arteritis reported in a Heplisav recipient in Study DV2-HBV-23; full review of these consults is found in Section 6.

5.5 Literature Reviewed

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

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 (Protocol DV2-HBV-10; NCT00435812)

A revised CSR for Study DV2-HBV-10 was submitted with the CR on 16 March 2016. The Applicant determined that a revision to Study DV2-HBV-10 was necessary to correct errors in the CSR for this study, which was submitted previously to the BLA in 2012. The Applicant stated that it detected errors in an audit of this study, performed after another regulatory agency's inspections had identified concerns with data quality in a study not submitted to the BLA.

The objectives, study design, immunogenicity endpoints, safety monitoring procedures and safety analysis of Study DV2-HBV-10 were previously addressed in the original BLA review of Heplisav dated 26 February 2013 and are not reviewed here. Please see section 8 for review of the safety information submitted for several subjects in DV2-HBV-10 in response to items in the CR letter.

The submitted revised immunogenicity data for this study were reviewed but are not able to be verified, despite several attempts to verify the changes to the immunogenicity data. The immunogenicity dataset (.xpt file) submitted to support the revised CSR for DV2-HBV-10 does not include newly included subjects, which are necessary for an accurate determination of the revised immunogenicity data. The clinical review team is unable to verify at the time of this review that the revised immunogenicity data submitted in the CR are correct.

Reviewer comment: *The Applicant submitted a master dataset for Study DV2-HBV-10 in amendment 125428/0.68; submitted to FDA on 08 October 2016. This dataset presumably contains the PP population changes between 2012 and 2016. An additional document was also submitted that provides an explanation of the methodology used for preparing the master dataset and the Excel file of the revised PP population, along with more detailed information on how the number of subjects in the revised PP population was derived. We will conduct a complete review of the revised immunogenicity data in the next review cycle.*

6.2 Trial #2

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 (Protocol DV2-HBV-16; NCT01005407)

A revised CSR for Study DV2-HBV-16 was submitted with the Applicant's CR on 16 March 2016. Similar to Study DV2-HBV-10, the Applicant determined that a revision to Study DV2-HBV-16 was necessary to correct errors in the CSR, which was submitted previously to the BLA in 2012. The Applicant detected errors in an audit of Study DV2-HBV-16, performed after another regulatory agency's inspections had identified concerns with data quality in a study not submitted to the BLA.

The objectives, study design, immunogenicity endpoints, safety monitoring procedures and safety analysis of Study DV2-HBV-16 were previously addressed in the original BLA review of Heplisav dated 26 February 2013 and are not reviewed here. Please see section 8 for review of the safety information submitted for several subjects in DV2-HBV-10 in response to items in the CR letter.

The submitted revised immunogenicity data for this study were reviewed but are not able to be verified, despite several attempts to verify the changes to the immunogenicity data. The immunogenicity dataset (.xpt file) submitted to support the revised CSR for DV2-HBV-16 does not include newly included subjects, which are necessary for an accurate determination of the revised immunogenicity data. The clinical review team is unable to verify at the time of this review that revised subject accounting and revised immunogenicity data submitted in the CR are correct.

Reviewer comment: *The Applicant submitted a master dataset for Study DV2-HBV-16 in amendment 125428/0.68; submitted to FDA on 08 October 2016. This dataset presumably contains the correct PP population changes for the non-inferiority and lot consistency PP populations between 2012 and 2016. An additional document was also submitted that provides an explanation of the methodology used for preparing the master dataset and the Excel file of the revised PP populations, along with more detailed information on how the number of subjects in the revised non-inferiority and lot consistency PP populations were derived. We will conduct a complete review of the revised immunogenicity data for this study in the next review cycle.*

6.3 Trial #3

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"

Study Initiation Date (first subject randomized): 18 April 18 2014

Study Completion Date (last subject last visit): 16 October 16 2015

Report Date: 1 March 2016

6.3.1 Objectives

The study objectives as stated by the Applicant are the following:

Primary Objectives

- To evaluate the overall safety of Heplisav with respect to clinically significant adverse events (AEs)
- To demonstrate the non-inferiority of the seroprotection rate (SPR, defined as the percentage of subjects with a serum concentration of antibodies to hepatitis B

surface antigen [anti-HBs] ≥ 10 mIU/mL) induced by Heplisav compared with the SPR induced by Engerix-B at Week 28 in subjects with type 2 diabetes mellitus

Secondary Objectives

- To describe the frequency of new-onset granulomatosis with polyangiitis (GPA) and Tolosa-Hunt syndrome (THS) in Heplisav recipients and Engerix-B recipients
- To describe the frequency of new-onset thrombotic/thromboembolic AEs in Heplisav recipients and Engerix-B recipients
- To describe the frequency of new-onset abnormal thrombotic screens in Heplisav recipients and Engerix-B recipients
- To describe the frequency of new-onset laboratory abnormalities suggesting compromised renal function or renal injury in Heplisav recipients and Engerix-B recipients
- To demonstrate that the SPR at Week 28 induced by Heplisav is statistically significantly higher than the SPR induced by Engerix-B in subjects with type 2 diabetes mellitus, only if it is established that Heplisav is non-inferior to Engerix-B with regard to SPR at Week 28
- To demonstrate that the SPR at Week 24 induced by Heplisav is non-inferior to the SPR at Week 28 induced by Engerix-B in all subjects and in the following subgroups: by age, sex, body mass index (BMI), and smoking status
- To demonstrate that the SPR at Week 24 induced by Heplisav is statistically significantly higher than the SPR at Week 28 induced by Engerix-B in all subjects and in the following subgroups: by age group, sex, BMI, and smoking status, only if it is established that Heplisav is non-inferior to Engerix-B with regard to SPR

Reviewer comment: *In the context of the previously noted safety concerns of vasculitic granulomatous disease and the primary objective of evaluation of overall safety of Heplisav in response to Item 1 in the 22 February 2013 Complete Response Letter, the clinical reviewer considers a description of the occurrence of any new onset systemic granulomatous or vasculitic disease, and the comparison of overall rates of immune-mediated diseases, associated with study vaccination to be critical to the evaluation of vaccine safety. FDA had advised the Applicant that the design of Study DV2-HBV-23 was insufficient to meet the stated primary objective of demonstrating non-inferiority of the immune response in diabetics; thus, the corresponding immunogenicity data are not included in this review. Although a secondary endpoint, immunogenicity in all per protocol population subjects (SPR at Week 24 in Heplisav vaccinated subjects compared to the SPR at Week 28 in Engerix-B vaccinated subjects) is included in this review to mitigate previously stated concerns regarding the quality of the immunogenicity data from Studies DV2-HBV-10 and -16.*

6.3.2 Design Overview

DV2-HBV-23 was a randomized, observer-blinded, active-controlled, multicenter, phase 3 trial in which eligible subjects were randomized in a 2:1 ratio to receive Heplisav or Engerix-B (approximately 5500 Heplisav subjects and 2750 Engerix-B subjects). 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, were to be enrolled. Enrollment was stratified by site, age group (18 to 39, 40 to 70 years), and type 2 diabetes mellitus status. The Heplisav group received a 2-dose series of Heplisav at Weeks 0 and 4 and placebo at 24 weeks.

The Engerix-B group received a 3-dose series of Engerix-B at 0, 4, and 24 weeks. Immunogenicity laboratory assessments were performed at Weeks 0, 24 and 28 and anti-HBsAg antibody level in Heplisav recipients at Week 24 (20 weeks following the second and final dose) was compared to anti-HBsAg antibody level in Engerix-B recipients at Week 28 (4 weeks following the third and final dose).

All subjects were monitored for safety by the collection of medically-attended adverse events (MAEs) reported as occurring through the completion of the trial (Week 56) or early discontinuation. All MAEs reported were further assessed by the investigator for meeting criteria for adverse events of special interest (AESI) and/or serious adverse events (SAEs).

Reviewer comment: *Solicited adverse events and unsolicited adverse events not evaluated by medical personnel were not reported in DV2-HBV-23. For an analysis of these events reported in previous studies, please see the original BLA clinical review.*

A laboratory substudy enrolling 300 subjects randomized 2:1 to receive Heplisav or Engerix-B at two participating sites was planned. This subset of subjects had blood and urine collected at pre-specified time points through Week 56 for safety laboratory assessments of renal function, coagulation, and antiphospholipid antibodies. Baseline assessment also included assessment of genetic factors predisposing subjects to coagulation abnormalities.

Reviewer comment: *In the previous studies, five subjects in the Heplisav group and no subjects in the Engerix-B group, reported pulmonary embolism following vaccination, including one fatal event in a male subject with no risk factors for thrombosis. Based on review of repeat dose toxicity studies, in which rats had interstitial nephritis following Heplisav, FDA requested that Study DV2-HBV-23 incorporate assessment of renal function, including early markers of kidney injury, such as urine microalbumin/creatinine ratio.*

6.3.3 Population

Relevant eligibility criteria included:

- Adults 18 to 70 years of age, inclusive
- No previous receipt of any hepatitis B vaccine
- No history of hepatitis B or human immunodeficiency virus (HIV) infection or positive test for HBsAg, anti-HBs, antibody to hepatitis B core antigen (anti-HBc), or antibody to HIV
- No history of autoimmune disorder
- No receipt of any of the following within the specified time frame prior to the first injection:
 - Any vaccine, systemic corticosteroids (more than three consecutive days), other immunomodulators or immune suppressive medication, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), or any other investigational medicinal agent within 28 days
 - Blood products or immunoglobulin within 90 days
 - Injection of DNA plasmids or oligonucleotide at any time

- Undergoing chemotherapy or expected to receive chemotherapy during the study period; had a diagnosis of cancer within the last five years other than squamous or basal cell carcinoma of the skin
- For the laboratory sub-study: History of venous thrombosis or pulmonary embolism or taking anticoagulants

Reviewer comment: *In order to simulate the “real world” of vaccine delivery and in keeping with the intent of a large-scale phase 3 trial to closely mirror current medical care, DV2-HBV-23 enrollment was not limited to “healthy” adults. Therefore, enrollment exclusions were limited, and subjects with multiple comorbidities were eligible to enroll. Based upon baseline medical conditions, it appears the Applicant was successful in enrolling a population that had more chronic medical conditions as compared to prior studies, and that the proportion of subjects with baseline medical conditions was similar between treatment groups.*

6.3.4 Study Treatments or Agents Mandated by the Protocol

Heplisav: Each 0.5 mL dose contains 20 mcg of recombinant HBsAg subtype adw produced in *Hansenula polymorpha* yeast cells and 3000 mcg of 1018 phosphorothioate oligodeoxynucleotide formulated in an 8 mM sodium phosphate/154 mM sodium chloride/ 0.01% w/w polysorbate 80/pH 7.0 buffer. The placebo was a 0.5 mL commercially available preservative-free, normal saline for injection (Sodium Chloride Injection, USP, 0.9%).

The study included a control group in which subjects were administered a 1 mL dose of Engerix-B, a licensed HBV vaccine, manufactured by GlaxoSmithKline.⁸ Please see the Engerix-B Package Insert for product information.

Subjects were randomly assigned in a 2:1 ratio to receive Heplisav or Engerix-B. Unblinded study personnel used an interactive voice and web response system (b) (4) to obtain a subject number and vial number for each subject.

The subjects and the study personnel conducting clinical safety evaluations were blinded to treatment assignment. Study drug was not packaged or labeled in a blinded manner; therefore, designated study site personnel with no other study responsibilities were unblinded so they could prepare and/or administer the study injections. An unblinded study monitor with no other study responsibilities confirmed drug accountability. Unblinded staff were not involved in assessing safety events and were instructed not to communicate treatment assignments to the personnel responsible for assessing safety.

Reviewer comment: *The planned randomization was deemed adequate by the statistical reviewer. In review of a draft protocol of this study under IND 12692, regarding blinding procedures, FDA noted the Applicant’s proposal to prevent subjects from knowing whether they were receiving 0.5 mL of candidate vaccine or 1.0 mL of Engerix-B by having subjects turn their heads away when vaccinated. FDA raised concerns about potential for unblinding and requested that the Applicant provide the rationale for concluding that this approach would maintain the study blind, or propose another means of blinding subjects to treatment. The Applicant’s rationale was that the difference in volumes was unlikely to be perceived by a subject during injection and that the method of blinding subjects was similar to that used in previous studies, including Studies DV2-HBV-10 and -16. In addition to the subjects themselves, the investigator*

and study staff evaluating the subjects were to remain unaware of the treatment assignment. Based on the reasons stated in the review of DV2-HBV-10 and -16 in the initial BLA submission, this observer-blind approach for HBV-23 was also deemed appropriate.

6.3.5 Directions for Use

Each 0.5 mL dose of Heplisav or placebo and each 1 mL dose of Engerix-B was to be administered into the deltoid muscle.

6.3.6 Sites and Centers

This study was conducted by 40 investigators at 40 centers, all in the United States (US). The study sites and investigators are provided in Table 2 below.

Table 2. Participating clinical sites with number of subjects enrolled by study group into the Safety Population, Study DV2-HBV-23

Site #	Location	Heplisav Group n	Heplisav Group %	Engerix-B Group n	Engerix-B Group %	Total Enrolled n	Total Enrolled %
101	Murray, UT	58	2.1%	118	2.1%	176	2.10%
102	Aurora, CO	46	1.7%	92	1.6%	138	1.65%
103	Mesa, AZ	63	2.3%	125	2.2%	188	2.25%
104	Henderson, NV	52	1.9%	106	1.9%	158	1.89%
105	Chandler, AZ	99	3.6%	198	3.5%	297	3.55%
106	Greer, SC	104	3.7%	207	3.7%	311	3.72%
107	Tempe, AZ	69	2.5%	135	2.4%	204	2.44%
108	Elkhorn, NE	33	1.2%	71	1.3%	104	1.24%
109	Phoenix, AZ	62	2.2%	127	2.3%	189	2.26%
110	Anderson, SC	36	1.3%	74	1.3%	110	1.31%
111	Plano, TX	23	0.8%	47	0.8%	70	0.84%
112	Glendale, AZ	91	3.3%	183	3.3%	274	3.27%
113	Vista, CA	41	1.5%	79	1.4%	120	1.43%
114	Santa Rosa, CA	46	1.7%	92	1.6%	138	1.65%
115	Evansville, IN	49	1.8%	100	1.8%	149	1.78%
116	San Antonio, TX	85	3.1%	172	3.1%	257	3.07%
117	Centennial, CO	35	1.3%	72	1.3%	107	1.28%
118	Council Bluffs, IA	64	2.3%	129	2.3%	193	2.31%
119	Birmingham, AL	73	2.6%	145	2.6%	218	2.61%
120	Anderson, SC	113	4.1%	227	4.1%	340	4.06%
121	Tucson, AZ	52	1.9%	107	1.9%	159	1.90%
122	Chicago, IL*	197	7.1%	389	7.0%	586	7.00%
123	Phoenix, AZ	35	1.3%	67	1.2%	102	1.22%
124	Las Vegas, NV	45	1.6%	90	1.6%	135	1.61%
125	Pinellas Park, FL	109	3.9%	218	3.9%	327	3.91%
126	Cincinnati, OH	82	2.9%	170	3.0%	252	3.01%
128	Edina, MN	57	2.0%	114	2.0%	171	2.04%
129	Dallas, TX	94	3.4%	189	3.4%	283	3.38%
130	Akron, OH	105	3.8%	206	3.7%	311	3.72%

Site #	Location	Heplisav Group n	Heplisav Group %	Engerix-B Group n	Engerix-B Group %	Total Enrolled n	Total Enrolled %
131	Phoenix, AZ	78	2.8%	161	2.9%	239	2.86%
132	Columbus, OH	60	2.2%	117	2.1%	177	2.12%
133	Chandler, AZ	56	2.0%	111	2.0%	167	2.00%
134	Mesa, AZ	105	3.8%	206	3.7%	311	3.72%
135	Colorado Springs, CO	86	3.1%	166	3.0%	252	3.01%
136	Scottsdale, AZ	66	2.4%	137	2.5%	203	2.43%
137	St. Louis, MO	42	1.5%	89	1.6%	131	1.57%
138	Atlanta, GA	62	2.2%	131	2.3%	193	2.31%
139	Fremont, NE	76	2.7%	156	2.8%	232	2.77%
140	Omaha, NE	50	1.8%	101	1.8%	151	1.80%
141	Chandler, AZ	37	1.3%	75	1.3%	112	1.34%
222	Chicago, IL*	45	1.6%	88	1.6%	133	1.59%

Source: Adapted from - BLA 125428/0.42, Module 5.3.5.1, CSR DV2-HBV-23, Appendix 16.1.4

Total proportions may not add up to 100% due to rounding of proportions at individual sites.

* Sites 122 and 222 were the same site under the same investigator, but were assigned two site numbers due to the number of subjects screened.

n = number of subjects

The Applicant provided a list of twenty-four subjects who transferred sites during the study. These subjects were analyzed by the center at which they were originally enrolled and randomized.

Reviewer comment: *The site in Chicago, IL (122 and 222) enrolled more subjects than any other site. The remaining sites enrolled a median of 2.25% of the total vaccinated cohort. Subjects who transferred sites represented a small number of subjects of the total vaccinated cohort and are unlikely to significantly impact immunogenicity outcomes. However, to evaluate whether handling of these transferred subjects influenced or reflected the quality of study conduct and data monitoring, the reviewer recommends clarifying the reasons for transfer and procedures for following these subjects.*

6.3.7 Surveillance/Monitoring

Subjects participated in a screening period up to four weeks prior to first dose and could be rescreened one time if they had equivocal laboratory results or if they were unable to receive vaccination during the screening window. Subjects completed study-specific assessments through clinic visits scheduled at Weeks 0, 4, 24, 28, and 56 and through completion of an internet questionnaire about health care encounters at Weeks 8, 40, and 52. Subjects who reported a medically attended adverse event (MAE) were contacted by telephone to provide relevant information. Otherwise, over the course of the trial, all subjects received a monthly reminder by text message or email to answer questions about health care encounters immediately after they happened.

In most subjects, immunogenicity assessments, but no safety laboratory assessments, were conducted. In the laboratory sub-study, a subset of subjects had blood and urine collected at Weeks 0, 4, 8, 24, and 56 for the following safety assessments: renal function (blood chemistry, creatinine, complete blood count with differential, urine microalbumin, and urinalysis including microscopic), clotting (prothrombin time, partial thromboplastin time), and antiphospholipid antibodies (lupus anticoagulant; anti-cardiolipin immunoglobulin [Ig]G and IgM; and anti-beta2 glycoprotein 1 IgG and IgM). In

addition at Week 0, blood was collected for Protein C, Protein S, antithrombin 3, and genetic testing for factor V Leiden deficiency. Only clinically significant laboratory abnormalities, as determined by the investigator, were to be recorded as MAEs.

Use of any medication during the 28 days prior to first injection through Week 56 or the early discontinuation visit was solicited from each subject and recorded in source documents. However, in the CRF, all concomitant medications through 4 weeks after the last study injection (Week 28) were recorded. After Week 28, only the following medications were entered in the CRF: immunosuppressive medications; immunoglobulins; blood products; vaccines; any medications, including over-the-counter medications, administered for treatment of a MAE, AESI, AIAE, or SAE; and any prohibited medication pre-specified in the protocol.

Reviewer comment: *Concomitant medication monitoring for approximately six months following vaccination may not assist in capturing some immune-mediated events that may follow an indolent course and/or require an extended period of time prior to diagnosis.*

Subjects who reported MAEs that were assessed by the investigator as potential AESIs were referred to an appropriate specialist for assessment. Regardless of the assessment of the specialist, the MAE was subsequently reviewed by an independent Safety Evaluation and Adjudication Committee (SEAC). The SEAC was a blinded committee comprised of two experts in autoimmune diseases and one infectious disease physician, all external to the Applicant and not otherwise involved in the study. The SEAC was responsible for reviewing clinical information on all potential AESIs to determine if the event was autoimmune in etiology. If the event was determined to be autoimmune, the SEAC assessed whether the event was pre-existing or new-onset and whether the event was related to treatment based on a > 50% probability. The SEAC provided adjudication results to the Applicant or its designee and these results were provided to FDA and the DSMB. For selected subjects with a potential autoimmune disorder, autoantibody testing was performed by the central laboratory on selected stored serum samples (typically the Week 0 sample) to determine if the event was autoimmune and pre-existing or new-onset.

Reviewer comment: *FDA reviewed the SEAC charter under IND 12692, as well as the revised SEAC charter and found the revised charter acceptable. As the SEAC Chair had presented for the Applicant at the VRBPAC meeting, FDA requested that the Applicant submit financial disclosure information for the Chair, as well as the other two members of the SEAC. In response, the Applicant submitted financial disclosure information for the SEAC members in which all three members declared no financial interest.*

AIAEs were defined as MAEs not included in the list of AESIs but adjudicated as autoimmune by the SEAC. As no AIAEs were identified, they are not further discussed. As per the protocol and SEAC Charter, only events that were determined by the SEAC to be autoimmune required the SEAC to assess whether the event was new-onset and related to vaccination. The AESI list includes conditions that do not meet a strict definition of autoimmune (evidence of autoantibodies) but may be immune-mediated (for example, Bell's palsy). The SEAC was not required to assess these events for onset or relationship to vaccination.

For subjects who reported a venous thrombotic/thromboembolic event (VTE), such as a deep vein thrombosis (DVT), superficial thrombophlebitis, or pulmonary embolus (PE), the protocol specified additional evaluations. Risk factors predisposing the subject to thrombotic events were collected and subjects were to return to the study site to have the following blood tests performed: Protein C, Protein S, antithrombin 3, genetic test for factor V Leiden deficiency, and antiphospholipid antibodies (lupus anticoagulant; anti-cardiolipin IgG and IgM; and anti-beta2 glycoprotein 1 IgG and IgM). If these samples could not be obtained, stored blood was to be tested for antiphospholipid antibodies.

The study was conducted under the supervision of a DSMB, which was composed of an infectious disease physician, an autoimmune disease expert, and a statistician that was external to the Applicant and were not otherwise involved in the study. The DSMB performed three pre-specified reviews.

Reviewer comment: *The DSMB convened an additional ad-hoc meeting, at the request of the Applicant, to review three myocardial infarctions and two deaths that occurred early in the trial, one of which occurred prior to vaccination. The recommendation after this ad-hoc meeting was to submit all fatal reports and cardiac SAEs to the DSMB on a regular basis throughout the trial, but no changes to the protocol were advised by the DSMB. The meeting minutes from each open session, but not closed session, were submitted to the FDA following each meeting.*

The Applicant used a contract research organization, (b) (4), for monitoring study procedure compliance and for data management. Study sites were monitored by (b) (4) according to GCP.

6.3.8 Endpoints and Criteria for Study Success

Primary Endpoints

- Proportion of subjects with new-onset MAEs
- Proportion of subjects with new-onset SAEs or deaths
- Proportion of subjects with new-onset AESIs
- Proportion of subjects with new-onset AESIs + AIAEs
- SPR at Week 28 in subjects with type 2 diabetes mellitus

Secondary Endpoints

- Proportion of subjects with new-onset GPA or THS
- Proportion of subjects with new-onset thrombotic events
- Proportion of subjects with new-onset abnormal thrombotic screens in the laboratory substudy
- Proportion of subjects with new-onset abnormal renal blood or urine tests in the laboratory substudy
- SPR at Week 24 in Heparisav subjects and at Week 28 in Engerix-B subjects

Secondary immunogenicity endpoints included the following:

- Comparison of the SPR induced by Heparisav at Week 24, to the SPR induced by Engerix-B at Week 28 in all study subjects.

- Comparison of the SPR induced by Heplisav at Week 24, to the SPR induced by Engerix-B at Week 28 for study subgroups by age group, sex, BMI, and smoking status.

For the secondary immunogenicity endpoints, Heplisav was considered to be non-inferior to Engerix-B if the lower limit of the 95% confidence interval (CI) of the difference in SPRs (Heplisav minus Engerix-B SPR) was greater than -10%. This analysis was based on the PP population.

Reviewer comment: *The statistical criteria for determination of non-inferiority between Heplisav and Engerix-B were the same for the primary and secondary immunogenicity endpoints. The Week 24 vs. Week 28 time points for the secondary endpoints for Heplisav and Engerix-B, respectively, were chosen for comparison because previous phase 3 studies showed that the Heplisav SPR peaked at Week 24 and the Engerix-B SPR peaked at Week 28.*

6.3.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Calculations

Agreement regarding the number of subjects enrolled followed a number of discussions with FDA regarding the need to increase the size of the total safety database for this product. The sample size of the trial was estimated to be approximately 8250 subjects, which included approximately 5500 Heplisav subjects and 2750 Engerix-B subjects. Assuming a 10% non-completion rate, this sample size was expected to provide approximately 5000 Heplisav subjects and 2500 Engerix-B subjects available to be evaluated at Week 56. Subjects who discontinued the study early were not replaced.

The Applicant provided an analysis of the probabilities of identifying certain AESIs in a study of 5000 Heplisav recipients. They estimated the rate of AESIs as reported in the Heplisav safety database prior to DV2-HBV-23 was 300/100,000. They concluded that with 5000 Heplisav recipients, they would expect 15 new-onset autoimmune disorders in the Heplisav group, which would rule out an incidence greater than 0.49% with a type I error rate of 5%.

Reviewer comment: *The Applicant estimated their expected rate of AESIs based upon their previous Heplisav database. However, this number may not be accurate because only DV2-HBV-16 included prospective monitoring for AESIs for one-year following vaccination. Additionally, this number does not identify the number of AESIs expected if Heplisav plays no role in the onset or diagnosis of such events. A true baseline of all AESIs is much more complicated to estimate and thus, a comparison of reported events between groups is likely to provide more information.*

The Applicant calculated that a disease with a 0.02% incidence rate could be expected to occur in one subject in a study of 5000 subjects, yielding a 95% CI of 0%, 0.1%. With respect to rare immune-mediated diseases, such as the GPA and THS that were reported in the previous studies, they noted that if the true incidence of these diseases following vaccination is 2/4425, there would be a 90% chance that at least one case of GPA or THS would occur among a study of 5000 Heplisav recipients. The Applicant noted that a population-based incidence of GPA in the United States has not been

reported. In one population-based study, the prevalence of GPA has been reported to be 3 per 100,000 (1:33,000).⁹ The Applicant's analysis of National Hospital Discharge Survey data from 2005 to 2009 found an incidence of GPA of 1.5 per 100,000. Thus, they estimate the incidence of GPA to be between 1.5 and 3 per 100,000 (average = 2.25 per 100,000). Using the average estimated incidence, they calculated an 11% probability that at least one event with a rate of 1 in 44,000 would occur among these 5000 Hecplisav subjects. If the background incidence of these events is 1 in 44,000, they estimated the probability that at least two such events would occur in 5000 subjects is 0.6%.

Reviewer comment: *The sample size necessary to definitively rule out an association between an investigational product and a rare disease is prohibitive in a pre-licensure study.*

Demographics

Descriptive statistics were used to summarize demographic and other baseline characteristics.

Immunogenicity Assessments

The per protocol population was the primary analysis population for all immunogenicity analyses. Both Week 24 and Week 28 SPR and geometric mean concentration (GMC), as well as (95%) confidence limits, were computed in Hecplisav and Engerix-B subjects as a secondary immunogenicity endpoint. Additional sensitivity analyses were performed to account for factors such as diabetes severity, duration, and control. No imputations were made for missing data for the immunogenicity analysis.

Safety Assessments

All safety data were analyzed descriptively and analyses were based on the Safety Population. Summary descriptive statistics were used to describe the incidence of MAEs, AESIs, AESIs + AIAEs, SAEs, and deaths reported through the Week 56 visit. Incidence of new-onset VTE AEs was also summarized by treatment group. The number and percentage of subjects reporting specific concomitant medications and non-study vaccinations during the specified study period were summarized by treatment group.

Reviewer comment: *The protocol specified that 95% confidence interval for MAEs, AESIs, AESIs + AIAEs, SAEs, and deaths could have been constructed by treatment group and, when appropriate, a measure of relative risk between treatment groups could be estimated. However, the Applicant did not provide these analyses as they "decided they were not necessary."*

Changes from baseline laboratory results were summarized at each study visit for each treatment group and shift tables were provided. The proportion of subjects with abnormal test results was summarized by treatment group. Abnormal test results were determined based on the central laboratory reference standards. The Center for Biologics Evaluation and Research (CBER) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials was used for grading the severity of laboratory abnormalities.

6.3.10 Study Population and Disposition

A total of 12,207 subjects were screened. Of subjects screened, 3,883 (32%) were screen failures. In Amendment 125428/0.54, in response to an IR sent on 28 June 2016, the Applicant submitted an additional dataset containing reasons for screen failure. Reasons for screen failure as determined by the reviewer-generated analysis appear in the table below.

Table 3. Reasons for screen failure, screened population, DV2-HBV-23

Reason	n	%
History of hepatitis B or HIV infection or positive test for HBsAg, anti-HBs, anti-HBc, or antibody to HIV	2513	65.6
Other medical condition	434	11.3
Able to comprehend and availability for all required study procedures	339	8.8
History of autoimmune disorder	289	7.5
Previous receipt of hepatitis B vaccine	103	2.7
Able and willing to provide informed consent	70	1.8
Received prohibited medication within 28 days: any vaccine, systemic corticosteroids > 3 consecutive days, other immunomodulators or immune suppressive medication, G-CSF, GM-CSF, or any other investigational medicinal agent	48	1.3
Diagnosis of cancer within the last 5 years, undergoing chemotherapy, or expected to receive chemotherapy	36	0.9
If female, subject is pregnant, nursing, or planning to become pregnant during the trial period	16	0.4
History of venous thrombosis, pulmonary embolism, or taking anticoagulants	12	0.3
History of sensitivity to any component of study vaccines	7	0.2
Woman of childbearing potential not consistently using an acceptable method of contraception or abstinence through Week 28	5	0.1

Source: BLA 125428/0.54, Module 5.3.5.1, Reviewer-generated analysis from dataset ADSF

n number of subjects with inclusion or exclusion criteria

Total % does not equal 100% because subjects may have multiple reasons for screen failure.

Reviewer comment: *The proportion of subjects who failed screening and the primary reasons for screen failure are not unlike other similarly designed vaccine trials.*

Six subjects were randomized but not treated, five subjects randomized to Heplisav and one subject randomized to Engerix-B. The reasons for study discontinuation of these six subjects were consent withdrawn (three subjects randomized to Heplisav, one subject randomized to Engerix-B) and physician decision (two subjects randomized to Heplisav).

Reviewer comment: *The number of subjects who discontinued following randomization and prior to treatment is small and would have been unlikely to significantly impact the immunogenicity outcomes.*

6.3.10.1 Populations Enrolled/Analyzed

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.

The modified Intent-To-Treat (mITT) population was defined as: all randomized subjects who received at least one study injection and had at least one post-injection immunogenicity evaluation. The mITT population was used for supportive and confirmatory immunogenicity analyses.

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 population was the primary analysis populations for all safety analyses.

6.3.10.1.1 Demographics

The table below shows the demographic characteristics in the SP in study DV2-HBV-23.

Table 4. Demographics for the Safety Population, Study DV2-HBV-23

Demographic	Category	Heplisav n = 5587	Engerix-B n = 2781	Total n = 8368
Age	Mean (SD)	50.36 (11.74)	50.37 (11.68)	50.37
	Median	52	52	11.72
	Minimum	18	18	18
	Maximum	71	70	71
Age	18 – 29 years	260 (4.7%)	131 (4.7%)	391 (4.7%)
	30 – 39 years	872 (15.6%)	430 (15.5%)	1302 (15.6%)
	40 – 49 years	1269 (22.7%)	632 (22.7%)	1901 (22.7%)
	50 – 59 years	1765 (31.6%)	895 (32.2%)	2660 (31.8%)
	≥ 60 years	1421 (25.4%)	693 (24.9%)	2114 (25.3%)
Gender	Male	2844 (50.9%)	1391 (50.0%)	4235 (50.6%)
	Female	2743 (49.1%)	1390 (50.0%)	4133 (49.4%)
Race	White	3968 (71.0%)	2007 (72.2%)	5975 (71.4%)
	Black or African American	1461 (26.1%)	696 (25.0%)	2157 (25.8%)
	Asian	57 (1.0%)	38 (1.4%)	95 (1.1%)
	American Indian or Alaska Native	60 (1.1%)	24 (0.9%)	84 (1.0%)
	Native Hawaiian or Other Pacific Islander	14 (0.3%)	7 (0.3%)	21 (0.3%)
	Other	25 (0.4%)	9 (0.3%)	34 (0.4%)
	Unknown	2 (0.0%)	0 (0.0%)	2 (0.0%)
Ethnicity	Hispanic or Latino	521 (9.3%)	239 (8.6%)	760 (9.1%)
	Not Hispanic or Latino	5062 (90.6%)	2541 (91.4%)	7603 (90.9%)
	Unknown	4 (0.1%)	1 (0.0%)	5 (0.1%)

Source: Adapted from - BLA 125428/0.42; Module 5.3.5.1, CSR DV2-HBV-23, Table 10-5, p.60
SD: standard deviation

Subjects vaccinated had a mean age of 50.4 years and were 50.6% male; 71.4% White, 25.8% Black, 1.1% Asian, 1.0% American Indian or Alaska Native; 90.9% not Hispanic, and 9.1% Hispanic. In the Heplisav group, there were slightly higher proportions of men (50.9% Heplisav, 50.0% Engerix-B) and Hispanics (9.3% Heplisav, 8.6% Engerix-B),

and a slightly lower proportion of Asians (1.0% Heplisav, 1.4% Engerix-B) compared with the Engerix-B Group.

Reviewer comment: *Study groups had similar demographics in the safety population and any differences are small and unlikely to impact the outcomes in a clinically significant way. Based on the discussion during the VRBPAC Meeting on 15 November 2012, some Advisory Committee members recommended that the Applicant pursue enrollment of a more diverse study population and enroll greater numbers of certain groups, such as Asians and Hispanics. Asians did not make up a large subpopulation in study DV2-HBV-23.*

Subject demographics for the PP population were similar to that of the safety population and summarized in Table 14.1.2.1.3 of the CSR for DV2-HBV-23. There were no significant differences between these two populations that would have impacted interpretation of safety or effectiveness. One of the enrolled subjects who was excluded from the per protocol population was a 71 year old male subject assigned to the Heplisav group. The two study groups in the PP population had similar proportions of male subjects.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The Applicant presents an analysis of baseline medical and behavioral characteristics of the subjects in DV2-HBV-23 in the CSR and the Clinical Summary of Safety (CSS).

Most subjects reported at least one medical condition: 91.8% of subjects in the Heplisav and 91.1% of subjects in the Engerix-B group. The most commonly reported medical history terms by preferred term (PT) were hypertension (35.4% Heplisav, 34.6% Engerix-B), seasonal allergy (22.5% Heplisav, 23.1% Engerix-B), depression (17.0% Heplisav, 17.0% Engerix-B), osteoarthritis (16.5% Heplisav, 16.1% Engerix-B), gastroesophageal reflux disease (15.6% Heplisav, 15.6% Engerix-B), and hyperlipidemia (15.2% Heplisav, 14.7% Engerix-B).

Reviewer comment: *In terms of distribution of medical history, the randomization appears adequate. In general, the clinical reviewer did not identify any differences likely to be clinically significant. Baseline rates of specific conditions of interest are discussed below and with the description of the appropriate MAEs (see section 6.3.12.2).*

Baseline cardiac medical conditions were examined closely in the Applicant's Summary of Clinical Safety, given the safety findings of DV2-HBV-23 (section 6.3.12.2). The tables below (Tables 5 and 6) summarize the risk factors for cardiovascular disease and pre-existing coronary artery ischemic disease between the two study groups. The reviewer generated an analysis of hypertension and diabetes based on medical history, which were not provided by the Applicant.

Table 5. FDA analysis of number and proportion of subjects with medical history and baseline characteristics indicating increased risk for cardiovascular disease, Safety Population, DV2-HBV-23

Condition or characteristic	Heplisav N=5587 n (%)	Engerix-B N=2781 n (%)
Type 2 Diabetes*	762 (13.6)	381 (13.7)
Diabetes and impaired glucose	800 (14.3)	379 (13.6)

Condition or characteristic	Heplisav N=5587 n (%)	Engerix-B N=2781 n (%)
metabolism by medical history†		
Hypertension‡	2045 (36.6)	985 (35.4)
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)

Source: Adapted from 125428/0.42; Module 2.7.4, Summary of Clinical Safety; Table 2.7.4-27, p. 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

‡ Reviewer-generated analysis using dataset ADMH, defined as subjects with at least one medical history preferred term for Hypertension SMQ narrow, excluding hypertensive diseases of pregnancy, which are presumed to not be current

§ Defined as subjects with at least one medical history preferred term for Dyslipidemia SMQ narrow

Table 6. Number and proportion of subjects with medical conditions at baseline indicating cardiac ischemia, Safety Population, DV2-HBV-23

Condition or characteristic	Heplisav N=5587 n (%)	Engerix-B N=2781 n (%)
At least one baseline medical diagnosis of cardiac ischemia*	211 (3.8)	99 (3.6)
Coronary artery disease	140 (2.5)	65 (2.3)
Myocardial infarction	72 (1.3)	35 (1.3)
Coronary arterial stent insertion	56 (1.0)	27 (1.0)
Coronary artery bypass	47 (0.8)	16 (0.6)
Arteriosclerosis Coronary Artery	19 (0.3)	4 (0.1)
Angina Pectoris	18 (0.3)	12 (0.4)
Ischemic Cardiomyopathy	3 (0.05)	1 (< 0.05)
Myocardial ischemia	3 (0.05)	0
Coronary Artery Occlusion	2 (0.04)	2 (0.1)
Coronary artery stenosis	2 (0.04)	0
Acute coronary syndrome	1 (0.02)	0
Acute myocardial infarction	1 (0.02)	1 (0.04)
Angina unstable	1 (0.02)	1 (0.04)
Arteriospasm coronary	1 (0.02)	0
Prinzmetal angina	1 (0.02)	0
Silent myocardial infarction	1 (0.02)	0
Troponin increased	1 (0.02)	0
Coronary Angioplasty	0	5 (0.2)

Source: Adapted from 125428/0.42; Module 2.7.4, Summary of Clinical Safety; Table 2.7.4-27, p. 84-86

* Defined as subjects with at least one medical history preferred term within the narrow SMQs of Myocardial Infarction and Other Ischemic Heart Disease

There are small differences between study populations in baseline characteristics indicative of increased risk for coronary artery disease. The greatest imbalances are in obesity (48.8% Heplisav, 46.2% Engerix-B), hypertension (36.6% Heplisav, 35.4% Engerix-B), and female \geq 56 years of age (18.4% Heplisav, 19.3% Engerix-B). There are very small differences between study populations in history of specific cardiac ischemic events at baseline, but the number of subjects with at least one of these conditions is balanced at baseline (3.8% Heplisav, 3.6% Engerix-B).

Reviewer comment: *Rates of cardiac risk factors and history of cardiac ischemic disease are similar between groups. The potential effect of these small differences between study groups on the differences noted in cardiac SAEs (section 6.3.12.4) will be assessed after review of additional analyses submitted by the Applicant in the next review cycle.*

The Applicant presents an analysis of subjects in the diabetes group. As per their analysis, HbA1C at baseline, the proportion of subjects with one or more complications of diabetes (84.1% Heplisav, 82.2% Engerix-B), and the proportion of subjects who had diabetes for 5 or more years (66.7% Heplisav, 67.0% Engerix-B) were similar between the treatment groups. Of the diabetic subjects tested at Week 24, 19.2% of Heplisav subjects and 23.3% of Engerix-B subjects had HbA1C levels $<$ 6.5%, 62.0% of Heplisav subjects and 55.7% of Engerix-B subjects had HbA1C levels 6.5% to 9.0%, and 18.9% of Heplisav subjects and 21.1% of Engerix-B subjects had HbA1C levels $>$ 9.0%.

Reviewer comment: *At baseline, diabetic control was the same in both treatment groups. In contrast to baseline measurements, at Week 24, there are slightly more subjects in the Heplisav group with poorly controlled diabetes HgbA1C \geq 6.5% (80.9%) compared to the Engerix-B group (76.7%). This is consistent with an increase in hyperglycemic MAEs reported in the Heplisav group.*

Prior to vaccination, the rates of subjects reporting concomitant medication use in the 28 days prior to vaccination was the same between treatment groups (77.0% Heplisav, 76.9% Engerix-B). Specifically, the rates of the following medication classes, which are indicative of cardiovascular disease, were similar between groups: agents acting on the renin-angiotensin system (25.2% Heplisav, 24.2% Engerix-B); lipid modifying agents (23.6% Heplisav, 23.4% Engerix-B), antithrombotic agents (15.8% Heplisav, 15.7% Engerix-B), drugs used in diabetes (14.2% Heplisav, 13.9% Engerix-B), beta blocking agents (10.4% Heplisav, 10.0% Engerix-B), diuretics (9.7% Heplisav, 8.7% Engerix-B), calcium channel blockers (8.2% Heplisav, 7.6% Engerix-B), anti-hypertensives (1.7% Heplisav, 1.2% Engerix-B), and cardiac therapy (1.3% Heplisav, 1.3% Engerix-B). Other classes of medications which are pertinent to MAE findings were also similar between groups: psychoanaleptics (18.2% Heplisav, 19.6% Engerix-B) and psycholeptics (11.2% Heplisav, 11.2% Engerix-B).

Reviewer comment: *The clinical reviewer identified no clinically significant differences between study groups in class of medication reported at baseline. While there are very small differences, up to 1%, which could indicate more medication use in the Heplisav group, it is unclear how that would influence reporting of MAEs and SAEs. More medication use could indicate that subjects in one group have more medical conditions or greater severity of medical conditions at baseline, or it could indicate that subjects in that group are being treated more aggressively and have better disease control.*

6.3.10.1.3 Subject Disposition

Subject disposition data for Study DV2-HBV-23 showed that the majority of study subjects randomized to the study, completed study treatment. The overall proportion ($\leq 6.5\%$) of subjects who discontinued the study was consistent with the proportions seen in phase 3 studies of Heplisav (Studies DV2-HBV-10 and -16). The most common reason for study discontinuation was loss to follow-up ($\leq 5.7\%$ all groups), followed by withdrawal of study informed consent ($\leq 1.8\%$ all groups). The PP population, used for immunogenicity analysis, comprised approximately 82% of the randomized study population. A summary of subject disposition data is provided in Table 7 below.

Table 7. Subject Disposition, Study DV2-HBV-23

Disposition	Heplisav n (%)	Engerix-B n (%)	Total n (%)
Randomized	5592 (100%)	2782 (100%)	8374 (100%)
Treated	5587 (>99.9%)	2781 (>99.9%)	8368 (>99.9%)
Not treated	5 (<0.1%)	1 (<0.1%)	6 (<0.1%)
Completed Study Treatment ^a	5221 (93.4%)	2606 (93.7%)	7827 (93.5%)
Discontinued Study Treatment	366 (6.5%)	175 (6.3%)	541 (6.5%)
Completed Study ^b	5092 (91.1%)	2567 (92.3%)	7659 (91.5%)
Discontinued Study	500 (8.9%)	215 (7.7%)	715 (8.5%)
Consent withdrawn	100 (1.8%)	39 (1.4%)	139 (1.7%)
Physician Decision	8 (0.1%)	1 (<0.1%)	9 (0.1%)
Pregnancy	2 (1.0%)	2 (0.3%)	20 (0.8%) ^b
Protocol violation	1 (<0.1%)	0	1 (<0.1%)
Subject lost to follow-up	319 (5.7%)	153 (5.5%)	472 (5.6%)
Medically-attended AE	4 (<0.1%) ^c	0	4 (<0.1%)
Non-compliance	7 (0.1%)	1 (<0.1%)	8 (<0.1%)
Other	34 (0.6%)	14 (0.5%)	48 (0.6%)
Death	8 (0.4%) ^d	2 (0.3%) ^e	10 (0.4%)
Per-protocol analysis population	4537 (81.1%) ^f	2289 (82.3%)	6826 (81.5%)
Modified Intent-to-treat analysis population	5278 (94.4%)	2635 (94.7%)	7913 (94.5%)
Safety analysis population	5587 (>99.9%)	2781 (99.9%)	8368 (>99.9%)
Laboratory Safety Substudy	207 (3.7%)	102 (3.7%)	309 (3.7%)

Source: BLA STN 125428/042, DV2-HBV-23, CSR, Table 10-3, page 56, Table 14.1.1.1.

n number of subjects

AE: adverse event

^a Subjects who received three injections.

^b Subjects who had a Week 56 visit.

Reviewer comment: The proportion of subjects who completed a Week 56 visit in both treatment groups is consistent with the Applicant's sample size calculation assumption that 10% of subjects will discontinue prior to study completion. The proportion of subjects that comprised the PP population was similar to that seen in the other two phase 3 studies of Heplisav, reviewed in the original BLA application (approximately 75-88% of the total randomized population). The reasons for subject discontinuation from the study were also similar to those of studies DV2-HBV-10 and -16, with the most common reason in for discontinuation in all three studies being 'lost-to-follow-up'.

The Applicant states that they utilized a vendor to research the status of 271 of 469 subjects considered lost to follow-up, but do not describe how these 271 subjects were chosen. In the 9 September 2016 IR, the FDA asked the Applicant to describe the basis upon which subjects were referred to the vendor and their response will be reviewed in the next review cycle.

Additional analysis of the PP population examined reasons for study exclusion, which are provided in Table 8 below:

Table 8. Reasons for Exclusion, Per Protocol Population, Study DV2-HBV-23

	Heplisav N=5592 n (%)	Engerix- B N=2782 n (%)	Total N=8374 n (%)
PP Population	4537 (81.1%)	2289 (82.3%)	6826 (81.5%)
Total Excluded Subjects	1055 (18.9%)	493 (17.7%)	1548 (18.5%)
Not meeting ≥ one enrollment criteria	67 (1.2%)	36 (1.3%)	103 (1.2%)
Pre-existing autoimmune disorder	39 (0.7%)	23 (0.8%)	62 (0.7%)
Receipt of exclusionary medication/blood product	19 (0.3%)	8 (0.3%)	27 (0.3%)
Other	9 (0.2%)	5 (0.2%)	14 (0.2%)
Mis-stratified by diabetic status/age	26 (0.5%)	10 (0.4%)	36 (0.4%)
Did not receive correct vaccine as randomized	0	0	0
Did not receive all study injections	371 (6.6%)	176 (6.3%)	547 (6.5%)
Vaccine given outside window	164 (2.9%)	76 (2.7%)	240 (2.9%)
Anti-HBs serum sample collected outside four weeks (± 7 days)	190 (3.4%)	86 (3.1%)	276 (3.3%)
No anti-HBs levels obtained at Week 28	431 (7.7%)	188 (6.8%)	619 (7.4%)
Received prohibited concomitant medications	217 (3.9%)	113 (4.1%)	330 (3.9%)
Systemic corticosteroids	209 (3.7%)	112 (4.0%)	321 (3.8%)
Other immunomodulators or immune suppressive medications (exception inhaled steroids)	1 (< 0.1%)	1 (< 0.1%)	2 (< 0.1)
Blood products or immunoglobulin	9 (0.2%)	0	9 (0.1)
DNA plasmids or oligonucleotides	0	0	0
Other investigational medication	0	1 (< 0.1%)	1 (< 0.1%)
Other	0	0	0

Source: BLA STN 125248/042, DV2-HBV-23, CSR, Table 10-2, page 53, Tables 14.1.1.2 and 14.1.1.4.

N number of subjects per treatment group

n number of subjects with each characteristic

Anti-HBs: antibody against hepatitis B surface antigen; DNA: deoxyribonucleic acid

PP Per protocol

Reviewer comment: The reasons provided for exclusion from the PP population are consistent with those seen in Studies DV2-HBV-10 and -16 and deemed reasonable by the clinical reviewer. For Study DV2-HBV-23 the most common reason for exclusion (in decreasing order) was: lack of anti-HBs antibody levels obtained at Week 28, subjects not receiving all study vaccinations, receipt of prohibited concomitant medications, collection of the anti-HBs serum sample outside the specified window, and receipt of vaccination outside the visit window at Week 4. However, pre-existing autoimmune disease or administration of improperly stored vaccine was not a significant reason for exclusion from the PP population, as it was in Study DV2-HBV-10 and -16, respectively.

On 2 November 2016, the clinical review team learned from discussions with the BIMO reviewer that inspections of select Study DV2-HBV-23 sites 122/222 identified data inconsistencies in a subset of randomly selected subjects (25% or 3/12). These subjects were found to have major protocol deviations and were incorrectly labeled as PP subjects. Please see the BIMO review for full details and Section 6.11.3.2., (Secondary Immunogenicity Endpoints) for a further discussion of the implications of the new BIMO finding on the validity of the immunogenicity results for Study DV2-HBV-23.

Of subjects excluded from the PP population, 19.6% of Heplisav subjects and 18.0% of Engerix-B subjects had a major protocol deviation. The most frequent major protocol deviations were visits outside of the visit schedule (for example Week 4 visit occurred out of window), procedures and tests that were not performed according to protocol (for example: anti-HBs serum sample collected outside the pre-specified window), and subjects taking a disallowed medication (for example systemic corticosteroids given for ≥ three consecutive days). A summary of major protocol deviations for the randomized population is provided in Table 9 below.

Table 9. Major Protocol Deviations, Randomized Population, Study DV2-HBV-23

Deviation Category	Heplisav n (%) ^a	Engerix- B n (%) ^a	Total n (%) ^a
Number of randomized subjects	5592 (100%)	2782 (100%)	8374 (100%)
Total protocol deviations	3734	1799	5533
Major protocol deviations	1729 (46.3%)	803 (44.6%)	2532 (45.8%)
Visit Schedule	644 (17.2%)	293 (16.3%)	937 (16.9%)
Procedures/Tests	484 (13.0%)	230 (12.8%)	714 (12.9%)
Disallowed Medications	330 (8.8%)	171 (9.5%)	501 (9.1%)
Investigational Product Administered	82 (2.2%)	34 (1.9%)	116 (2.1%)
Informed Consent	67 (1.8%)	18 (1.0%)	85 (1.5%)
Inclusion/Exclusion Criteria	57 (1.5%)	24 (1.3%)	81 (1.5%)
Other	33 (0.9%)	16 (0.9%)	49 (0.9%)
MAE/SAE	31 (0.8%)	18 (0.9%)	48 (0.9%)
Withdrawal Criteria	1 (< 0.1%)	0	1 (<0.1%)

Source: BLA STN 125248/042, DV2-HBV-23, CSR, Table 10-4, page 57, Table 14.1.5.1.

n number of subjects

MAE medically-attended adverse event; SAE: serious adverse event.

^a Denominators for percentage are the total number of protocol deviations for each column.

Reviewer comment: Since subjects with comorbidities were allowed to enroll in this study, the types of major protocol deviations seen were not unexpected, but more likely reflected the study population enrolled in DV2-HBV-23.

Site Level Unblinding

The CSR for Study DV2-HBV-23 stated that the treatment assignments of several subjects were prematurely known to study personnel who should not have had access to this information, thereby resulting in accidental unblinding of these subjects. There were seven sites involving nine subjects where the study subjects were accidentally unblinded. In addition, the principal investigator at Site 124 was unblinded to treatment assignment on two separate occasions by signing follow-up letters from the unblinded site monitor that contained treatment assignment information on several subjects. This investigator was instructed to restrict further contact with the subjects that were

unblinded and the subinvestigator assumed responsibility for safety assessment and follow-up care.

Reviewer comment: *The clinical reviewer's assessment of the information the Applicant provided in the CSR regarding the handling of accidental unblinding is that it appears reasonable. The handling appears to have been addressed in a way to reduce potential bias.*

Subject Unblinding at the Level of the Applicant/CRO

Also described in the CSR were nine occasions involving 145 subjects where study team personnel at Dynavax and/or the CRO, (b) (4), prematurely received information regarding treatment assignment of several subjects and became accidentally unblinded. These various instances included: access of study personnel to unblinded vial assignment reports, access to the unblinded subject dosing worksheets, and receipt of communications (for example, email) which included unblinded subject information. Based on the total number of randomized subjects, the impact of this excursion was negligible (< 2% of randomized subjects).

Reviewer comment: *The overall impact of this excursion involving 145 subjects, given the large number of subjects enrolled, was minimal. The finding of unblinding in this study suggests potential Quality Control (QC) issues, and the BIMO reviewer has recommended requests for further information to support an assessment be included in the CR letter.*

Preliminary BIMO Inspection Findings of Study DV2-HBV-23, Site 122/222:

The clinical review team was informed by BIMO on 2 November 2016 (see email correspondence Bhanu Kannan 2 November 2016 and 3 November 2016) that the inspection findings for sites 122/222 (n=719 total subject enrollees) indicated that of the total 76 subjects chosen for audit at this site, 15 subjects were classified as being 'lost to follow-up' (LTFU). Of these 15 LTFU subjects, 12 randomly selected LTFU subjects were identified and three of these subjects (25%, 3/12) were further identified as having been incorrectly classified as 'per protocol' population subjects. The three subjects were found to have a major protocol deviation (based on the having an out-of-window Week 28 visit and blood sampling) which should have precluded inclusion into the per protocol population.

Also provided with the preliminary BIMO inspection results, was the BIMO inspector's finding that the protocol deviation log for Study DV2-HBV-23 was maintained as an Excel spreadsheet without any access control or password protection. This finding raises the theoretical concern protocol deviation data could be easily manipulated or changed.

Reviewer comment: *The BIMO inspection finding of incorrect labeling of subject population status in a random sampling of Study DV2-HBV-23 subjects at two study sites and the issue of the protocol deviation excel spreadsheet that was not password protected and in which data could be changed at will and without ability to track who changed the data and when, brings into question whether more pervasive data inconsistencies are prevalent in the datasets for this study. Further recommendations from BIMO regarding additional actions are pending at the time of this review.*

6.3.11 Efficacy Analyses

The efficacy analysis of Study DV2-HBV-23 was an immunogenicity-based effectiveness evaluation focused on the comparison of the SPR between Heplisav and Engerix-B in the general adult population. Subgroup analyses by diabetic status, BMI, or smoking status were not evaluated, as FDA had communicated to the Applicant that this information would not be included in the package insert for Heplisav (pre-BLA meeting dated 25 January 2012, teleconference dated 14 May 2014).

6.3.11.1 Analyses of Primary Endpoint(s)

The Applicant's primary immunogenicity endpoint is not presented or discussed in this clinical review because, as previously communicated to the Applicant, FDA found the design of Study DV2-HBV-23 to be unlikely to meet evaluation of that endpoint.

In addition, specific reasons were provided by FDA why subgroup analysis of Heplisav in diabetics was not warranted for making definitive conclusions regarding effectiveness.

These reasons are summarized as follows:

- Effectiveness of Heplisav was previously established by a non-inferiority comparison to Engerix-B in the general adult population. The differential vaccine effect (Heplisav vs. Engerix-B) between diabetics and non-diabetics (i.e., interaction between vaccine effect and subgroup effect) has not been demonstrated to justify the analysis in the subgroup of diabetics in Study DV2-HBV-23. There was no treatment effect seen and the SPR between diabetics and non-diabetics was similar.
- Without evidence of heterogeneity between diabetics and non-diabetics with respect to vaccine effect of Heplisav compared to Engerix-B, the non-inferiority analysis in diabetics would place too much unjustified emphasis on the diabetic subgroup.
- FDA indicated on several occasions (e.g., pre-BLA meeting) that diabetic immunogenicity data from Study DV2-HBV-23 would not be presented in any section of the package insert.

6.3.11.2 Analyses of Secondary Endpoints

A comparison of the peak SPR of Heplisav at Week 24 with the peak SPR of Engerix-B at Week 28 for all per protocol study subjects was one of several secondary endpoints evaluated in Study DV2-HBV-23. The results of this analysis (see Table 10 below) showed that the SPRs of both study groups were comparable numerically. Because the 95% CI of the difference in SPR between Engerix-B and Heplisav was greater than 10%, Heplisav was shown to be noninferior to Engerix-B.

**Table 10. Secondary Immunogenicity Endpoint Analysis:
Comparison of Peak Seroprotection Rates between Heplisav (Week 24) and
Engerix-B (Week 28), Per Protocol Analysis Population, Study DV2-HBV-23**

Visit	Heplisav ^a SPR (%)	Engerix-B ^b SPR (%)	Estimated Difference in SPR ^c	Non-inferiority Criteria Met? ^e
	(n/N)	(n/N)	(Engerix-B – Heplisav (95%) CI)	(Yes/No)

Visit	Heplisav ^a SPR (%) (n/N)	Engerix-B ^b SPR (%) (n/N)	Estimated Difference in SPR ^c (Engerix-B – Heplisav (95%) CI)	Non-inferiority Criteria Met? ^e (Yes/No)
Week 24/ Week 28	95.4 % (94.8, 96.0) ^c 4176/4376	81.3 % (79.6, 82.8) ^d (1860/2289)	-14.2 (-12.5, -15.9)	Yes

Source: BLA 125248/042, DV2-HBV-23, CSR, Table 11-2, page 68.

CI = Confidence interval, N = number of subjects with non-missing results in the analysis population in the treatment group, n = number of subjects with post-injection anti-HBsAg levels \geq 10 mIU/mL; SPR: Seroprotection rate.

^a Study injections were given at Weeks 0, 4, 24 (placebo).

^b Study injections were given at Weeks 0, 4, 24.

^c 95% CIs were calculated using the two-sided Clopper-Pearson method.

^d The Miettinen and Nurminen method was used to calculate the 95% confidence interval.

^e Noninferiority is supported if the upper bound of the 2-sided 95% CI is $<$ 0.10 (+10%).

Reviewer comment: Although information submitted in a Complete Response that was not specifically requested in the Complete Response Letter is generally not reviewed during the Complete Response review cycle, due to the concerns with the revised immunogenicity data submitted for Studies DV2-HBV-10 and -16, this selected immunogenicity endpoint is included in this review. Other immunogenicity endpoints are not included. Evaluation of peak SPRs for Heplisav and Engerix-B showed no significant difference between the two vaccine groups for all subjects in the PP population, however preliminary BIMO findings of improper inclusion of subjects into the PP population raises quality control and possibly data integrity questions about Study DV2-HBV-23. Although, non-inferiority between these two groups was described in the CSR for this study, the finding of mislabeled PP population subjects demonstrates a similar data inconsistency issue for Study DV2-HBV-23 as seen in Studies DV2-HBV-10 and -16. Therefore, pending the Applicant's response to BIMO comments in the CR letter and further evaluation of the datasets submitted to support the immunogenicity data for Study DV2-HBV-23, no conclusions can be made at this time regarding the immunogenicity of Heplisav in Study DV2-HBV-23.

6.3.11.3 Subpopulation Analyses

Results of subpopulation analyses are not included in this review for reasons previously stated.

6.3.11.4 Dropouts and/or Discontinuations

Data from subjects who dropped out of the study were not imputed. A discussion of subject discontinuations is provided in Section 6.3.10.1.3.

6.3.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.3.12 Safety Analyses

6.3.12.1 Methods

MAEs, SAEs, and AESIs were monitored from screening through Week 56. Solicited AEs and unsolicited, non-medically-attended events were not reported. Adverse events

were assessed through clinic visits (Weeks 0, 4, 24, 28, and 56) and through internet questionnaires about health care encounters at Weeks 8, 40, and 52.

The severity of MAEs and laboratory abnormalities were graded based on “Guidance for Industry: Center for Biologics Evaluation and Research (CBER) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.” All fatal MAEs were to be graded as Grade 5. All MAEs not listed in the CBER toxicity grading scale were graded as follows:

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

The protocol specified that for all MAEs and SAEs, if there was a change in the severity after onset, the event was to be reported as a single entry with the maximum severity grading captured.

Reviewer comment: *Through the course of the review, several AEs were identified that appeared to be the same event but were reported more than once presumably because of a change in the seriousness of the event (MAE to SAE). These events had the same or similar PT and the end date of one was the same as the start date of the next. In some instances, this would be expected to impact event counts, but not subject counts which are presented below. However, when PTs for these events were different (for example chest pain then angina pectoris), this would impact subject counts of specific events. The Applicant was queried regarding this and a response was submitted in 125428/0.68. This response will be reviewed during the next review cycle for its potential impact on the data as well as the extent to which it is reflective of the QC of the study.*

Relationship was assessed by the investigator based on the following definitions:

- | | |
|------------------|--|
| Not Related | Another cause of the event is most plausible; or clinically plausible temporal sequence is inconsistent with the onset of the event and the study treatment administration; or a causal relationship is considered biologically implausible. |
| Possibly Related | An event that follows a reasonable temporal sequence from administration of the study treatment or a known or expected response pattern to the suspected drug, but that could readily have been produced by a number of other factors. |
| Probably Related | An event that follows a reasonable temporal sequence from administration of the study treatment, and there is a biologically plausible mechanism for study treatment causing or contributing to the AE [adverse event], and the event could not be reasonably explained by the known characteristics of the subject's clinical |

state. In addition, the relationship may be confirmed by improvement on stopping the study treatment and reappearance of the event on repeated exposure.

Please see the procedures for assessment of AESIs in section 6.3.7 above.

6.3.12.2 Overview of Adverse Events

Imbalances were noted between study groups in deaths due to all causes, cardiac SAEs (driven by an imbalance in acute myocardial infarction (AMI)), AESIs (in particular, Bell's palsy), and the medically attended event of herpes zoster.

Table 11. Summary of subjects experiencing adverse events during the protocol-specified periods for monitoring for each type of event, Safety Population, Study DV2-HBV-23

Adverse Event	Heplisav N = 5587 n (%)	Engerix-B N = 2781 n (%)
Deaths	25 (0.45)	7 (0.25)
Serious Adverse Events	345 (6.2)	148 (5.3)
Cardiac Serious Adverse Events	51 (0.91)	15 (0.54)
- Acute myocardial infarction	14 (0.25)	1 (0.04)
Adverse Events of Special Interest with SEAC-confirmed diagnoses*	10 (0.18)	1 (0.04)
Adverse events of Special Interest with SEAC-confirmed diagnoses not attributed to another condition by the clinical reviewer†	8 (0.14)	1 (0.04)
- Bell's palsy	5 (0.09)	1 (0.04)
Medically Attended Events	2569 (46.0)	1286 (46.2)
- Herpes zoster	38 (0.7)	9 (0.3)

Source: Adapted from BLA STN 125428/0.42, DV2-HBV-23, CSR 12.2, p. 79

* Number is based on SEAC's assessment of events, but is slightly different from the summary results presented by the Applicant in the CSR, as they exclude some events with an alternative cause and not others. No events were determined by the SEAC to be related, so all events regardless of SEAC-adjudicated etiology are captured here.

† Number is based on AESI events with SEAC-confirmed diagnosis (as in the row above) but does not include subjects with events that the SEAC and clinical reviewer attributed to another cause.

Reviewer comment: *In the opinion of the clinical reviewer, the greater proportions of subjects who received Heplisav and reported deaths, cardiac SAEs, AMI, and AESIs are clinically significant given the degree of the imbalance and the potential severity of the adverse events. Please see a full discussion of these events below.*

Medically-Attended Adverse Events

The rate of MAEs reported from vaccination through Week 56 study visit was approximately 46% in both study groups. The most common MAEs (>1%) in the Heplisav group are presented in the table below.

Table 12. Number and percent of subjects reporting common (>1%) medically attended adverse events from vaccination through Week 56 by treatment group, 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%)

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

Reviewer comment: *The most commonly reported MAEs were common complaints in an adult population and were reported at similar rates between study groups.*

The table below shows the events that occurred in at least 0.2% in the Heplisav group and at at least twice the rate of the Engerix-B group. Preferred terms that are likely to represent the same or very similar events are considered together.

Table 13. Number and percent of subjects reporting medically attended events from vaccination through Week 56 at a rate of at least 0.2% in the Heplisav group and at at least twice the rate of the Engerix-B group, Safety Population, Study DV2-HBV-23

Preferred Term	Heplisav N = 5587 n (%)	Engerix-B N = 2781 n (%)
Herpes zoster	38 (0.68%)	9 (0.32%)
Atrial fibrillation	16 (0.29%)	3 (0.11%)
Drug hypersensitivity	15 (0.27%)	3 (0.11%)
Bipolar and Bipolar I Disorder	15 (0.27%)	2 (0.07%)
Acute myocardial infarction	14 (0.25%)	1 (0.04%)
Fungal infection	13 (0.23%)	2 (0.07%)
Hordeolum	11 (0.20%)	2 (0.07%)
Ingrowing nail	11 (0.20%)	2 (0.07%)

Source: Reviewer-generated analysis from BLA STN 125428/0.42, Study DV2-HBV-23, dataset ADAE.

N number of subjects in each treatment group

n number of subjects reporting event

Imbalances are noted between study groups, with a higher proportion of subjects who received Heplisav reporting events, in several potentially significant events: herpes zoster, atrial fibrillation, drug hypersensitivity, and bipolar/bipolar 1 disorder. Please see section, 6.3.12.4 for a discussion of the imbalance in SAEs of AMI, all of which were assessed by investigators as SAEs, atrial fibrillation (MAEs), and bipolar disorder.

Reviewer comment: *It is possible that the imbalance in herpes zoster occurred by chance. As per the CDC, the incidence of herpes zoster is approximately 4 per 1,000 (0.4%) annually age-adjusted to the US population, or 10 per 1,000 (0.1%) in those 60 years and older.¹⁰ The incidences reported in both groups are within this range. However, it is theoretically possible that an agent that affects TLR9 could affect interaction between varicella zoster virus, a double stranded DNA virus, and TLR9. The timing of zoster events following the last active dose is as follows: 7 Heplisav subjects (18%) and one Engerix-B subject (11%) within one month, 5 Heplisav subjects (13%) and 4 Engerix-B subjects (44%) from 1-3 months. The remainder of subjects, and a majority of Heplisav subjects (68%), reported zoster greater than three months from the last active vaccination.*

Several of the unbalanced events from the table above are likely to have occurred by chance because 1) they are common and non-serious events, 2) analyses combining them with other very similar events eliminated the imbalance, and/or 3) based on the current body of knowledge, the clinical reviewer is not aware of a biologically plausible relationship between these events and the vaccine. All MAEs of drug hypersensitivity were attributed to other medications and none were considered related by investigators. In addition, hypersensitivity, including seasonal and environmental allergies was more common in Engerix-B subjects compared to Heplisav subjects. There was no imbalance between treatment groups when all fungal infections were considered. Because of the noted imbalances, and the potential for clinically significant morbidity if increased rates of herpes zoster and drug sensitivity were actually associated with Heplisav, the clinical reviewer recommends asking the Applicant for their assessment of imbalances in these two preferred terms and any biologically plausible mechanism contributing to the differences between study groups.

Additional information for subject 102-046 who reported only one MAE, diaphragmatic paralysis, will also be requested.

The table below shows the events that occurred in at least 0.2% in the Engerix-B group and at at least twice the rate of the Heplisav group.

Table 14. Number and percent of subjects reporting medically attended events from vaccination through Week 56 at a rate of at least 0.2% in the Engerix-B group and at at least twice the rate of the Heplisav group, Safety Population, Study DV2-HBV-23

Preferred Term	Heplisav N = 5587 n (%)	Engerix-B N = 2781 n (%)
Tooth infection	17 (0.30%)	17 (0.61%)
Exostosis	6 (0.11%)	14 (0.50%)
Actinic keratosis	11 (0.20%)	12 (0.43%)
Haemorrhoids	11 (0.20%)	11 (0.40%)
Eczema	9 (0.16%)	10 (0.36%)
Pyrexia	8 (0.14%)	9 (0.32%)
Otitis externa	9 (0.16%)	9 (0.32%)
Inguinal hernia	5 (0.09%)	8 (0.29%)
Localized infection	8 (0.14%)	8 (0.29%)
Arthropod sting	3 (0.05%)	8 (0.29%)

Preferred Term	Heplisav N = 5587 n (%)	Engerix-B N = 2781 n (%)
Ear pain	7 (0.13%)	7 (0.25%)
Folliculitis	6 (0.11%)	7 (0.25%)
Concussion	5 (0.09%)	7 (0.25%)
Glucose tolerance impaired	4 (0.07%)	7 (0.25%)
Musculoskeletal chest pain	7 (0.13%)	7 (0.25%)
Pleurisy	2 (0.04%)	7 (0.25%)
Vertigo positional	3 (0.05%)	6 (0.22%)
Rectal haemorrhage	4 (0.07%)	6 (0.22%)
Eye infection	5 (0.09%)	6 (0.22%)
Upper limb fracture	6 (0.11%)	6 (0.22%)
Hypomagnesemia	2 (0.04%)	6 (0.22%)
Temporomandibular joint syndrome	5 (0.09%)	6 (0.22%)

Source: Reviewer-generated analysis from BLA STN 125428/0.42, Study DV2-HBV-23, dataset ADAE.

N number of subjects in each treatment group

n number of subjects reporting event

Reviewer comment: A majority of the preferred terms noted above are not generally considered serious conditions and are relatively common. The possible exception to this assessment is pleurisy. None of the events of pleurisy was assessed by investigators as serious. There was one additional subject in the Heplisav group who reported pleuritic chest pain, which was considered serious. Taking into account the randomization ratio and the established safety record of Engerix-B, it is the assessment of the clinical reviewer that the imbalance in most, if not all, of the events in Table 14 occurred by chance. Furthermore, for some preferred terms, if similar preferred terms, which may represent the same entity, are considered, the imbalance is diminished (for example eczema).

In the 56-week study period, 902 subjects in the Heplisav group (16.1%) and 422 subjects in the Engerix-B group (15.2%) had MAEs assessed as Grade 3. In the 56-week study period, 58 subjects in the Heplisav group (1.0%) and 45 subjects in the Engerix-B group (1.6%) had MAEs assessed as possibly or probably related by the investigator.

Reviewer comment: *The rates of Grade 3 MAEs and of MAEs assessed as related were similar or lower in the Heplisav group compared to the Engerix-B group.*

Venous thromboembolism (VTE)

In the integrated safety review of the initial BLA submission in 2012, five subjects who had received Heplisav were identified who reported pulmonary embolism (PE), including one fatality in a 46 year-old man without risk factors. The remaining four subjects had at least one risk factor for thrombophilia. No subjects who had received Engerix-B reported pulmonary embolism. Cases of deep vein thrombosis (DVT) were balanced between the study groups.

As a result, VTE was monitored closely in DV2-HBV-23 and subjects with a qualifying event had further laboratory work-up for genetic risk factors for thrombosis and antiphospholipid antibodies. As only venous, and not arterial, events were previously noted to be imbalanced, the Applicant specified in the protocol and a letter to

investigators that only venous thrombotic and thromboembolic events were to be categorized as new-onset thrombotic events and assessed further. In the protocol, DVT and PE are noted as examples; in the CSR thrombophlebitis superficial, venous thrombosis, phlebitis superficial, and thrombosis are also included. One subject was identified by the Applicant who had an MAE of DVT that was misclassified in the datasets as not a VTE. The clinical reviewer identified an additional subject in the datasets who received Heplisav and reported an MAE with a preferred term of phlebitis superficial that was not categorized as a VTE. Including these events, twelve events of VTE were reported in 12 subjects in the Heplisav group (0.21%) and 9 events of VTE were reported in 7 subjects in the Engerix-B group (0.25%). Three Heplisav recipients and two Engerix-B recipients reported PE.

The Applicant reports that all subjects who reported a VTE had at least one risk factor predisposing them to hypercoagulation, with the exception of one Engerix-B subject. This includes genetic mutations that were identified through study-specified thrombophilia assessments. Laboratory evaluation for thrombophilia was assessed in all subjects reporting VTE. The Applicant did not provide a summary of these findings, or their interpretation of abnormalities in the CSR.

Reviewer comment: *In DV2-HBV-23, subjects reporting PE and other VTE events were balanced between treatment groups. The reviewer agrees with the assessment that all subjects who received Heplisav and reported VTE had risk factors for hypercoagulability, with the possible exception of the subject described below. The ADLB dataset was reviewed for laboratory assessments of thrombophilia in these subjects. Other than genetic mutations, abnormal results were those that could be affected by anticoagulation – protein C and S activity and lupus anticoagulant screen, confirmatory, and ratio tests. We will ask the Applicant to provide their assessment of these thrombophilia panels and to clarify why the subject reporting phlebitis superficial was not considered a VTE.*

One subject in the laboratory sub-study also reported a PE. Subject 140-099 was a 65 year-old man with a slightly elevated lupus anticoagulant screen at baseline (42.6 seconds, normal range 27 – 42), normal confirmatory test, elevated baseline prothrombin time (16.9 seconds, normal 9.7 – 12.3), normal PTT, and normal genetic risk factors and anti-phospholipid antibodies. The subject reported an acute myocardial infarction complicated by an LV thrombus 64 days following the second Heplisav injection and was treated with warfarin. At Week 24, the lupus anticoagulant screen increased to 73 seconds and the confirmatory test was elevated at 48.9 seconds (normal range 28-38). Approximately seven months after the hospitalization for the myocardial infarction and 285 days after the second Heplisav injection, the subject experienced SAEs of pulmonary embolus and a recurrence of the left ventricular thrombus. The thrombotic screen tests at the time of the pulmonary embolus, and 284 days following the second dose of Heplisav reported an additional event of LV thrombus and a PE.

Please also the narrative of a subject who received Heplisav and reported a VTE that was assessed as related in section 6.3.12.4.

Reviewer comment: *Further information regarding subject 140-099's SAE of AMI was requested in the 9 September 2016 IR and will be reviewed at a later date. We will ask the Applicant to clarify what they consider the subject's hypercoagulable risk to be,*

because it is not clear that an LV thrombus in the setting of a myocardial infarction (MI) would qualify as a risk factor for VTE.

Renal MAEs

Based upon repeat dose toxicity studies of the adjuvant in rats, showing diffuse proximal tubular degeneration, and limited follow-up periods in several previous clinical studies it was recommended that urinalyses, urinary microalbumin studies and serum chemistries be included in DV2-HBV-23. In the original integrated summary of safety (ISS), there was one SAE of renal failure identified in the Heplisav groups and none in Engerix-B groups.

In DV2-HBV-23, acute renal failure (ARF) was reported in 18 subjects in the Heplisav group (0.32%) and in six subjects in the Engerix-B group (0.22%). Of these subjects, ARF SAEs occurred in four Heplisav recipients and three Engerix-B recipients. Chronic renal failure was reported by 12 subjects in the Heplisav group (0.21%) and three subjects in the Engerix-B group (0.11%). All of these subjects, except for one Engerix-B subject, had baseline medical conditions that could predispose to renal failure. Two of the events with a preferred term of chronic renal failure in the Heplisav group were SAEs. Renal failure, unspecified was reported in three subjects in the Heplisav group (0.05%) and one subject in the Engerix-B group (0.04%), in which it was serious.

Please see section 6.3.12.6 for a discussion of the results of the laboratory substudy relating to renal function.

Reviewer comment: In HBV-23, there appears to be a small imbalance in reports of chronic renal failure and less so in acute renal failure between study groups, with more subjects in the Heplisav group reporting MAEs. Relationship to study vaccine is possible, with the toxicity findings in rats suggesting a possible mechanism, but not definite. Previous studies, as well as HBV-23, did not identify significant imbalances in between groups in reports of acute or chronic renal failure SAEs. Subjects in DV2-HBV-23 did report more medical conditions indicative of cardiovascular disease at baseline than prior study populations (section 8.2.2), and this was balanced between treatment groups. This could predispose subjects in HBV-23 to renal injury by vaccination or other factors. In the 9 September 2016 IR, the FDA requested additional information on subject 130-219 who reported an SAE of “end-stage renal disease” 10 days following dose 2 of Heplisav of only seven days duration, in order to evaluate this event.

6.3.12.3 Deaths

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

Table 15. Fatal adverse events, Total 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						

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
Cardiac						
50	M	Acute coronary syndrome*	1	7	(b) (6)	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						

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
44	M	Craniocerebral injury†	1	17	(b) (6)	N
55	M	Toxicity to various agents†	2	99		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 clearly due to overdose or injury.

‡ Initial event of chronic obstructive pulmonary disease exacerbation leading to hospitalization and tracheostomy, which led to pneumonia and acute respiratory failure, began six days following Dose 2.

§ Alcohol and drugs contributed.

Nine deaths in the Heplisav group and three deaths in the Engerix-B group were clearly due to 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%) died due to a medical issue. Of deaths due to a medical issue, there was one non-injury, non-poisoning death within one month of vaccination 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 medical deaths within 90 days in the Heplisav group and three in the Engerix-B group. Deaths due to events in the SOC of cardiac disorders occurred in eight Heplisav recipients (0.14%) and three Engerix-B recipients (0.11%).

Reviewer comment: *The rate of death due to medical causes in the Heplisav group is twice the rate in the Engerix-B group. There is no evidence of a close temporal relationship between a majority of these deaths and study vaccination. However, a difference in mortality due to medical causes is concerning. Subjects were randomized to the two treatment groups and an analysis of baseline medical characteristics demonstrates similar baseline conditions and cardiac risk factors between groups. Despite the notable imbalance in AMI, only slightly more subjects in the Heplisav group died of cardiac causes compared to the Engerix-B group. Please see the narratives and discussion of whether this assessment is accurate below. The following SOC's are also imbalanced, but with only one death each in the Heplisav group and none in the Engerix-B group: respiratory (without drug and alcohol contribution), infectious (hepatitis C), and hepatobiliary (non-alcoholic steatohepatitis). In the 9 September 2016 IR, the FDA asked the Applicant to provide any additional analyses they conducted to evaluate this imbalance.*

Brief narratives for deaths of probable or possible cardiac origin are presented here.

Subject 130-084 was a 50-year-old man with a relevant medical history of colon cancer, hypertension, dyspnea, mitral valve prolapse and prior mitral valve replacement surgery, chronic obstructive pulmonary disease (COPD), coronary atherosclerosis, cardiomyopathy, left ventricular hypertrophy, and alcohol and cocaine abuse. He was found dead at home (b) (6) days after his first injection of Heplisav with no sign of

trauma. The cause of death per the death certificate was “acute coronary syndrome, secondary to atherosclerosis” with cardiomyopathy, left ventricular hypertrophy and alcohol abuse as contributory factors. Autopsy results were unavailable (PT = acute coronary syndrome).

Subject 131-091 was a 69-year-old man with a relevant medical history of hypertension, edema, chronic renal failure, congestive heart failure, COPD, acute respiratory failure, supplemental oxygen, abdominal aortic aneurysm, neuropathy and smoking. He was found dead in his home (b) (6) days after his second injection of Heplisav. The cause of death listed in the death certificate was acute myocardial infarction due to atherosclerosis. An autopsy was not performed (PT = acute myocardial infarction).

Subject 112-311 was a 57-year-old man with hypertension, type 2 diabetes mellitus, diabetic peripheral neuropathy, microalbuminuria, acute kidney injury, and diabetic gastroparesis who was found dead in his home. An autopsy determined that the subject died as a result of hypertensive cardiovascular disease (b) (6) days after his second Heplisav injection. Yellow atherosclerotic plaques were seen in the left anterior descending artery. Toxicology testing was positive for alcohol and cyclobenzaprine, but it was determined this did not contribute to his death.

Subject 132-082 was a 63-year-old man with hypertension and depression who was found dead on the living room floor (b) (6) days after dose 2 of Heplisav. An external exam determined the death was due to hypertensive heart disease.

Subject 138-012 was a 58 year-old woman with medical history of obesity and hypertension who died in her sleep (b) (6) days following dose 2 of Heplisav. Autopsy was performed and demonstrated hypertensive cardiovascular disease, focal coronary atherosclerosis, severe pulmonary congestion, cerebrovascular disease with a small lacunar infarct in left basal ganglia, hepatomegaly and macrovesicular steatosis, and glomerulosclerosis. The cause of death was reported as hypertensive cardiovascular disease with (morbid) obesity noted as a contributing factor.

Subject 133-120 was a 71-year-old woman with obesity, hypertension, type 2 diabetes mellitus, stroke, and high cholesterol, who died from a cardiac arrest (b) (6) days after her dose 2 of Heplisav. A death certificate confirmed that the subject died of a cardiac arrest which was due or was a consequence of the subject’s medical history of diabetes. An autopsy was not performed.

Subject 122-613 was a 47-year-old man with a relevant medical history of type 2 diabetes, peripheral vascular disease, gangrene left leg, left leg below the knee amputation and right leg edema. (b) (6) days after his second dose of Heplisav, the subject experienced a fatal myocardial infarction and died in the hospital. Neither a death certificate nor autopsy results were available (PT = myocardial infarction).

Subject 104-152 was a 56-year-old woman with depression and possible alcohol abuse who was found unresponsive at home (b) (6) days after dose 2 of Heplisav. She was noted to be pale with bruising on her upper extremities. She was transported to an emergency department where she underwent resuscitative efforts that were ultimately unsuccessful. Her final diagnoses included cardiopulmonary arrest, gastrointestinal

bleed, and thrombocytopenia. A death certificate was unavailable and an autopsy was not performed.

Reviewer comment: *A clear cause of death is not known. The narrative is suspicious for physical abuse, though this is not specifically stated. In the opinion of the clinical reviewer, given the limited information, the totality of the evidence available suggests this is unlikely to be primarily cardiac in nature.*

Subject 119-318 was a 61 year-old woman with medical history of enlarged heart, depression, and anxiety who died (b) (6) days following dose 2 of Heplisav. The Applicant has no information regarding the cause of death. The subject had been considered lost to follow-up. Her death was discovered through the reengagement program.

Subject 119-290 was a 52-year-old woman with a medical history of headaches, depression, anxiety, and insomnia per study records. Additional history of hypertension, bipolar disorder, and heavy smoking was provided in the subject's medical and coroner's records. The subject was found dead (b) (6) days after dose 2 of Heplisav, sitting on her couch at home with no signs of foul play, alcohol, or drug abuse. The Applicant reports that the initial report of this event was Death – accidental overdose. The preferred term was changed to Death when it was determined that no autopsy results would be available.

Engerix-B

Subject 135-070 was a 52-year-old man with a relevant medical history of tobacco and marijuana use who was found down in a parking lot (b) (6) days after his first injection of Engerix-B. He died after unsuccessful resuscitative efforts with ventricular fibrillation arrest due to acute myocardial infarction listed as the cause of death. An autopsy determined that the cause of death was atherosclerotic cardiovascular disease (PT = myocardial infarction).

Subject 119-175 was a 48 year-old man with a medical history of hypertension, gout, and alcohol abuse who was found dead in the bed of a motel room. An empty beer can and an empty pint of vodka were found on the floor, as well as signs of tobacco and possible marijuana use. No autopsy was performed but a chest x-ray was consistent with pulmonary edema. Toxicology results included blood ethanol 0.32 gm/dL, vitreous ethanol 0.45 gm/dL, and other drugs of abuse. The coroner determined the cause of death to be hypertensive heart disease with contributory factors of cocaine, heroin, and ethanol use.

Reviewer comment: *This event is suspicious for alcohol poisoning contributing to, if not causing death.*

Subject 130-392 was a 70 year-old man with relevant medical history of type 2 diabetes mellitus, hypertension, dyslipidemia, atherosclerosis, coronary artery disease, patent foramen ovale, congestive heart failure, transient ischemic attack, anemia, and COPD (diagnosed on-study) who reported a cough, progressing to weakness, nausea, and vomiting, for which he was admitted. He had a bandemia of 25. Shortly after admission, he was found unresponsive. During the hospitalization, he was diagnosed with aspiration pneumonia, cerebrovascular accident, sepsis, acute renal failure, and gastrointestinal bleed. He was eventually transferred to a nursing home, where he was

found unresponsive while eating dinner in cardiopulmonary arrest and died. The cause of death per the death certificate was cardiorespiratory arrest due to chronic respiratory failure due to a cerebrovascular accident. No autopsy was performed.

Reviewer comment: *The information regarding all of these deaths is very limited, with the exception of subject 135-070. This subject received Engerix-B and had a documented cardiac arrhythmia, clinical evidence of an AMI on EKG, and an autopsy supporting this diagnosis. For all other events subjects were found dead and may or may not have had an autopsy. However, the most likely cause of sudden death in the absence of evidence of other causes (for example, other major or terminal medical conditions, illicit drug use, foul play) is cardiac. Most of these deaths may be presumed to be cardiac in nature, with the following possible exceptions. Subject 104-152, in the Heplisav group, appears unlikely to have a cause of death that is primarily cardiac; subject 119-175, in the Engerix-B group, had a significant blood alcohol level that at least contributed to his death; subject 130-392, in the Engerix-B group, had a prolonged hospital course with multiple SAEs suggesting a primarily respiratory cause of death. Additionally, subject 119-290 in the Heplisav group may have died due to a cardiac cause as it is not clear from the narrative why overdose was initially suggested. If the noted revisions are made to remove subjects that have an alternative plausible cause of death other than cardiac, eight subjects in the Heplisav group (0.14%) and one subject in the Engerix-B group died of a potential cardiac cause (0.03%).*

The imbalance in mortality and possible imbalance in cardiac deaths, noted between the study groups could be due to chance. If, on the other hand, it were due to an effect of the vaccine, such as an inflammatory response, the mechanism is not clear. In addition, this effect would have to be sustained for several months as a majority of the excess deaths, particularly cardiac, were reported at greater than 200 days post-vaccination in the Heplisav group.

6.3.12.4 Nonfatal Serious Adverse Events

Overall, SAEs were reported in 345 Heplisav subjects (6.2%) and 148 Engerix-B subjects (5.3%). Non-fatal SAEs were reported in 325 Heplisav subjects (5.8%) and 142 Engerix-B subjects (5.1%).

The most commonly reported SAEs for the Heplisav group from vaccination through Week 56 are presented in the table below.

Table 16. Number and percentage of subjects reporting the most commonly reported treatment-emergent SAEs (≥ 4 subjects) from vaccination through Week 56 in the Heplisav group, 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)
Cerebrovascular accident	7 (0.13)	3 (0.11)

Preferred Term	Heplisav n (%)	Engerix-B n (%)
Atrial fibrillation	6 (0.11)	3 (0.11)
Cardiac congestive failure	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)
Cholecystitis	5 (0.09)	2 (0.07)
Sepsis	5 (0.09)	1 (0.04)
Toxicity to various agents	5 (0.09)	1 (0.04)
Diabetic ketoacidosis	5 (0.09)	1 (0.04)
Depression	5 (0.09)	1 (0.04)
Asthma	5 (0.09)	1 (0.04)
Hypertension	5 (0.09)	3 (0.11)
Hypertensive heart disease	4 (0.07)	1 (0.04)
Cholelithiasis	4 (0.07)	4 (0.14)
Gastroenteritis	4 (0.07)	1 (0.04)
Urosepsis	4 (0.07)	2 (0.07)
Convulsion	4 (0.07)	1 (0.04)
Transient ischemic attack	4 (0.07)	1 (0.04)
Bipolar I disorder	4 (0.07)	0
Calculus ureteric	4 (0.07)	2 (0.07)
Renal failure acute	4 (0.07)	3 (0.11)
Pneumothorax	4 (0.07)	1 (0.04)
Deep vein thrombosis	4 (0.07)	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

Treatment-emergent SAEs reported in at least 0.05% of subjects in the Heplisav group (three subjects) and at at least twice the rate of the Engerix-B group were: acute myocardial infarction (0.25% Heplisav, 0.04% Engerix-B), bipolar and bipolar 1 disorder (0.13% Heplisav, 0.04% Engerix-B), acute respiratory failure (0.11% Heplisav, 0.04% Engerix-B), depression and depression suicidal (0.11% Heplisav, 0.04% Engerix-B), sepsis (0.09% Heplisav, 0.04% Engerix-B), toxicity to various agents (0.09% Heplisav, 0.04% Engerix-B), diabetic ketoacidosis (0.09% Heplisav, 0.04% Engerix-B), asthma (0.09% Heplisav, 0.04% Engerix-B), cardiac arrest (0.05% Heplisav, 0% Engerix-B), bronchitis (0.05% Heplisav, 0% Engerix-B), and gunshot wound (0.05% Heplisav, 0% Engerix-B). When acute respiratory failure is considered with respiratory failure and respiratory arrest, SAE rates are similar between groups (0.13% Heplisav, 0.14% Engerix-B). The imbalance in cardiac SAEs is discussed in the section below.

Reviewer comment: Bipolar disorder SAEs and MAEs and depression SAEs are reported more commonly in the Heplisav group compared to the Engerix-B group. Prior to study enrollment, rates of medical histories of bipolar/bipolar 1 disorder (2.5% Heplisav, 2.2% Engerix-B), depression/major depression (17.4% Heplisav, 17.6% Engerix-B), and any history in the system organ class (SOC) of psychiatric disorders (30.9% Heplisav, 31.8% Engerix-B), were similar between groups. Elevated expression of TLRs, including TLR9, in peripheral blood mononuclear cells has been reported in

subjects with depression.¹¹ It is also possible these differences were seen by chance, particularly given that they are not uncommon.

Sepsis is reported at a slightly higher rate in the Heplisav group compared to the Engerix-B group. TLR9 plays an integral role in fighting bacterial infections. However, per the adverse events reported, each of the subjects in the Heplisav group had an alternative plausible cause for sepsis and most had only a weak temporal association. SAEs in the SOC of infections and infestations were not imbalanced between groups.

An imbalance in diabetic ketoacidosis (DKA) SAEs is noted, as well as an imbalance in MAEs of impaired fasting glucose and elevated glycosylated hemoglobin, with subjects in the Heplisav group reporting more events of poor glycemic control than Engerix-B subjects. The reason for this is unclear, but corresponds with differences in HbA1C noted at Week 28 between the groups. It is not clear whether these differences could have contributed to the increase in AMI observed between groups.

We will ask the Applicant for their assessment of imbalances in bipolar and depression, sepsis, and DKA, and any biologically plausible mechanism that may be contributing to the differences between study groups.

The imbalance in asthma SAEs most likely happened by chance because: SAEs for COPD were slightly more commonly reported in Engerix-B recipients, MAEs for asthma and related events were balanced, and there was no close temporal relationship of asthma SAEs with study vaccination (one event was reported seven days following vaccination, the remainder were at three weeks or beyond).

Four SAEs in three subjects in the HEPLISAV group (0.05%) were assessed as related by investigators: one pregnant subject with intrauterine growth restriction in two twin infants and Ebstein's anomaly in one twin (see Section 9.1), electrophoresis protein abnormal, DVT. Four SAEs in four subjects in the Engerix-B group (0.14%) were assessed as related by investigators: Ebstein's anomaly, complex partial seizures, pulmonary embolism, and DVT. The narrative for the two non-pregnancy related SAEs follows.

Subject 117-125 was a 67-year-old man with a past medical history of COPD, emphysema, basal cell carcinoma, umbilical hernia, rosacea, and osteoarthritis of the right hand. Approximately three months after the second dose of Heplisav, he reported "throbbing of the hands," which is reported as resolved one month later. The subject had an abnormal serum protein electrophoresis nine months after the second dose of Heplisav. Abnormal results included immunoglobulins 2.1 g/dL (reference range 0.5 - 1.4 g/dL), IgG 1460 mg/dL (reference range 653 – 1310 mg/dL), and IgM 1140 mg/dL (reference range 57 – 230 mg/dL). The subject's laboratory results included normal values for alpha 1 globulin, alpha 2 globulin, beta globulin, IgA, and albumin. Laboratory notes reported that the "M-protein concentration was 0.93 g/dL, unchanged since [3 months previously]" and "quantitative immunoglobulins were essentially unchanged since last measured [4 months previously]." Hematocrit of 37.8% (normal 42-54) and monocytes 19.3% (2-11) were also noted. It was unclear why the serum protein electrophoresis was obtained. It was discovered the subject had been participating in an observational trial of COPD. Per the subject, there was no study medication administered; only x-rays and lab work were obtained. The subject informed the site that the throbbing in hands was due to "protein in blood." No other MAEs are reported aside

from a lipoma and lipoma removal. No final diagnosis, end date, or outcome is known. The site made multiple attempts to obtain source documents without success. The narrative states the subject will have additional follow-up in January 2016.

Reviewer comment: *The subject has an M-protein, elevated IgG and IgM, anemia, and a monocytosis. There are multiple inconsistencies in the narrative regarding the dates of the protein electrophoresis testing. There are two subjects who reported multiple myeloma following vaccination (one SAE) and two additional subjects who reported monoclonal gammopathy of undetermined significance (MGUS) in the HEPLISAV group. No subjects in the Engerix-B group reported these events. The incidence of MGUS in men and women at age 50 is estimated to be 120 per 100,000 and 60 per 100,000 population, respectively.¹² Therefore 2-3 reports would not be unexpected in this population. The annual incidence of multiple myeloma in the US is approximately 4 to 5 per 100,000 (0.0004%). Two reports is somewhat higher than might be expected in this population ($2/5587 = 0.04\%$). Further information will be requested from the Applicant regarding the events of multiple myeloma and the follow-up of the event of abnormal serum protein electrophoresis.*

Subject 126-234 was a 46-year-old African-American woman with a relevant medical history of a basilar artery clot in 2007 (reported in hospital notes). The subject was hospitalized 72 days after receiving the second dose of study vaccine after having experienced a syncopal episode followed by slurred speech. Evaluation by CT and MRI demonstrated that the subject had an acute cerebellar stroke. She was treated with a heparin drip and bridging to warfarin. During hospitalization she complained of right upper extremity pain. A B-mode ultrasound at that time showed a free floating clot in the internal jugular vein while being on a heparin drip. Lifelong anticoagulation at INR > 2.5 was recommended. Five days later, she was diagnosed with an acute deep vein thrombosis in the right internal jugular vein and an acute superficial venous thrombosis in the right proximal basilic veins. Factor V Leiden testing was negative. The narrative states that during the hospital course coagulation profile was negative except for deficiencies in proteins C and S. The investigator assessed the stroke as serious and as not related to the study vaccine. The investigator assessed the deep vein thrombosis as serious and as possibly related to the study vaccine. Thrombophilia assessment performed three months later, on anticoagulation, showed elevated lupus anticoagulant and low protein C and S activity.

Reviewer comment: *While this subject appears hypercoagulable following vaccination, she does have risk factors for thrombotic events. She reportedly had a history of a prior basilar artery clot that was not recorded in her study medical history. Her hospitalization for stroke also puts her at risk for thrombotic events. Lupus anticoagulant and protein C and S activity can be affected by anticoagulation. Other antiphospholipid antibody testing was negative three months following the event. Two SAEs and one MAE of VTE reported in subjects in the Engerix-B group were assessed by investigators as possibly related.*

Cardiac SAEs

While rates of MAEs in the SOC of cardiac disorders was similar between treatment groups (1.88% Heplisav, 1.62% Engerix-B), rates of cardiac SAEs were more frequent in the Heplisav group compared to the Engerix-B group (0.9% Heplisav, 0.5% Engerix-B). This imbalance was most notable in reports of the SAE of acute myocardial infarction

(AMI) in 14 subjects in the Heplisav group (0.25%) and one subject in the Engerix-B group (0.04%). An imbalance in the MAEs, but not SAEs, of atrial fibrillation was also noted, with reports occurring more frequently in the Heplisav group. An overview of all cardiac SAEs is shown in the table below.

Table 17. 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)
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

The Applicant presented an analysis of all events in the Medical Dictionary for Regulatory Activity (MedDRA) standard medical query (SMQ) narrow for myocardial infarction (MI), in an effort to categorize all events which are likely to represent AMI or acute cardiac ischemic disease, but may have been reported with a different PT. The table below summarizes the SAEs in this SMQ reported in DV2-HBV-23.

Table 18. Number of subjects with treatment-emergent myocardial infarction serious adverse events (MedDRA SMQ Narrow) 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
Acute myocardial infarction	14	1
Angina unstable	1	0
Coronary artery occlusion	1	1
Myocardial infarction	2	1
Total Subjects with at least one event	19 (0.34%)	3 (0.11%)

Source: Adapted from BLA STN 125428/0.040, CSR DV2-HBV-23, Table 12-17, p. 106.

N number of subjects in each treatment group

n number of subjects reporting event

Brief narratives for the events with a PT in the narrow SMQ for MI are presented here based upon narratives provided by the Applicant. CRFs for all of these events were not submitted in the 16 March 2016 IR and were requested, along with narratives and CRFs for all cardiac SAEs and any additional analyses of the noted imbalances in the 9 September 2016 IR. CRFs for the below events will be reviewed together in the next review cycle. Narratives of deaths due to MI are presented in section 6.3.12.3 (subjects 130-084, 131-091, 122-613, 135-070).

Heplisav

Subject 141-110 was a 61-year-old woman with a relevant medical history of chest pain, and hypertension who experienced a non-ST elevation myocardial infarction two days after the second injection of Heplisav, which was confirmed by cardiac catheterization (PT = acute myocardial infarction).

Subject 106-312 was a 65-year-old woman with a relevant medical history of type 2 diabetes, dyslipidemia, hypertension, coronary artery disease, heart palpitations, and sleep apnea. Twenty-four days following dose 1 of Heplisav she was seen by a cardiologist for three days of worsening heart palpitations and was prescribed isosorbide mononitrate. A percutaneous coronary intervention was attempted on an unknown date in the same month as dose 2, but was unsuccessful. The subject discontinued the isosorbide mononitrate due to side effects. Three weeks following dose 2 she informed the site she was scheduled for cardiac catheterization. Five weeks after dose 2, a cardiac nuclear perfusion scan performed showed ischemic changes. She underwent a cardiac catheterization, which demonstrated multi-vessel coronary artery disease and total occlusion of her third obtuse marginal artery. Four cardiac stents were placed. The Applicant conservatively considers the onset of this event to be 14 days after the first injection of Heplisav as the date of the first catheterization is unknown (PT = coronary artery occlusion).

Subject 113-011 was a 68-year-old woman with a relevant medical history of COPD, hyperlipidemia, coronary artery disease, and tobacco use who reported an inferior myocardial infarction, followed by non-sustained ventricular tachycardia 51 days following the second dose of Heplisav (PT = myocardial infarction).

Subject 134-373 was a 64-year-old man with a relevant medical history of hyperlipidemia, hypertension, and tobacco use who reported an ST elevation myocardial infarction 61 days after his second injection of Heplisav (PT = acute myocardial infarction).

Subject 112-090 was a 53-year-old man with a relevant medical history of hypertension, hyperlipidemia, type 2 diabetes, morbid obesity, sleep apnea, multiple prior abdominal surgeries, and alcoholism. He was admitted to the hospital with abdominal pain, diarrhea, a partial small bowel obstruction experienced, and acute kidney injury due to dehydration and diarrhea. He was treated medically and improved. On hospital day 3, he experienced a non-ST elevation myocardial infarction 63 days after his second injection of Heplisav. A cardiac catheterization showed multi-vessel disease and three stents were placed. (PT = acute myocardial infarction).

Subject 140-099 was a 66-year-old man with a relevant medical history of hypertension, coronary artery disease post-percutaneous intervention one year prior to study enrollment, and tobacco use. The subject experienced an ST elevation myocardial infarction 64 days after his second injection of Heplisav (PT = acute myocardial infarction).

Reviewer comment: *The narrative for this event could not be located in the 16 March 2016 CR submission. The subject went on to report SAEs of acute systolic heart failure, pulmonary embolism, and LV thrombus, for which a narrative is available, 284 days after dose 2 (discussed in section 6.3.12.2). The CSR and submitted narrative suggests this AMI was complicated by an LV thrombus. The narrative for the AMI was requested in the 9 September 2016 IR.*

Subject 126-206 was a 68-year-old man with a relevant medical history of coronary artery disease, prior MI with cardiac stent placement, hypertension, high cholesterol, sleep apnea on continuous positive airway pressure, deep vein thrombosis, Factor V Leiden mutation (unknown at study enrollment), and paroxysmal atrial fibrillation. He experienced an acute myocardial infarction with cardiogenic shock, requiring percutaneous intervention, intra-aortic balloon pump, and left ventricular assist device placement, 84 days after his second injection of Heplisav (PT = acute myocardial infarction).

Subject 122-174 was a 56-year-old man with a relevant medical history of hypertension, gout, hypercholesterolemia, septic shock, deep venous thrombosis, paroxysmal atrial fibrillation, morbid obesity, and prior tobacco use. He had multiple hospitalizations for urosepsis, atrial fibrillation, and latent tuberculosis (rule out active tuberculosis). The narrative states the subject lived in a shelter. He was admitted for unstable angina 95 days after his second injection of Heplisav, reporting intermittent chest pain for the previous three weeks. A perfusion scan showed a reversible/partially reversible defect, but a cardiac catheterization showed “no significant coronary artery disease.” He had multiple subsequent hospitalizations, including for dyspnea and mycobacterium avium intracellular complex infection (PT = unstable angina).

Reviewer comment: *Based on the narrative, which states the cardiac catheterization did not show significant disease, this most likely does not represent an MI or unstable angina.*

Subject 139-037 was a 39-year-old woman with a relevant medical history of tobacco use, obesity, asthma, and hypertension. The subject experienced a non-ST elevation myocardial infarction 173 days after her second injection of Heplisav (PT = acute myocardial infarction).

Subject 103-189 was a 47-year-old man with a relevant medical history of hyperlipidemia, sleep apnea, hypertension, obesity, and low testosterone (taking testosterone). He experienced a non-ST elevation myocardial infarction 175 days after the second injection of Heplisav. Troponin-1 was elevated to 11.48 ng/mL and cardiac catheterization showed signs of a recent ruptured plaque in the proximal left anterior descending and medical management was recommended (PT = acute myocardial infarction).

Subject 101-154 was a 70-year-old woman with a relevant medical history of obesity and dyslipidemia who reported a non-ST elevation myocardial infarction 207 days after the dose 2 of Heplisav. She received a catheterization, but no percutaneous intervention, and was treated medically (PT = acute myocardial infarction).

Subject 122-992 was a 53-year-old man with a relevant medical history of prior heroin addiction, hypertension, and prostate cancer, diagnosed prior to vaccination. He was discontinued from treatment at Week 4 when the site became aware of his prostate cancer. He experienced an ST-elevation myocardial infarction 294 days after the first injection of Heplisav (PT = acute myocardial infarction).

Subject 115-076 was a 69-year-old man with a relevant medical history of obesity, type 2 diabetes, hypertension, hyperlipidemia and prior tobacco use. He was taking phentermine beginning three years prior to study enrollment. The narrative reports the subject was seen by his PCP twice since study start for chest pressure, diagnosed as indigestion. These events are not reported as MAEs. He reported chest pain, was found have paroxysmal ventricular tachycardia and atrial fibrillation with rapid ventricular response. He was placed on anti-arrhythmics and multiple attempts at cardioversion were unsuccessful. He was then diagnosed with a non-ST elevation myocardial infarction 308 days after the second injection of Heplisav. Cardiac catheterization showed severe single-vessel coronary artery disease with thrombus, requiring thrombectomy and percutaneous intervention. Subsequently, he had a cardiac arrest and an implantable cardiac defibrillator was implanted. He recovered. (PT = acute myocardial infarction).

Subject 101-118 was a 63-year-old man with a relevant medical history of dyslipidemia, obesity, hypertension, coronary artery disease with two prior percutaneous interventions with stent placement. The narrative also notes a prior myocardial infarction. He experienced an ST elevation myocardial infarction 318 days after the second injection of Heplisav. He received cardiac catheterization with stent placement (PT = acute myocardial infarction).

Subject 130-045 was a 64-year-old woman with a relevant medical history of type 2 diabetes, hypertension, obesity, peripheral vascular disease, sleep apnea, and chronic kidney disease. She experienced a non ST-elevation myocardial infarction 318 days after her second injection of Heplisav, confirmed by cardiac catheterization (PT = acute myocardial infarction).

Subject 121-050 was a 61-year-old man with a relevant medical history of hypertension, low testosterone (on testosterone), and hypercholesterolemia who experienced an ST-elevation myocardial infarction 328 days after the second injection of Heplisav, confirmed by cardiac catheterization (PT = acute myocardial infarction).

Engerix-B

Subject 112-291 was a 66-year-old man with a relevant medical history of hypertension, hyperlipidemia, type 2 diabetes, obesity. He had a syncopal episode and was diagnosed with a non-ST elevation myocardial infarction 113 days after his third injection of Engerix-B. He underwent a six-vessel coronary artery bypass graft (PT = acute myocardial infarction).

Subject 138-102 was a 55-year-old man with a relevant medical history of angina due to possible arterial blockage, dyslipidemia, and former alcohol and cocaine dependency. As part of the evaluation for knee surgery the subject had a cardiac catheterization that showed multi-vessel disease. Nine days later and 202 days following the third dose of Engerix-B, the subject reported chest pain and underwent coronary artery bypass grafting (CABG) (PT = coronary artery occlusion).

Reviewer comment: *With the exception of the subject with “unstable angina” and a cardiac catheterization demonstrating no abnormalities, the clinical reviewer considers the other events acute coronary ischemic events. Three fatal events reported as myocardial infarction by the investigator and/or medical examiner in the Heplisav group, were reported in which the subject was found dead with no or unavailable autopsy (see section 6.12.2). One of these events occurred one week following dose 1. All subjects reported medical conditions that are risk factors for coronary artery disease, including history of coronary artery disease, hypertension, diabetes, hyperlipidemia, smoking, age, and medications that could increase the risk of cardiac events. However, the Applicant has indicated that this population is somewhat representative of a real-world population that might be expected to receive the vaccine. A safety signal, indicated by an imbalance between treatment groups, requires careful evaluation to determine the risk-benefit of the vaccine in this population.*

There was one additional subject (105-059), a 54 year-old woman who reported an SAE of AMI during the screening period prior to vaccination and is also not included in the table above. This subject was treated with balloon angioplasty, recovered, and received two doses of Heplisav beginning thirteen days after the event onset. The only other MAE she reported was pharyngitis.

There were three additional subjects who reported a non-serious MAE in the SMQ narrow for MI who are not included in the table above. One Heplisav subject (128-042) reported an MAE of MI 112 days following the first injection of Heplisav of one day duration and coded as treatment-emergent in the datasets. In the CSR, on page 106,

the Applicant reports that this event was actually a history of MI and not an acute treatment-emergent event. 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.

Based upon the table above and narratives, excluding the Heplisav subject who had no significant disease on cardiac catheterization, treatment-emergent SAEs of MI were reported in 18 Heplisav subjects (0.32%) and 3 Engerix-B subjects (0.11%). As per the statistical reviewer, the relative risk is 2.99 (95% CI 0.96, 17.83). All subjects had risk factors for cardiovascular disease and/or prior known cardiovascular disease. Narratives and CRFs were submitted for 12 of 22 subjects with SAEs identified by the SMQ Narrow for MI with the DV2-HBV-23 CSR. Narratives without CRFs were submitted for all but one of the additional subjects identified by this SMQ in Module 2.7.4. Narratives were not submitted for the 3 subjects with non-serious MAEs identified by the same SMQ.

Subjects identified in the Heplisav group who reported myocardial infarction ranged in age from 39 to 69 years; fifteen were male (68%). Subjects in the Engerix-B group ranged in age from 52 to 65 years; all were male. The table below shows the timing of the events of AMI in each arm.

Table 19. Timing of Treatment-emergent myocardial infarction SAEs (MedDRA SMQ Narrow) with respect to last active dose by treatment group, Safety Population, Study DV2-HBV-23

Time Interval	Heplisav N = 5587 n	Heplisav Days of Onset following last active dose	Engerix-B N = 2781 n (%)	Engerix-B Days of Onset following last active dose
1 week	1	2	0	-
> 1 week - 30 days	2	7†‡, 13‡	1	12†
> 30 - 90 days	6	53, 57†, 61, 63, 63, 84	0	-
> 90 - 180 days	3	96*, 173, 174	1	114
> 180 days	7	207, 287†, 294, 308, 318, 318, 328	1	202

Source: Reviewer-generated analysis from BLA STN 125428/0.42, Module 3.5.3.1, dataset ADAE for DV2-HBV-23

N number of subjects in each treatment group

n number of subjects reporting event

* Event of unstable angina likely does not represent a myocardial infarction.

† Fatal event

‡ Following Dose 1

There may be a small cluster of events at 30-90 days following vaccination with Heplisav. Events during this time occur at a slightly higher rate than would be expected if all events were evenly distributed by length of observation time. In the first three months following any vaccination, there are nine SAEs of MI in the Heplisav group compared to one in the Engerix-B group.

Reviewer comment: *There is an imbalance in myocardial infarction. As per the statistical reviewer, the relative risk (RR) of MI in the Heplisav group = 2.99 (95% CI 0.96, 17.83). While the 95% CI crosses 1, the lower bound very close to 1 and a high*

upper bound is suggestive of an increased risk. This was a randomized study, with similar demographics and cardiac medical conditions between the groups at baseline. In the opinion of the clinical reviewer, this imbalance is a potentially clinically significant safety signal.

Given the degree of the imbalance, the seriousness of the event, and the potential for this product to be given to a population with similar risk factors, a thorough evaluation of this imbalance is necessary to assess the risk benefit profile of the vaccine. Review of the additional CRFs not submitted in the 16 March 2016 submission is required to accomplish this. Differences were also observed between treatment groups in cardiac SAEs overall. FDA also considers review of all of these events necessary to assess cardiac risk.

FDA requested the additional narratives and CRFs for all cardiac SAEs, as well as two subjects in the Engerix-B group (122-631, 125-359) who reported non-serious MAEs that may indicate MI, in the 9 September 2016 IR. The Applicant responded to this IR on September 26, 2016, and these narratives will be reviewed following issuance of a CR. Further information on the three subjects who reported non-serious MAEs in the narrow SMQ of MI will also be requested, as well as narratives and CRFs for subjects with an SAE of chest pain or non-cardiac chest pain. For the purposes of further describing the imbalance for this review, the remainder of the analyses for MI is based upon the SAEs in the SMQ narrow for MI. Final conclusions as to which events are AMIs may change based upon review of the additional information.

In addition to the SAEs of MI, 16 subjects in the HEPHISAV group (0.29%) reported 16 MAEs of atrial fibrillation, of which six were SAEs (0.11%). Three subjects in the Engerix-B group (0.11%) reported four MAEs of atrial fibrillation, each subject reporting at least one serious event (0.11%). Subjects in the group who reported atrial fibrillation were 50 to 70 years of age and reported the event onset on day 8 to 327 after the last active injection. Subjects in the Engerix-B group were 59 to 67 years of age and reported the event onset on day 47 to 189 days after the last active injection. Two subjects in the group reported the onset within two weeks of the last active injection compared to none in the Engerix-B group.

Reviewer comment: *We will ask the Applicant for their analysis of the differences in MAEs of atrial fibrillation between treatment groups.*

Of note, because of the cardiac findings and the previous imbalance in PE, events of stroke due to ischemic causes were evaluated. As per the ADAE dataset, 17 subjects who received HEPHISAV (0.30%) and 8 (0.29%) subjects who received Engerix-B reported an MAE of stroke/TIA (PTs of cerebrovascular accident, embolic stroke, ischemic stroke, lacunar infarction, thalamic infarction, thrombotic stroke, and transient ischemic attack). When considering SAEs, 15 subjects who received HEPHISAV (0.26%) and five subjects who received Engerix-B (0.18%) reported an SAE with one of these PTs. Six HEPHISAV subjects (0.11%) and one Engerix-B subject (0.04%) reported an SAE with one of these PTs within three months of vaccination.

Reviewer comment: *The rate of stroke SAEs within three months of vaccination in the HEPHISAV group exceeded the rate reported in the Engerix-B group, though the numbers are very small. Given that the pathogenesis of myocardial infarction, stroke, and venous*

thrombotic events, may overlap, we will ask the Applicant to provide the narratives and CRFs for these events, in order to assess the risk-benefit profile of the vaccine.

In the 9 September 2016, the FDA also requested additional information for subject 105-314 who reported an SAE of COPD six days following dose 1 of Heplisav and for subject 125-113 who reported an SAE of lung cancer.

Concomitant Medications

All concomitant medications were entered into the CRFs from 28 days prior to vaccination through Week 28 and select concomitant medications (immunosuppressive medications; immunoglobulins; blood products; vaccines; any medications, including over-the-counter medications, administered for treatment of a MAE, AESI, AIAE, or SAE; and any prohibited medication pre-specified in the protocol) were collected from Week 28 through Week 56. As discussed in section 6.3.10.1.2, no clinically significant differences were noted in baseline medication use. The Applicant did not provide a specific analysis of concomitant medication use after vaccination. The below analyses are reviewer-generated.

A similar proportion of subjects in each treatment group reported concomitant medication use or change through both Week 28 (49.3% Heplisav, 49.4% Engerix-B) and through Week 56 (56.8% Heplisav, 57.0% Engerix-B). The subjects in each treatment group reported a similar average number of new or changed concomitant medications (3.2 Heplisav and 3.3 Engerix-B through Week 28; 4.4 Heplisav and 4.4 Engerix-B through week 56). The table below shows the number and proportion of subjects reporting new or changed concomitant medication of select medication classes.

Table 20. FDA-generated analysis of number and proportion of subjects reporting new or changed concomitant medications in medication classes potentially used to treat cardiac conditions or adverse events of special interest, Safety Population, Study DV2-HBV-23

Medication Class	Through Week 28 Heplisav N = 5587 n (%)	Through Week 28 Engerix-B N = 2781 n (%)	Through Week 56 Heplisav N = 5587 n (%)	Through Week 56 Engerix-B N = 2781 n (%)
Agents acting on the renin-angiotensin system	170 (3.0%)	88 (3.2%)	240 (4.3%)	113 (4.1%)
Analgesics	645 (11.5%)	341 (12.3%)	907 (16.2%)	492 (17.7%)
Antibiotics and chemotherapeutics for dermatological use	42 (0.8%)	12 (0.4%)	68 (1.2%)	21 (0.8%)
Antihypertensives	23 (0.4%)	13 (0.5%)	34 (0.6%)	16 (0.6%)
Anti-inflammatory and antirheumatic products	409 (7.3%)	202 (7.3%)	570 (10.2%)	290 (10.4%)
Antipsoriatics	1 (0.02%)	0	1 (0.02%)	0

Medication Class	Through Week 28 Heplisav N = 5587 n (%)	Through Week 28 Engerix-B N = 2781 n (%)	Through Week 56 Heplisav N = 5587 n (%)	Through Week 56 Engerix-B N = 2781 n (%)
Antithrombotic agents	113 (2.0%)	42 (1.5%)	194 (3.5%)	76 (2.7%)
Beta blocking agents	90 (1.6%)	36 (1.3%)	142 (2.5%)	55 (2.0%)
Calcium channel blockers	63 (1.1%)	31 (1.1%)	101 (1.8%)	45 (1.6%)
Cardiac therapy	28 (0.5%)	18 (0.7%)	53 (1.0%)	25 (0.9%)
Corticosteroids for systemic use	302 (5.4%)	156 (5.6%)	463 (8.3%)	243 (8.7%)
Corticosteroids, dermatological preparations	55 (1.0%)	44 (1.6%)	88 (1.6%)	62 (2.2%)
Diuretics	76 (1.4%)	39 (1.4%)	109 (2.0%)	51 (1.8%)
Drugs used in diabetes	180 (3.2%)	93 (3.3%)	266 (4.8%)	133 (4.8%)
Immune sera and immunoglobulins	1 (0.02%)	0	2 (0.04%)	1 (0.04%)
Immunosuppressants	2 (0.04%)	0	2 (0.04%)	0
Lipid modifying agents	160 (2.9%)	77 (2.8%)	225 (4.0%)	108 (3.9%)

Source: Reviewer-generated analysis from BLA STN 125428/0.42, Module 5.3.5.1, dataset ADCM of Study DV2-HBV-23

There were no striking differences between study groups in select medication classes potentially used to treat cardiac conditions or AESIs through Week 28 or Week 56. Antibiotics for dermatologic use were reported more frequently in Heplisav recipients. It is possible that certain dermatologic AESIs may be treated as infections initially. However, corticosteroids for dermatologic use were reported more frequently in Engerix-B recipients. Antithrombotic agents, which include aspirin used for cardio-protection, and beta-blocking agents are reported at slightly higher rates in subjects who received Heplisav compared to subjects who received Engerix-B. Aspirin use in this class was reported by 1.8% of Heplisav subjects and 1.4% of Engerix-B subjects.

Reviewer comment: *This analysis did not identify any safety concerns with regard to medications, such as anti-inflammatories, that could potentially be used to treat AESIs prior to diagnosis. There are slight imbalances in antithrombotic agents, including aspirin, and beta-blockers, which, in the context of the cardiac events observed in this study, may be supportive evidence of an imbalance in cardiac events.*

6.3.12.5 Adverse Events of Special Interest (AESI)

61 subjects reported at least one potential new-onset AESI that was referred to the SEAC for evaluation. As per the CSR, the Applicant reports 65 events in these 61 subjects; the datasets and the Adverse Events Listings Table 16.12.6.1 shows 68 events evaluated by the SEAC in 61 subjects. Thirty-nine subjects who received Heplisav (0.70%) reported 41 events and 22 subjects who received Engerix-B (0.79%) reported 27 events.

Reviewer comment: *The Applicant will be asked to clarify this discrepancy.*

A summary of the findings of the SEAC adjudication and the clinical reviewer's findings appear below. These are followed by a table listing the individual potential AESIs

referred to the SEAC and narratives for cases where there was some disagreement between the SEAC and the clinical reviewer, additional information is being requested, or diagnoses may not yet be definitive.

The following is a summary of SEAC adjudications:

- No events were related to study vaccination
- Four events in four subjects in the Heplisav group were new-onset autoimmune events – alopecia areata (subject 108-013), ulcerative colitis (136-200), polymyalgia rheumatica (126-038), and hypothyroidism (136-149)
- Five events of Bell's palsy (VIIth cranial nerve palsy) in the Heplisav group and one in the Engerix-B group were not considered autoimmune events by the SEAC, but were new in onset. FDA considers Bell's palsy an AESI.
- One AESI of 6th nerve palsy (134-064) in the Heplisav group was adjudicated by the SEAC (and 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, as per the SEAC, and thus, the SEAC did not consider the events an AESIs – rheumatoid arthritis (102-163), Takayasu's arteritis (131-109), 6th nerve palsy (subject 106-271), and Sjogren's syndrome and Reynaud's phenomenon in the same subject (132-154).
- As a result, the Applicant and the SEAC determined that there were nine confirmed new-onset AESIs in the Heplisav group (Bell's palsy in five subjects, alopecia areata, ulcerative colitis, polymyalgia rheumatica, and hypothyroidism) and one new-onset AESI in the Engerix-B group (Bell's palsy).

Reviewer comment: *The SEAC's blinded assessment using strict criteria for diagnosis of autoimmune disease determined that there was an imbalance in AESIs between treatment groups (0.16% Heplisav, 0.04% Engerix-B)). It is not entirely clear why the Applicant includes some events and excludes others from this count. In the summary of new-onset AESIs and AIAEs, on page 88 of the CSR, the Applicant neglects to include the AESI of diplopia, which was determined by the specialist and the SEAC to be due to a third cranial nerve palsy, secondary to diabetes. This event was reported in a subject who also reported Bell's palsy and does not change their final count of nine subjects in the Heplisav group and one subject in the Engerix-B group. They also do not appear to include the 6th cranial nerve palsy that they determined was attributed to diabetes. However, by this logic, it is unclear why they continue to include the event of hypothyroidism in this count, when the SEAC has attributed this to papillary thyroid cancer. They may have included this event because the SEAC considers it autoimmune.*

In conclusion, the reviewer understands that the SEAC confirmed the diagnoses of 11 events that appear on the AESI list in 10 subjects in the HEPLISAV group and one event in one subject in the Engerix-B group (0.18% Heplisav, 0.04% Engerix-B, RR = 4.98, 95% CI 0.85, 128.5). Excluding subjects with events that the SEAC attributed to another cause, there were eight subjects in the HEPLISAV group and one subject in the Engerix-B group with SEAC-confirmed AESIs not due to an alternative plausible cause (0.14% Heplisav, 0.04% Engerix-B). This does not include an event of granulomatous dermatitis, for which sarcoidosis was not ruled out (see discussion below). While there is an imbalance between treatment groups, numbers are small, diagnoses are varied across different diseases and organ systems, and the AESIs diagnosed are relatively

common immune-mediated events. However, with the exception of one event of Bell's palsy in a subject who received Engerix-B, adjudicated AESI diagnoses were reported exclusively in the Heplisav group. In the 9 September 2016 IR, the FDA asked the Applicant for any additional analyses they conducted to evaluate this imbalance.

The reporting of new-onset AESIs, including autoimmune events, is difficult to capture even in the setting of a controlled clinical trial for the following reasons:

- Onset may be insidious or evolve over time, symptoms are often non-specific, and diagnosis may not be immediate.
- Subjects may have pre-existing conditions that complicate the diagnosis (for example, osteoarthritis), particularly in the population in which DV2-HBV-23 was conducted
- Variations among experts regarding diagnostic criteria

Reviewer comment: *The clinical reviewer reviewed the narratives, which included SEAC adjudication, for all of the events referred to the SEAC. In the opinion of the clinical reviewer, the SEAC tended to evaluate events as not autoimmune unless sufficient evidence was provided to establish autoimmunity. For the reasons stated above, in many cases a diagnosis was not clearly established, onset of symptoms was in question, or there was disagreement between treating physician, specialist, and/or the SEAC. The clinical reviewer's assessment attempted to include additional events which may represent AESIs but that were not determined definitively to be by the SEAC. In this analysis, if a physician or specialist diagnosed a subject with an AESI and sufficient evidence was not presented to determine that diagnosis was most likely pre-existing or incorrect, the event was assessed as a new-onset AESI.*

The following is a summary of the Reviewer's assessments:

- The reviewer agreed that four events in four subjects in the Heplisav group were new-onset autoimmune events – alopecia areata (subject 108-013), ulcerative colitis (136-200), polymyalgia rheumatica (126-038), and hypothyroidism (136-149). The event of hypothyroidism has an alternative plausible cause of papillary thyroid cancer.
- The reviewer agreed that five AESIs of Bell's palsy were reported in the Heplisav group and one in the Engerix-B group, none with known alternative plausible causes. One subject in the Heplisav group had another AESI of diplopia (117-119), assessed as a 3rd nerve palsy, with an alternative plausible cause of diabetes.
- One AESI of 6th nerve palsy (134-064) in the Heplisav group was a new-onset AESI with an alternative plausible cause of diabetes.
- Of the five additional new-onset events in four subjects who received Heplisav, in which a diagnosis was not confirmed by the SEAC,
 - The reviewer agrees that a diagnosis of rheumatoid arthritis was not made by the specialist. This may represent an evolving AESI as new-onset laboratory abnormalities were noted.
 - Takayasu's arteritis (131-109) was confirmed by two FDA consultants. However, the consultants determined that the diagnosis was not new-onset (see details below).

- The diagnosis of 6th nerve palsy (106-271) was not confirmed. However, the specialist recommended an evaluation to rule out multiple sclerosis, which was not done. Thus, this will be considered a new-onset AESI.
- One subject (132-154) reported two potential AESIs. Clinical Sjogren's syndrome was diagnosed by the rheumatologist, but appears to be long-standing. Raynaud's phenomenon, also reported as an AESI, was noted by the rheumatologist, but information regarding onset is not provided. This event will be considered a new-onset AESI.
- Two events of hypothyroidism in the Heplisav group (103-108, 138-141) and two events in the Engerix-B group (112-170, 126-098) were diagnosed by the subjects' physician without sufficient information available to fully rule out the diagnosis.
- The following events were confirmed by the SEAC to be autoimmune or are AESIs, without sufficient information for the clinical review to determine them to be definitely pre-existing: Graves' disease (114-027), ulcerative colitis (122-076), systemic lupus erythematosus (129-084), and granulomatous dermatitis (131-035) in the Heplisav group and lichen planus (101-181) in the Engerix-B group.
- One additional event of lichenoid drug eruption in the Engerix-B group (103-119) was determined by the SEAC not to be autoimmune, but is considered by the reviewer to be a new-onset potential immune-mediated event.
- In conclusion, the clinical reviewer determined that there were 18 new-onset AESIs in 17 subjects in the Heplisav group (alopecia areata, ulcerative colitis, polymyalgia rheumatica, hypothyroidism in three subjects, Bell's palsy in five subjects, 3rd cranial nerve palsy, 6th cranial nerve palsy in two subjects (one rule-out MS), Raynaud's phenomenon, Graves' disease, ulcerative colitis, systemic lupus erythematosus, and granulomatous dermatitis) and five new-onset AESI in five subjects in the Engerix-B group (Bell's palsy, hypothyroidism in two subjects, lichen planus, and lichenoid drug eruption). Of these events 16 events in 16 subjects in the Heplisav group (alopecia areata, ulcerative colitis, polymyalgia rheumatica, hypothyroidism in two subjects, Bell's palsy in five subjects, 6th cranial nerve palsy/rule-out MS, Raynaud's phenomenon, Graves' disease, ulcerative colitis, systemic lupus erythematosus, granulomatous dermatitis) and five events in five subjects the Engerix-B group (Bell's palsy, hypothyroidism in two subjects, lichen planus, and lichenoid drug reaction) had no alternative plausible cause.

Reviewer comment: *Using the broader, clinical reviewer's definition of AESI, a small imbalance between the two groups is still noted, with 0.29% of Heplisav subjects and 0.18% Engerix-B subjects reporting new-onset AESIs without alternative plausible causes (per the statistical reviewer, RR = 1.59, 95%CI 0.61, 5.40).*

A tabular summary of events referred to the SEAC in each study group appears in the tables below (Tables 21 and 22). Brief narratives of the events follow, with reviewer assessment in italics.

Table 21. Adverse events of special interest referred to the Safety Evaluation and Adjudication Committee for evaluation in the Heplisav Group, Safety Population, Study DV2-HBV-23

Subject #	Age	Sex	Adverse Event	Last Active Dose	Onset (Days Since Last Active Dose)	Duration if Resolved (Days)	Outcome	Related per investigator	AI per SEAC	New Onset per SEAC	Related per SEAC
Endocrine											
130115	49	F	Autoimmune thyroiditis	1	0	-	Not recovered	Possibly	Y	N	N
125133	45	F	Autoimmune thyroiditis	2	14	-	Not recovered	Possibly	Y	N	N
108070	51	F	Hypothyroidism	2	45	-	Not recovered	No	Y	N	N
123086	59	F	Hypothyroidism	2	139	103	Recovered	No	N	-	-
110030	51	F	Hypothyroidism (autoimmune)	2	160	60	Recovered	No	Y	N	N
103108	59	F	Hypothyroidism	2	213	-	Not recovered	No	N	-	-
138141	43	F	Hypothyroidism	2	233	-	Not recovered	No	N	-	-
136149	60	F	Hypothyroidism*†	2	245	-	Recovering	No	Y	Y	N
112326	51	M	Hypothyroidism	2	337	-	Not recovered	Possibly	N	-	-
114027	54	M	Basedow's Disease	2	43	-	Not recovered	No	Y	N	N
118056	46	F	Basedow's Disease	2	64	17	Recovered	No	Y	N	N
107140	59	M	Hyperthyroidism	1	3	-	Not recovered	No	Y	N	N
128042	64	M	Hyperthyroidism	1	15	413	Recovered	No	N	-	-
133107	43	M	Thyroid function normal	2	165	1	Recovered	No	N	-	-
GI/Liver											
114022	67	M	Colitis ulcerative	2	219	-	Not recovered	No	Y	N	N
136200	46	F	Colitis ulcerative*	2	220	-	Not recovered	No	Y	Y	N
125442	44	M	Colitis ulcerative	2	232	91	Recovered	No	Y	N	N
122076	32	M	Colitis	2	91	-	Not recovered	No	Y	N	N
139035	63	F	Colitis	2	307	-	Unknown	No	N	-	-
109055	53	F	Biliary cirrhosis primary	2	248	-	Not recovered	No	Y	N	N
Metabolic											
104070	60	M	Type 1 diabetes mellitus	2	189	-	Not recovered	No	Y	N	N
Musculoskeletal											
134228	68	M	Myalgia	0	-2402	-	Not recovered	No	N	-	-
129084	62	F	Systemic lupus erythematosus	2	41	-	Not recovered	Possibly	Y	N	N

Subject #	Age	Sex	Adverse Event	Last Active Dose	Onset (Days Since Last Active Dose)	Duration if Resolved (Days)	Outcome	Related per investigator	AI per SEAC	New Onset per SEAC	Related per SEAC
132154	54	F	Sjogren's Syndrome (and Raynaud's)	2	207	-	Not recovered	No	N	-	-
102163	45	F	Rheumatoid arthritis	2	279	-	Not recovered	No	N	-	-
126038	68	M	Polymyalgia rheumatica*	2	291	-	Not recovered	Possibly	Y	Y	N
Neurologic											
105198	66	M	Diabetic lumbosacral plexopathy (initially CIDP)	0	-30	-	Not recovered	No	N	-	-
134044	49	M	VIIth nerve paralysis	1	9	77	Recovered	Possibly	N	-	-
102146	49	F	VIIth nerve paralysis	2	0 (55 after Dose 1)	29	Recovered	No	N	-	-
116323	31	F	VIIth nerve paralysis	2	169	38	Recovered	No	N	-	-
117119	49	M	VIIth nerve paralysis (and diplopia)	2	171	-	Not recovered	No	N	-	-
131028	52	M	VIIth nerve paralysis	2	255	-	Recovering	No	N	-	-
106271	43	M	VIth nerve paralysis	2	120	35	Recovered	No	N	-	-
134064	49	M	VIth nerve paralysis†	2	158	69	Recovered	Possibly	N	-	-
117119	49	M	Diplopia† (and VIIth nerve paralysis)	2	101	112	Recovered	No	N	-	-
111056	61	F	White matter lesion	2	145	-	Not recovered	No	N	-	-
Skin											
133026	43	M	Dermatitis psoriasiform (initially psoriasis)	2	18	-	Not recovered	Possibly	N	-	-
131035	43	F	Interstitial granulomatous dermatitis	2	70	-	Recovering	Possibly	N	-	-
108013	52	F	Alopecia areata*	2	228	-	Recovering	Possibly	Y	Y	N
Vascular											
131109	49	M	Takayasu's arteritis	2	61	-	Not recovered	No	N	-	-

Subject #	Age	Sex	Adverse Event	Last Active Dose	Onset (Days Since Last Active Dose)	Duration if Resolved (Days)	Outcome	Related per investigator	AI per SEAC	New Onset per SEAC	Related per SEAC
132154	54	F	Raynaud's phenomenon (and Sjogren's)	2	207	-	Not recovered	No	N	-	-

Source: Reviewer-generated analysis from BLA STN 125428/0.42, Module 5.3.5.1, dataset ADAE of Study DV2-HBV-23

* SEAC assessed new-onset autoimmune event

† Alternative plausible cause by SEAC and reviewer assessment

Table 22. Adverse events of special interest referred to the Safety Evaluation and Adjudication Committee for evaluation in the Engerix-B Group, Safety Population, Study DV2-HBV-23

Subject #	Age	Sex	Adverse Event	Last Active Injection	Days Since Last Active Injection	Duration (Days)	Outcome	Related per investigator	AI per SEAC	New Onset per SEAC	Related per SEAC
Endocrine											
128156	62	F	Autoimmune thyroiditis	2	45	-	Not recovered	No	Y	N	N
139090	57	M	Autoimmune thyroiditis	3	14	-	Not recovered	Possibly	Y	N	N
112170	70	F	Hypothyroidism (and Celiac)	3	76	-	Not recovered	Possibly	N	-	-
126098	57	F	Hypothyroidism	3	129	-	Not recovered	Possibly	N	-	-
134305	50	F	Hypothyroidism	3	137	-	Not recovered	No	Y	N	N
114044	65	F	Hypothyroidism	3	139	-	Not recovered	Possibly	N	-	-
118111	39	F	Hypothyroidism	3	161	-	Not recovered	No	Y	N	N
141052	36	M	Basedow's disease	2	42	98	Recovered	No	Y	N	N
128175	60	F	Basedow's disease (and cerebral ischemia)	3	144	-	Recovered	Possibly	Y	N	N
139254	60	M	Blood thyroid stimulating hormone increased	2	19	268	Recovered	No	N	-	-
GI											
112170	70	F	Celiac disease (and hypothyroidism)	1	14	-	Not recovered	No	Y	N	N
133214	70	M	Celiac disease	3	96	-	Not recovered	Possibly	Y	N	N
115124	67	F	Dry mouth (initially reported as Sjogren's)	2	237	-	Not recovered	No	N	-	-
Musculoskeletal											

Subject #	Age	Sex	Adverse Event	Last Active Injection	Days Since Last Active Injection	Duration (Days)	Outcome	Related per investigator	AI per SEAC	New Onset per SEAC	Related per SEAC
112015	37	F	Arthralgia (and migraine and rash)	1	19	-	Not recovered	Possibly	N	-	-
125181	47	M	Arthralgia (and myalgia)	1	20	-	Not recovered	Possibly	N	-	-
125181	47	M	Myalgia (and arthralgia)	1	20	-	Not recovered	Possibly	N	-	-
116118	35	F	Mixed connective tissue disease	2	69	-	Not recovered	No	Y	N	N
Neurologic											
112015	37	F	Migraine	1	2	168	Recovered	Possibly	N	-	-
129112	69	F	Demyelinating polyneuropathy	2	39	-	Recovering	No	N	-	-
134123	29	M	VIIIth nerve paralysis	3	26	178	Recovered	Possibly	N	-	-
128175	60	F	Cerebral ischemia (and Basedow's disease)	3	186	-	Not recovered	No	N	-	-
111014	39	F	Retinal exudates	3	92	40	Recovered	No	N	-	-
Skin											
128207	64	F	Cutaneous lupus erythematosus	3	196	-	Not recovered	Possibly	Y	N	N
112015	37	F	Rash	2	23	58	Recovered	Possibly	N	-	-
122091	63	F	Lichen planus	3	29	-	Not recovered	No	Y	N	N
101181	63	M	Lichen planus	3	117	-	Not recovered	No	Y	N	N
103119	66	M	Lichenoid keratosis	3	50	117	Recovered	Possibly	N	-	-

Source: Reviewer-generated analysis from STN 125428/0.42, DV2-HBV-23, dataset ADAE

Potential AESI narratives for subjects in the Heplisav group

103-108 Elevated thyroid stimulating hormone (TSH) (4.83 mIU/L, normal range 0.45 - 4.50) and normal free T4 noted on routine assessment following vaccination. Levothyroxine was started by the subject's primary care physician. Pre-vaccination study laboratory draw showed normal TSH (3.64 µIU/mL, normal range 0.34-5.60) and free T4. The investigator did not agree with the primary care physician's diagnosis of hypothyroidism. However, the subject declined evaluation by an endocrinologist and further laboratory assessment of hypothyroidism.

Reviewer comment: The SEAC's assessment that the event was not an autoimmune event is premature as no testing for thyroid autoantibodies was performed. The diagnosis of hypothyroidism is unclear as no follow-up TSH testing was provided. It is possible this subject had an evolving autoimmune thyroiditis following vaccination. The event will be considered an AESI, as the treating physician diagnosed hypothyroidism and autoimmune thyroiditis is the most common cause. We will ask the Applicant to provide the results of testing of the banked Week 28 (approximately two months prior to

diagnosis) serum for TSH and thyroid autoantibodies and the banked study baseline serum for thyroid autoantibodies, if autoantibodies are found at Week 28 in order to assess the validity of this diagnosis.

138-141 Subject was diagnosed with hypothyroidism by her PCP following vaccination and began levothyroxine. No laboratory results were available. Analysis of pre-vaccination and Week 28 (two months prior to diagnosis) study laboratory draw showed normal TSH, anti-TPO, and anti-TG antibodies. The subject declined site access to medical records and referral to a specialist.

Reviewer comment: *The SEAC's assessment that the hypothyroidism is not autoimmune is premature as the information available is very limited. The diagnosis of hypothyroidism is unclear; however, assuming the primary physician's diagnosis is correct, autoimmune thyroiditis is the most likely cause. The event will be considered an AESI.*

136-149 Elevated TSH (7.15 mIU/L, normal range 0.45-4.50) and anti-TG antibody (1060 IU/mL (normal range 0.0 - 40.0) noted following vaccination. Subject was ultimately diagnosed with papillary thyroid carcinoma with Hashimoto's thyroiditis. Pre-vaccination study laboratory draw showed normal TSH and anti-TPO antibody. Baseline anti-TG does not appear to have been tested.

Reviewer comment: *The SEAC's adjudication of the event as a new-onset autoimmune event with an alternative plausible cause of thyroid cancer is reasonable. The narrative submitted with the CSR states that the SEAC noted the Week 28 laboratory assessment was written in their narrative as if the results were from baseline. In the 9 September 2016 IR, the FDA asked the Applicant to describe the events that led to the error and the procedures that were put in place to prevent similar events.*

112-326 Elevated TSH (9.06 µIU/mL, normal range 0.50 - 6.00) was noted following vaccination with negative anti-TPO and anti-TG antibody. Analysis of pre-vaccination study laboratory draw showed normal TSH and negative anti-TPO. The narrative provides no specialist assessment of the etiology of the hypothyroidism.

Reviewer comment: *The SEAC's assessment that the hypothyroidism is a new-onset event that is not autoimmune appears reasonable, but another explanation for the hypothyroidism is not provided and will be requested of the Applicant.*

114-027 Low TSH (0.23 µIU/mL, normal range 0.4-6.0) and two positive thyroid stimulating immunoglobulin (TSI) (435-647%, normal range < 140) results noted following vaccination. Anti-TPO and anti-TG were negative. Pre-vaccination laboratory results over the prior eight years showed TSH generally in the low range of normal (0.39 – 0.56 µIU/mL, normal range 0.4 - 6.0). The subject also had evidence of osteoporosis approximately five months following the second vaccination. The narrative states that the endocrinologist assessed that the pre-vaccination laboratory results suggested subclinical hyperthyroidism and that it was possible the subject "had had mild Graves' disease for some time." The subject was treated with methimazole. Analysis of pre-vaccination study laboratory assessment showed the subject had TSH within normal limits and negative anti-TPO. No pre-vaccination TSI was provided.

Reviewer comment: *The SEAC's assessment that the event is autoimmune is reasonable; however, their assessment that the event is pre-existing may not be accurate. With the information provided there is no evidence of autoimmunity prior to vaccination and, based on the TSH, the event appears to have worsened following vaccination. We will ask the Applicant to provide evidence of pre-existing autoimmunity (baseline TSI), if available.*

133-107 Low free T4 (0.76 ng/dL, normal 0.77 - 1.61) was reported following vaccination. Paradoxically, follow-up laboratory assessment showed low TSH (0.21 μ IU/mL, normal range 0.34 - 4.82), and normal free T4 (0.96 ng/dL, normal range 0.77 - 1.61). The primary care physician diagnosed hypothyroidism and prescribed levothyroxine, apparently in error. The subject was evaluated by an endocrinologist for hypothyroidism. Anti-TPO and anti-TG were negative and a thyroid ultrasound showed multinodular goiter. Analysis of pre-vaccination study laboratory assessment showed normal TSH (0.86 μ IU/mL, normal range 0.34-5.60). The investigator retracted the event of hypothyroidism.

Reviewer comment: *The SEAC's assessment that the event was not autoimmune is reasonable given the limited and contradictory information. The subject's apparent subclinical hyperthyroidism appears not to have been evaluated and we will ask the Applicant to clarify this. However, there is no evidence for autoimmunity on studies performed following both laboratory abnormalities (low T4 and later subclinical hyperthyroidism).*

114-022 The subject had a history of chronic diarrhea, irritable bowel syndrome, and unspecified colitis. Following vaccination, he reported that he was treated with steroids for Crohn's disease. He was evaluated by a gastroenterologist and was diagnosed with ulcerative colitis. The subject's history was unreliable but it appears he did have a chronic inflammatory bowel condition prior to vaccination. *The SEAC's assessment that the event was a pre-existing autoimmune event is reasonable.*

122-076 The subject was hospitalized with pseudomembranous colitis approximately three months following the second vaccination. A colonoscopy at that time could not rule out ulcerative colitis. Reports of a flexible sigmoidoscopy at approximately the same time showed ulcerative proctitis. The narrative states that a reference was made in the medical records to a colonoscopy and esophagogastroduodenoscopy performed one year prior to the recent procedures that "inferred that a diagnosis of inflammatory bowel disease was made." The subject denied a history of IBD prior to enrollment and rescinded permission to view his medical records.

Reviewer comment: *The chronology of disease presentation and diagnosis is unclear. SEAC's assessment was that the event was a pre-existing autoimmune event. However, as the subject reports diagnosis occurred following vaccination and the records appear inconsistent, in the opinion of the clinical reviewer this has not been definitively shown to be pre-existing.*

134-228 The subject had a history of fibromyalgia. He was hospitalized for pneumonia and his stay was prolonged due to severe headaches with diminishing vision in his left eye. A history of eye pain prior to study enrollment was reported. He had a

temporal artery biopsy that did not show temporal arteritis or signs of vasculitis. He subsequently received a course of steroids reportedly because of the intermittent headaches with diminishing vision, a reportedly elevated ESR and CRP, and chronic myalgias, which were reported as an AESI. Upon follow-up with his rheumatologist, he received one or two more courses of steroids, one to treat increasing back pain. He had an elevated ESR and CRP at this time. At the Applicant's request, he was evaluated by another rheumatologist, who assessed the subject as having myalgias and polyarthralgia due to spinal disease (history of prior back surgeries) and fibromyalgia, leukopenia, and thrombocytopenia without evidence of autoimmune disease. A laboratory draw at this time showed a normal ESR, CRP, and autoantibody panel.

Reviewer comment: *The SEAC's assessment that the event was pre-existing and not autoimmune in nature appears reasonable. It is possible the subject has an evolving process but there is no clear evidence of an immune-mediated event given the available information. FDA requested further information regarding the headaches and visual changes leading to the temporal artery biopsy in the 9 September 2016 IR. A response was submitted, which will be reviewed subsequent to this review.*

129-084 The subject had a history of bilateral hand osteoarthritis for nine years and a family history of ankylosing spondylitis. Approximately 1.5 months following last active injection, she developed worsening hand pain. She was evaluated by a rheumatologist who noted signs of joint inflammation and assessed her as having systemic lupus erythematosus (SLE). Laboratory results at the time of diagnosis included ANA 1:640 (normal range < 1:40), homogenous pattern, leukopenia, anemia, double stranded DNA antibody 25 IU/mL (normal < 5), positive Sjogren's antibody (SS-A), positive ribosomal P antibody, and negative Smith, RF, cyclic citrullinated peptide (CCP) antibodies, SS-B, and remainder of the autoantibody panel. Analysis of pre-vaccination study laboratory assessment showed an ANA 1:160, homogenous pattern, negative double stranded DNA (90 IU/mL, negative < 100). The SEAC assessed the event as a pre-existing autoimmune event.

Reviewer comment: *While this is possible, it is also possible that the subject developed the condition following vaccination. Following vaccination, the subject appears to meet diagnostic criteria for SLE. Prior to vaccination, no hematology is reported and anti-ds DNA is at the high limit of normal. In addition, she reported acute worsening of symptoms and further elevation in an abnormal ANA were reported following vaccination. It is possible the vaccine worsened the pre-existing condition or that it contributed to the development of SLE in a susceptible subject.*

132-154 Four months following last active vaccination, the subject, who had a possible history of fibromyalgia, was evaluated for Sjogren's syndrome based upon concerns from her PCP and ophthalmologist. She reported symptoms of dry eyes and mouth for 6-7 years prior to study enrollment. Extractable nuclear antigen screen was negative for SSA, SSB, Smith, RNP, SCL-70, and Jo-1. ESR, RF, and serum protein electrophoresis were normal. The rheumatologist assessed her as having a clinical diagnosis of Sjogren's syndrome and symptoms of Raynaud's phenomenon in her toes. No further details, including onset, is given for Raynaud's phenomenon. The rheumatologist noted that a lip biopsy was needed for definitive diagnosis of Sjogren's, but the subject opted for empiric treatment instead. The subject discontinued the first line treatment due to side effects and the symptoms were reported as ongoing at study

conclusion. The SEAC assessed the events of Sjogren's syndrome and Raynaud's phenomenon as not autoimmune events, noting that the subject's sicca symptoms were pre-existing.

Reviewer comment: *The clinical reviewer agrees with the assessment that the sicca symptoms were pre-existing and are not reported as worsening following vaccination. However, the Applicant has not provided any evidence to determine whether the subject's Raynaud's was pre-existing or new-onset and thus, it will be considered a new-onset AESI as Raynaud's phenomenon is considered.*

102-163 The subject reported left shoulder and neck pain with finger paraesthesia approximately ten months following the last active injection. She was evaluated in an emergency room, received an X-ray, and was reportedly diagnosed with rheumatoid arthritis. No treatment was given. Four months later, she was evaluated by a rheumatologist who diagnosed impingement syndrome based on history, physical, and X-rays of multiple joints without evidence of inflammatory arthropathy. ANA was positive (1:320, normal range < 1:80) and CRP was elevated (9.9 mg/L, normal 0 – 4.9), but the remainder of the autoantibody tests were negative, including anti-RF and anti-CCP. Analysis of a pre-vaccination study laboratory draw showed a negative ANA.

Reviewer comment: *The SEAC's assessment of the event as not an autoimmune event is reasonable and consistent with the specialist's assessment. The clinical reviewer agrees with the SEAC's notation that there may be an underlying autoimmune disorder developing, particularly as the subject's ANA became positive following vaccination. But at the time of evaluation, after Week 56, there was not clear clinical evidence, for diagnosis of an autoimmune event.*

102-146 A 49 year-old woman with no relevant medical history reported a right sided facial paralysis that was consistent with Bell's palsy 55 days after having received dose 1 of Heplisav and on the evening after having received dose 2. She also reported three days of severe headaches prior to the event. She was evaluated in the ER and a head CT was normal. She was treated with oral prednisone and valacyclovir. She was referred for neurologic evaluation, but did not complete it. One month later the event was resolved. The subject did not complete the study and was lost to follow-up. The SEAC adjudicated the event as not an autoimmune event.

Reviewer comment: *This event is considered a new-onset AESI. The timing is concerning for possible relationship to Heplisav.*

117-119 The subject's history included hypertriglyceridemia and type 2 diabetes. Prior to study initiation, he was stable on metformin, pitavastatin, and fenofibrate. Unintentional weight loss, and possibly polyuria and polydipsia, are noted beginning two months after second vaccination. The subject reported double vision (first AESI) with mild headache three months following vaccination in the setting of a rapid elevation in his cholesterol (761 mg/dl, normal range 125-200), triglycerides (6266 mg/dL, normal <150), and HbA1c (12.2 %, normal <5.7%). Hypertriglyceridemia was considered serious because it was life-threatening. His medications were adjusted and he began insulin. He was evaluated by a neurologist, who noted mild third or fourth cranial nerve palsy, suspected to be due to his uncontrolled diabetes. The neurologist did not think he had a cavernous sinus thrombosis. Approximately five months following the last active

dose, he reported Bell's palsy (second AESI). Upon evaluation by the neurologist one week later, the diplopia had resolved and the seventh cranial nerve palsy was suggested to be due to uncontrolled diabetes. A neuro-ophthalmologist also attributed the third nerve palsy to diabetes and assessed the seventh nerve palsy as not related to vaccine. The SEAC assessed both events as not autoimmune disorders and not related.

Reviewer comment: *The reviewer agrees that the subject's uncontrolled diabetes likely caused his third nerve palsy. While diabetes and microvascular disease is a proposed mechanism for Bell's palsy, as is herpes simplex and herpes zoster, it is not considered an alternative plausible cause by this reviewer. Additionally, the Bell's palsy is reported at the time the third nerve palsy resolved and after starting insulin and other medication adjustment. Both events are considered AESIs. Of note, the PT for this event is diplopia, which the Applicant does not include in their PT list of AESIs. As a consequence, this event is not considered in several of the Applicant's analyses of AESIs in the CSR and the integrated summary of safety (ISS).*

106-271 Approximately four months following last active injection, the subject was seen in the emergency room for right foot drop. One week later, he reported diplopia (noted in the narrative later to be right sided) and resolved foot drop. The emergency room visit note is contradictory, apparently noting "extraocular movements intact in the right eye" and "an obvious 6th cranial nerve palsy." A CT of the head was normal. Findings were discussed with a neurologist and the subject was not admitted. A brain MRI showed a "mild to moderate degree of nonspecific T2 white matter hyperintensities clearly pathologic and unusual for the subject's age." Eleven days after the diplopia was evaluated, symptoms had at least partially resolved and a normal cranial nerve exam was noted by the subject's PCP. He was evaluated by a neurologist approximately two months later, reporting dysphagia, but no more foot drop or diplopia. The neurologist recommended a lumbar puncture to evaluate for MS, but the subject declined, noting that his symptoms had resolved. The SEAC assessed the event as not an autoimmune event. The SEAC also noted that giant cell arteritis or vasculitis could cause a sixth cranial nerve palsy, but symptoms would be unlikely to be transient with no other abnormalities.

Reviewer comment: *The clinical reviewer agrees with the SEAC that the 6th cranial nerve palsy is unconfirmed as only one note appears to mention it and also contradicts the finding. While there is no laboratory evidence of MS, the clinical reviewer does not consider that this diagnosis was adequately ruled out, given the neurologist's recommendations.*

134-064 A 49 year-old man with a ten-year history of diabetes, which was poorly controlled (HbA1c 10%), dyslipidemia, and hypertension reported left-sided diplopia following vaccination. He was evaluated by his PCP and an ophthalmologist who diagnosed 6th cranial nerve palsy. ESR and CRP were normal. Brain MRI showed non-specific bilateral lesions, possibly related to microvascular ischemic white matter disease. His ophthalmologist recommended control of his medical conditions. Symptoms resolved approximately two months later. He was then evaluated by a neurologist, who attributed the resolved diplopia to microvascular disease and diabetes. The SEAC adjudicated the event as not autoimmune.

Reviewer comment: *The event is a new-onset AESI with an alternative plausible cause of microvascular disease.*

131-035 A 43 year-old Hispanic female subject with a history of obesity, hypertension, rosacea, and bilateral ankle cellulitis for which she was hospitalized twice 2-3 months prior to study enrollment, reported a rash of her shins and forearms 97 days following first vaccination and 69 days following second. She was initially diagnosed clinically with erythema nodosum and treated with oral steroids. She was also on antibiotics for an unclear reason. She was evaluated two days later by a dermatologist and a biopsy of her forearm demonstrated non-caseating granulomatous inflammation. Shin biopsy was nonspecific. She reported that a tuberculin skin test and chest X-ray were normal but no information about the timing or reason for those studies is reported. The rash initially improved with steroids but followed a recurring course over the next several months. She continued to deny systemic symptoms. A repeat skin biopsy again demonstrated granulomatous dermatitis with an interstitial pattern (staining negative for fungus and mycobacteria); differential diagnosis per the dermatopathologist was sarcoidosis, coccidioides, and granuloma annulare. She was treated with prednisone taper and was told to discontinue her blood pressure medications (angiotensin receptor blocker and hydrochlorothiazide at the time) in case it was a drug reaction. An angiotensin converting enzyme level was elevated (86 U/L, normal range 9-67). Coccidioides antibody complement fixation was negative. The subject's insurance company refused a pulmonary consult and chest computed tomography (CT) and consequently, the subject declined these evaluations. The rash was reported as resolving at the study conclusion, but also intermittent and ongoing as per the narrative. The SEAC adjudicated the event as not autoimmune.

Reviewer comment: *Etiology and chronology of the rash is unclear. However, the rash on the upper extremities is granulomatous and appears to be new in onset. As sarcoidosis is a leading differential diagnosis and this was not ruled out, the clinical reviewer currently considers this event an AESI. The Applicant submitted more information regarding this subject in response to the September 9, 2016 IR, which will be reviewed following this review.*

131-109 Subject was a 49 year-old U.S. Hispanic man with a relevant history of type 2 diabetes, cerebrovascular disease, cardiovascular disease, hypertension, morbid obesity, gastric bypass surgery, fatty liver disease, former smoker, and alcohol user (few times a month). Following gastric bypass surgery in 2010, the subject's BMI decreased from 45 kg/m² to 34.1 kg/m² at study enrollment and he was able to control his hyperglycemia with diet and exercise instead of metformin, which he was previously taking. Family history included Crohn's disease. Nine years prior to study enrollment, he was diagnosed with a transient ischemic attack (TIA) versus lacunar infarct, age-indeterminate left thalamic infarct.

Two months after receiving the second dose of study vaccine, he was hospitalized for an acute thalamic infarct. A computed tomography angiography of the chest was performed to evaluate the incidental findings noted on imaging of the head and neck, which demonstrated "smooth, concentric mural thickening of the aortic arch," concerning for a large vessel vasculitis. Erythrocyte sedimentation rate (ESR) was 33 mm/hr (normal 0-20) and a high-sensitivity C-reactive protein (CRP) was 2.8 mg/L (no normal range provided). With the exception of a chest x-ray performed four years earlier, which

was reported by the Applicant as normal, there are no known prior imaging studies of the subject's chest. At the Applicant's request, the subject received multiple subsequent imaging studies, each demonstrating stable mural thickening. A rheumatologist diagnosed him with Takayasu's arteritis. The SEAC assessed the events as not autoimmune and questioned the diagnosis of Takayasu's arteritis.

Reviewer comment: *Because of the possibility of a new-onset granulomatous vasculitis in the Heplisav group, the FDA obtained two consults, regarding this case – one rheumatologist and one cardiac imaging specialist. Both consultants agreed the most likely diagnosis was Takayasu's arteritis, but that the disease was likely chronic, beginning prior to study enrollment. Consults are appended to this document. The Applicant, in consultation with external consultants, proposes aortic intramural hematoma. Per the clinical reviewer's discussion with FDA's consultant on 25 May 2016, the FDA consultant did not consider this diagnosis plausible based upon evaluation of imaging.*

Potential AESI narratives for subjects in the Engerix-B group

112-170 Following an event of celiac disease, which was assessed as a pre-existing autoimmune event, elevated TSH (5.34 mU/L, normal range 0.45 - 4.50) and normal free T4 was noted in the setting of evaluation for fatigue and levothyroxine was started. Analysis of pre-vaccination study laboratory draw showed TSH (4.56 uIU/mL, normal range 0.34-5.60) within normal limits and negative anti-TPO and anti-TG. The subject declined referral to an endocrinologist and no thyroid autoantibody testing was reported following diagnosis of hypothyroid. Analysis of Week 24 (2 ½ months prior to diagnosis) and Week 28 (almost two months prior to diagnosis) study laboratory draw, performed by the Applicant, showed negative anti-TPO and anti-TG at Week 24 and negative anti-TPO at Week 28. The SEAC appears to question the diagnosis of hypothyroidism as it was based on one mildly abnormal TSH. They assess the hypothyroidism as not autoimmune based upon incomplete information.

Reviewer comment: *As the treating physician's diagnosis is hypothyroidism and limited information is available, the event will be considered a new onset AESI, as it is possible the subject had an autoimmune thyroiditis that was not apparent on Week 24 or 28 laboratory assessment.*

126-098 Elevated TSH (4.45 uIU/mL, normal range 0.27-4.20) noted on routine testing following vaccination. The subject was started on levothyroxine. Analysis of pre-vaccination study laboratory draw showed TSH (4.17 uIU/mL, normal range 0.34-5.60) within normal range and negative anti-TPO. Subject declined expert consultation and declined to release any further information regarding the hypothyroidism. No Week 24 and 28 testing is reported. No thyroid autoantibody testing was reported following diagnosis of hypothyroidism. The SEAC questioned whether the event was actually hypothyroidism, given the borderline TSH and normal free T4, and assessed the hypothyroidism as not autoimmune.

Reviewer comment: *As the treating physician's diagnosis is hypothyroidism and limited information is available, the event will be considered a new onset AESI.*

112-015 The subject's history included migraines and resolved hives of unknown etiology. Over the two months following the first vaccination, the subject reported

increased migraines, followed by polyarthralgia (hands and feet), and a rash on her torso, among other symptoms. A brain MRI showed periventricular white matter foci consistent with migraine or an inflammatory condition. The rash resolved two months later and was not evaluated by a dermatologist. A rheumatologist's impression was fibromyalgia, despite being unable to elicit any tender points. Laboratory results were notable for a positive RF (24 IU/mL, normal range < 14) with a "negative" repeat (18.6, normal not provided), a negative ANA (<1:40) with a positive repeat (1:80, speckled pattern), two elevated ESRs (29 mm/hr, normal 0-20, and 46 mm/hr, normal 0-15), and normal CRP, CCP, SS-A, SS-B, anti-double stranded DNA. A neurologist evaluated the subject's migraines.

Reviewer comment: *The SEAC's assessment of the events as not autoimmune is reasonable given the limited information. The clinical reviewer agrees with the SEAC's notation that there may be an underlying autoimmune disorder developing, particularly given the laboratory abnormalities. But there appears to be no clear autoimmune diagnosis.*

101-181 A 63 year-old man with no relevant past medical history was evaluated by a dermatologist for several skin lesions 25 days following first vaccination. An asymptomatic rash of erythematous papules with trailing scale on the lower back, which was improving somewhat with betamethasone, was observed. The subject reported the rash had been present for two months. He had not reported the rash, nor was it evaluated at screening. Pityriasis rosea was diagnosed. The next report of the rash in the narrative was approximately seven months later. The subject reports this rash on his back was "similar to the one that he's had before," but the dermatologist's note states it had a different appearance. Upon reevaluation by the dermatologist, and based upon a biopsy, he was diagnosed with lichen planus. The SEAC assessed the event as a pre-existing autoimmune event.

Reviewer comment: *The start date of the rash is in question. The subject reports the lichen planus rash was similar to the rash that pre-dated study enrollment. The investigator reported the rash onset at day 117 following dose 3. The reason for selecting this particular date is unclear as it appears to be after the PCP reevaluation and before the dermatologist's reevaluation of the rash. However, because, with this start date the investigator appears to suggest it is a distinct rash, the dermatologist evaluates it as having a distinct appearance, and a significant time passed between reports of the rash, this clinical reviewer considers this autoimmune event to be new in onset.*

103-119 A 66 year-old man, with a relevant medical history of stroke with left foot drop, lumbar degenerative joint disease, lumbar radiculopathy, peripheral neuropathy, bilateral chronic knee pain, and chronic fatigue syndrome, reported a trunk rash, assessed as a "bullous dermatitis" by his PCP and treated with oral prednisone and cephalexin. Approximately three weeks later, his PCP determined his rash had improved and assessed it as guttate psoriasis, prescribing an oral prednisone taper. Also at this visit, he reports left foot pain, which appears to be different than his previously reported pain. Following oral steroids, he was prescribed topical steroids, and also gabapentin for peripheral neuropathy. The subject was evaluated by a dermatologist, who noted a resolving unspecified dermatitis, consistent with a drug reaction. Biopsy showed small foci of lichenoid lymphocytic infiltrates, or patchy

lichenoid dermatitis. Differential diagnosis included drug eruption, pityriasis lichenoides, and connective tissue disease. The dermatologist indicated that the event was a suspected drug reaction and possibly related to study vaccine. No other medications were started by the subject during the study prior to the start date of the rash. The rash was considered resolved 117 days after it was reported. The SEAC assessed the rash as not an autoimmune disorder, with one member noting that it was possibly autoimmune. In contrast to the dermatologist, the SEAC determined the event was unlikely to be due to study vaccine, given that the event occurred 191 days following second vaccine dose and that it was more likely to be due to other medications the subject was taking.

Reviewer comment: Presumably, the SEAC's assessment refers to the event's relationship to Heplisav only, as the rash is reported within two months of the third dose of Engerix-B. The event could represent a drug reaction (possibly to Engerix-B), pityriasis lichenoides, or a connective tissue disorder, though this may be less likely given its resolution without ongoing treatment and clear onset of other symptoms. Assuming the etiology is as the dermatologist assessed it, a drug reaction, which is lichenoid in nature, the clinical reviewer considers this event a new-onset possible immune-mediated event.

In the 9 September 2016 IR, additional information was requested for subject 115-124 who reported an MAE of dry mouth, which was referred to the SEAC. Additional information will be requested for the subject 118-111 who reported hypothyroidism following Engerix-B, which was referred to the SEAC. The clinical reviewer agreed with the SEACs assessment of these events; thus, they are not presented in the narratives above.

The following events are not on the list of AESIs and were not referred to SEAC, but occurred exclusively in the Heplisav group and may be immune-mediated.

Subject 108-065 was a 46 year-old woman with a history of type 2 diabetes, COPD, and "generalized pain", who reported granuloma annulare of the right hand and behind the left knee beginning on Day 15 following the first injection of Heplisav. The event was non-serious and was not referred to the SEAC for evaluation. It was treated with betamethasone dipropionate and clotrimazole, and resolved 23 days later. She also reported "worsening diabetes" and "sensory diabetic neuropathy" 53 days following the second dose.

Subject 113-016 was a 68 year-old woman with a history of "ulcers right lower leg", type 2 diabetes, hypertension, hyperlipidemia, obesity, mitral regurgitation, cardiac septal hypertrophy, sleep apnea, arthralgia, iron deficiency anemia, anxiety, depression, and multiple ear problems. Twenty-five days after the first dose of HEPLISAV, she reported eczema of her right lateral leg and methicillin-resistant staphylococcus aureus (MRSA) of unknown location. Her eczema was treated with topical fluocinonide followed by triamcinolone. MRSA was treated with oral ciprofloxacin, ketorolac, and topical mupirocin. Eczema was reported resolved three months later and MRSA was reported resolved five months later. She also reported pyoderma gangrenosum of her right distal shin 18 days after dose 2 of Heplisav. She was treated with topical clobetasol and it resolved approximately 4.5 months later.

Subject 118-221 was a 56 year-old woman with a history of asthma, allergic rhinitis, osteoporosis, GERD, and anxiety. She reported allergic urticaria on the day of dose 1 of Heplisav, which was treated with three days of prednisone and the event was considered resolved 8 days later. This event was assessed by the investigator as possibly related. No urticaria is reported after dose 2. Approximately six months after dose 2, she reported serum sickness, which was described by the investigator as “allergic reaction to allergy immunotherapy” and assessed as not related. She was treated with diphenhydramine and fexofenadine and the event was considered resolved 13 days later. She also reported a urinary tract infection, right femur fracture, post-procedure anemia, and right lower extremity edema during the study.

Subject 123-049 was a 44 year-old man with a history of leukopenia, asthma, allergies to multiple environmental allergens, and attention deficit hyperactivity disorder. On the day the subject received dose 2 of Heplisav, he reported serum sickness, which was described by the investigator as “anaphylaxis reaction secondary to allergy serum,” and GERD. His “anaphylaxis” was treated with seven days of prednisone and resolved that day. Thirty seven days following dose 2, he reported hypersensitivity (“allergic reaction secondary to industrial exposure” and “hypertensive response secondary to allergic reaction”) and non-cardiac chest pain. The allergic reaction was considered serious. He was treated with methylprednisolone, ipratropium, ipratropium/albuterol, lisinopril, aspirin, and morphine. All events resolved within two days and were assessed by the investigator as not related.

Reviewer comment: *The events of granuloma annulare, pyoderma gangrenosum, and “anaphylaxis reaction secondary to allergy serum” reported on the day of dose 2 are potential immune-mediated events that may be related to Heplisav, in the opinion of the clinical reviewer. We will request further information from the applicant regarding these events.*

Thyroid MAEs

Version 4 of the SEAC Charter, dated 18 November 2014 included a change in process for referral of newly identified events of hypothyroidism to the SEAC. After this date, banked baseline sera was first examined and if the subject was determined to have evidence of thyroid disease prior to study vaccination, SEAC did not evaluate the event.

Reviewer comment: *The assessment of events referred to SEAC is limited by this change. The clinical reviewer recommends requesting a list of all subjects who had their baseline sera examined for evidence of hypothyroidism from the Applicant.*

Because the referral procedures changed mid-study, the most common cause of both hypothyroidism and hyperthyroidism in the U.S. is autoimmune, and both clinical states can present as goiter, hypothyroidism or hyperthyroidism, an analysis of all thyroid MAEs is presented in the table below.

Table 23. Thyroid MAEs reported from vaccination through Week 56, Safety Population, Study DV2-HBV-23

Preferred Term	Heplisav N = 5587 n (%)	Engerix-B N = 2781 n (%)
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Preferred Term	Heplisav N = 5587 n (%)	Engerix-B N = 2781 n (%)
At least one event	22 (0.4)	13 (0.5)
Hypothyroidism	10 (0.2)	6 (0.2)
Autoimmune thyroiditis	2 (0.04)	2 (0.1)
Basedow's disease (Grave's)	2 (0.04)	2 (0.1)
Goitre	2 (0.04)	0
Hyperthyroidism	2 (0.04)	0
Primary hypothyroidism	0	1 (0.04)
Thyroid mass	0	1 (0.04)
Blood thyroid stimulating hormone abnormal	2 (0.04)	0
Blood thyroid stimulating hormone increased	2 (0.04)	2 (0.1)
Thyroid function test normal*	1 (0.02)	0

Source: Adapted from BLA STN 125428/0.42, CSR DV2-HBV-23, Table 12-12, p. 94.

N number of subjects in each treatment group

n number of subjects reporting event

* Subject 133-107 was reported to have low free T4 and low TSH at different times following vaccination, but was diagnosed as hypothyroid by his primary care physician. SEAC and investigator ultimately assessed the event as normal thyroid function.

Reviewer comment: In total thyroid MAEs occurred at similar rates between both study groups.

6.3.12.6 Clinical Test Results

Subjects enrolled at sites 121 and 140 were eligible for the laboratory sub-study; all but one subject from site 121 participated. Approximately 300 subjects 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 multiple urinalysis tests including creatinine, urine microalbumin, urine microalbumin/creatinine ratio, and microscopy for cells, casts, crystals, mucous, bacteria, and yeast. The mean and median serum creatinine levels at baseline and Weeks 4, 8, 24, and 56 in Heplisav recipients were similar to that of Engerix-B recipients. An analysis conducted by the reviewer demonstrated that 14 Heplisav subjects (6.8%) and 3 Engerix-B (2.9%) subjects had at least one abnormal serum creatinine and an increase of ≥ 0.2 mg/dL from baseline for at least one post-vaccination laboratory draw. None of these subjects had MAEs of renal dysfunction reported. One subject had an increase of > 0.5 mg/dL in creatinine noted: a 58 year-old female (121-149) in the Heplisav group with a baseline creatinine of 0.9 mg/dL, had an increase to 1.7 mg/dL at Week 56. The mean and median urine microalbumin creatinine measurements were higher for Engerix-B subjects compared to Heplisav subjects at baseline and at post-vaccination time points. A similar percentage of subjects (11.6 – 11.8%) in each group had normal baseline urine microalbumin/creatinine ratio with abnormal post-vaccination values. No RBC casts, which could be indicative of specific immune-mediated diseases, were reported.

Reviewer comment: No clear patterns of renal injury following Heplisav were noted in the laboratory sub-study in DV2-HBV-23. There were no differences between study groups identified that would help explain the small imbalance noted in acute and chronic renal failure MAEs noted in section 6.3.12.2.

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 Weeks 0, 4, 8, 24, and 56.

The mean PT and PTT values, standard deviations, medians, and minimum, values as well as change from baseline by treatment group and study visit were similar between treatment groups. Maximum values PTT were higher in the Heplisav group at Baseline and Weeks 8, 24, and 56. Maximum values for PT were higher in the Heplisav group at Weeks 24 and 56, in part due to subject 140-099 who received anticoagulation (see section 6.3.12.2).

New-onset 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 Week 8 values 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 (140-060) 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.

Reviewer comment: *Antiphospholipid antibody testing is usually performed in the setting of a clinical suspicion for the syndrome, such as in a young patient with multiple thrombotic events or spontaneous abortions. Repeat testing is usually performed again at least 12 weeks later, as transiently elevated values can be detected following infection or drug exposure. While there are more subjects in the Heplisav group with new-onset elevated anti-beta2 glycoprotein 1 IgM and lupus anticoagulant screen at Week 8, the clinical significance of an abnormal test in the setting of no or low suspicion of antiphospholipid syndrome is uncertain. Subjects who reported VTE had laboratory assessments for thrombophilia. As per the reviewer's analysis of subjects who reported VTE, no subjects were identified with anti-beta2 glycoprotein 1 or cardiolipin IgM or IgG abnormalities following VTE (see section 6.3.12.2).*

The mean chemistry and hematology values, standard deviations, medians, minimum and maximum values as well as change from baseline by treatment group and study visit were similar between treatment groups.

6.3.12.7 Dropouts and/or Discontinuations

Excluding fatalities, early discontinuation from study treatment due to a treatment-emergent MAE was reported in 0.54% Heplisav (30 subjects), 0.50% Engerix-B (14 subjects) recipients. Early discontinuation from study treatment due to an MAE assessed by the investigator as related was reported in seven subjects in the Heplisav group (0.1%) and five subjects in the Engerix-B group (0.2%): 1) migraine, 2) diarrhea, 3) hypoaesthesia and paraesthesia on face with nausea, vomiting and diarrhea, 4) deep vein thrombosis (DVT), 5) Bell's palsy, 6) throat tightness and urticaria, and 7) hypersensitivity in Heplisav and 1) arthralgia, migraine, and rash, 2) rash, 3) diarrhea, 4) DVT, and 5) nausea and vomiting in the Engerix-B group. An additional adverse event (AE) of urticaria reported two days following first injection with Heplisav, resulted in discontinuation of study treatment, and was assessed as unrelated.

Reviewer comment: Rates of discontinuation from study treatment due to a treatment-emergent MAE were similar in treatment groups. In the 9 September 2016 IR, FDA requested further information on subject 124-171 who reported urticaria as described above, subject 115-124 who reported xerostomia for which study drug was withdrawn, and subject 126-079 who reported several MAEs for which study drug was withdrawn. The Applicant was also asked to clarify why several events noted in the datasets to be possibly related and for which study drug was withdrawn appear to be omitted from the CSR. The Applicant's responses will be reviewed in the next review cycle.

6.3.13 Study Summary and Conclusions

Although Study DV2-HBV-23 was designed primarily as a safety study, clinical immunogenicity was evaluated in all per protocol subjects as a secondary endpoint. A comparison of the peak SPR of Heplisav at Week 24 with the peak SPR of Engerix-B at Week 28 for all per protocol study subjects was performed. The timing of evaluation of the SPR for the Heplisav group differed in Study DV2-HBV-23 (Week 24) from Studies DV2-HBV-10 (Week 12) and -16 (Week 12) in that a later time point was used for evaluating Heplisav. Immunogenicity results presented by the Applicant in the CSR for Study DV2-HBV-23 indicated that the SPRs of both study groups were comparable numerically. Because the 95% CI of the difference in SPR between Engerix-B and Heplisav was greater than -10%, Heplisav was shown to be noninferior to Engerix-B. Results of this study were consistent, numerically and statistically, with those seen in studies DV2-HBV-10 and -16. However, because subject disposition inaccuracies have been detected during BIMO inspection of two select sites (122/222) in this study, as per preliminary BIMO report findings summarized by Bhanu Kannan on 2 November 2016, and the potential that such inaccuracies were systemic in this study, immunogenicity data for Study DV2-HBV-23 cannot be verified at this time.

The Safety Population consisted of 8368 subjects, 5587 who received at least one dose of Heplisav and 2781 who received at least one dose of Engerix-B. As intended, subjects reported more baseline medical conditions than previous studies; but conditions and cardiac risk factors were balanced between study groups.

Key safety endpoints of MAEs, SAEs, and AESIs were monitored through Week 56. Overall, the rate of all MAEs and SAEs reported in the 56-week study period were similar between the Heplisav and Engerix-B groups. Potentially clinically significant imbalances were noted in deaths and acute myocardial infarction. Even after excluding deaths that were clearly due to overdose or injury, a small imbalance remained (0.29%

Heplisav, 0.14% Engerix-B). There was not a close temporal relationship between most of the deaths and Heplisav. However, the difference between groups remains concerning given the study was randomized. The clinical significance of the imbalance in acute myocardial infarction is unable to be fully assessed at this time as narratives for all events, and all cardiac SAEs were not submitted with the CSR.

Smaller imbalances were noted in the following MAEs, the clinical significance of which are unknown: herpes zoster, renal failure (acute and chronic), and atrial fibrillation. No differences between study groups were noted in pulmonary embolism or other venous thromboembolic events.

A similar number of subjects in each treatment group reported potential AESIs that were referred to the Safety Evaluation and Adjudication Committee for evaluation. No new-onset vasculitic AESIs were identified during the 56-week study period. Based upon the clinical reviewer's understanding of the SEAC's assessments, 10 subjects in the Heplisav group (0.18%) and one subject in the Engerix-B group (0.04%) reported a new-onset event with a SEAC-confirmed diagnoses that qualified as an AESI. The SEAC determined that none of the events were related to study vaccination and that three of the events in the Heplisav group were clearly due to another cause, making eight subjects in the Heplisav group (0.14%) and one subject in the Engerix-B group (0.04%) who reported SEAC-confirmed AESIs. A reviewer-analysis determined that there were 16 subjects in the Heplisav group (0.29%) and 5 subjects in the Engerix-B group (0.18%) who had physician or specialist diagnosed or suspected AESIs, not definitively demonstrated to be pre-existing or ruled out, and without an alternative plausible cause. While no events of GPA or THS were identified, an event of granulomatous dermatitis with a differential diagnosis of sarcoidosis as per the dermatopathologist was reported in one subject in the Heplisav group.

A laboratory sub-study was conducted in 309 subjects enrolled at two sites. Review of chemistry, hematology, and urinalysis assessments conducted at various time points through the 56-week study period did not identify any notable differences between study groups. Assessments of renal function, including urine microalbumin, in Heplisav recipients were reassuring. 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. The significance of one abnormal antiphospholipid antibody level and its possible role, if any, in imbalances of events noted in this study is not known.

7. INTEGRATED OVERVIEW OF EFFICACY

The study design and timing of the primary immunogenicity analysis differed between Studies DV2-HBV-10, -16 and -23. Therefore, integration of the SPR data for the primary immunogenicity endpoint analysis in the Integrated Summary of Effectiveness is not appropriate.

7.1 Indication #1 Not applicable

7.1.8 Persistence of Efficacy

Persistence of efficacy was previously addressed in the original clinical review of this application. Please refer to the clinical review for BLA STN 125428/0000 dated 26 February 2013.

8. INTEGRATED OVERVIEW OF SAFETY

The Applicant performed two integrated safety assessments on the primary safety population (PSP) and the total safety population (TSP). A summary of the studies used in these integrated assessments is in the table below.

Table 24. Studies included in the Integrated Safety Summary presented by the Applicant evaluating Heplisav and Heplisav constituents

Applicant's Integrated Population	Study # and Phase	Age (years)	Formulation of Heplisav	Heplisav Doses (mcg/mcg), Schedules, Number vaccinated	Comparator Schedules, Number vaccinated
PSP, TSP	DV2-HBV-23 Phase 3	18-70	Proposed	20/3000 Weeks 0, 4, N = 5587	Engerix-B Weeks 0, 4, 24, N = 2781
PSP, TSP	DV2-HBV-16 Phase 3	40-70	Proposed	20/3000 Weeks 0, 4, N = 1968	Engerix-B Weeks 0, 4, 24, N = 481
PSP, TSP	DV2-HBV-10 Phase 3	11-55	Proposed	20/3000 Weeks 0, 4, N = 1821, including 11 pediatric subjects	Engerix-B Weeks 0, 4, 24, N = 607, including 2 pediatric subjects
TSP	DV2-HBV-22 Phase 1	50-70	Proposed	20/3000 Weeks 0, 4, N = 25	None
TSP	DV2-HBV-14 Phase 2	11-55	Proposed	20/3000 Weeks 0, 4, N = 207	None
TSP	DV2-HBV0001 Phase 1	18-55	Previous	20/300, N = 8 20/650, N = 8 20/1000, N = 8 20/3000, N = 8 HBsAg alone 20 mcg, N = 8 1018 alone 300 mcg, N = 2 650 mcg, N = 2 1000 mcg, N = 2 3000 mcg, N = 2 All Weeks 0, 8	None
TSP	DV2-HBV-02 Phase 2	18-65	Previous	20/3000 One injection, N = 30	Engerix-B One injection, N = 29
TSP	DV2-HBV-03 Phase 2	18-28	Previous	20/3000 Weeks 0, 8, N = 48	Engerix-B Weeks 0, 8, 24, N = 51

Applicant's Integrated Population	Study # and Phase	Age (years)	Formulation of Heplisav	Heplisav Doses (mcg/mcg), Schedules, Number vaccinated	Comparator Schedules, Number vaccinated
TSP	DV2-HBV-04 Phase 2	40-70	Previous	20/3000 Weeks 0, 8, 24, N = 206	Engerix-B Weeks 0, 4, 24, N = 206
TSP	DV2-HBV-05 Phase 2	40-70	Previous	20/3000 Weeks 0, 8, 24, N = 48	Engerix-B Weeks 0, 4, 24, N = 47
TSP	DV2-HBV-08 Phase 2	18-39	Previous	20/3000 Weeks 0, 4 20/3000 Weeks 0, 8 10/1500 Weeks 0, 4 N = 61	None

Source: Adapted from BLA STN 125428/0.42, Summary of Clinical Safety, Table 2.7.4-1, p. 16-20.

N number of subjects in the Safety population

PSP Primary Safety Population

TSP Total Safety Population

The Applicant included the three pivotal, Phase 3 trials in their PSP. Their TSP included all of the studies conducted evaluating Heplisav, including studies that utilized different doses, formulations, and schedules of the vaccine. Some subjects who received HBsAg alone (N = 8) or 1018 adjuvant alone (N = 8) were included as comparator subjects.

An integrated safety summary was conducted at the time of the original BLA submission. Safety information from two studies not included in the original BLA submission was included in the ISS submitted in this Complete Response, Studies DV2-HBV-23 (reviewed in section 6.3), and DV2-HBV-22, a phase 1 study of 25 subjects without a comparator vaccine.

8.1 Safety Assessment Methods

Please see section 8.2.1 for a description of the length of time the Applicant monitored AEs, MAEs, SAEs, and AESIs in each of their studies. The Applicant does not provide a description of the methods of collection of these adverse events (for example subject diary) in their Summary of Clinical Safety. Please see section 6.3.12.1 for a description of methods for DV2-HBV-23, and the initial clinical review for the methods used in DV2-HBV-10 and -16.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The table below highlights for each of the Applicant's ISS populations the studies included and the length of time for which each presented category of safety event was monitored.

Table 25. Length of time after the first dose for safety outcome monitoring in studies included in the integrated safety summary presented by the Applicant

Applicant's Integrated Population	Study #	AEs	MAEs	SAEs	AESIs
PSP, TSP	DV2-HBV-23	None	56 weeks	56 weeks	56 weeks
PSP, TSP	DV2-HBV-16	28 weeks	None	52 weeks	52 weeks
PSP, TSP	DV2-HBV-10	28 weeks	None	28 weeks	None
TSP	DV2-HBV-22	12 weeks	None	56 weeks	56
TSP	DV2-HBV-14	28 weeks	None	28 weeks	None
TSP	DV2-HBV0001	62 weeks	None	62 weeks	None
TSP	DV2-DV2-HBV-02	28 weeks	None	60 weeks	None
TSP	DV2-HBV-03	28 weeks	None	50 weeks	None
TSP	DV2-HBV-04	24 weeks	None	50 weeks	None
TSP	DV2-HBV-05	12 weeks	None	32 weeks	None

Source: Adapted from 125428/0.42, Summary of Clinical Safety, Table 2.7.4-1, p. 16-20.

DV2-HBV-23 and DV2-HBV-22, the two studies previously not submitted to the BLA, did not include monitoring for solicited adverse events; DV2-HBV-23 did not include monitoring for AEs for which subjects did not seek medical attention. DV2-HBV-23 was the only study of Heplisav which monitored MAEs. FDA does not consider it appropriate to integrate the AE information collected in studies other than DV2-HBV-23 and the MAE information collected in DV2-HBV-23. Therefore, solicited adverse events and an integrated summary of AEs and MAEs were not reviewed with this submission. Please see the clinical review of the initial submission dated 26 February 2013 for an integrated summary of solicited adverse events and adverse events associated with Heplisav. Please see section 6.3.12.2 for a summary of MAEs reported in DV2-HBV-23. This ISS will focus on SAEs and AESIs.

FDA has other concerns with the populations for which the Applicant chose to conduct the ISS. Studies included in the Applicant's PSP monitored SAEs for varying lengths of time: 28 weeks following the first dose in DV2-HBV-10, 52 – 56 weeks in DV2-HBV-23 and DV2-HBV-16. Some studies included in the Applicant's TSP used a previous formulation of the vaccine and included subjects who received antigen and adjuvant only. Due to these concerns, FDA's presentation of the ISS for SAEs below uses the following populations:

- Primary Safety Population
 - 6 month PSP:
 - DV2-HBV-10, DV2-HBV-16, DV2-HBV-23

- SAEs reported from vaccination through 6 months following the first dose (day 197 was chosen to include all SAEs reported in HBV-10)
 - 1 year PSP:
 - DV2-HBV-16, DV2-HBV-23
 - SAEs reported from vaccination through study end (Week 52-56)
 - Modified Total Safety Population (mTSP)
 - DV2-HBV-10, DV2-HBV-14, DV2-HBV-16, DV2-HBV-22, DV2-HBV-23
 - SAEs reported from vaccination through 6 months following the first dose (day 197)

The mTSP is presented through six months only because only three studies monitored SAEs for one year: Studies DV2-HBV-23, DV2-HBV-16, and DV2-HBV-22. No subjects in DV2-HBV-22 reported SAEs or AESIs. Therefore, a one-year mTSP would be equivalent to the one-year PSP. It should be noted that because DV2-HBV-14 and DV2-HBV-22 were uncontrolled studies, the mTSP only adds subjects to the Heplisav group, not the comparator group. Also of note, the following presentations include 13 subjects (11 Heplisav, 2 Engerix-B) who were younger than 18 years of age and were enrolled in DV2-HBV-10. The inclusion of this small number of young subjects is not expected to significantly impact the analyses because they did not report any of the medical history risk factors or adverse events examined in detail below.

Reviewer comment: *The FDA will ask the Applicant to present an analysis of safety based upon the populations described above.*

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Subjects in the mTSP were well-balanced by gender (female 50.9%), and predominantly white (77.6%), not Hispanic (92.6%), with a mean age of 49 years (standard deviation 11.6). The predominant non-white racial groups were Black or African American (19.3%), followed by Asian (1.5%). Eleven pediatric subjects were enrolled in DV2-HBV-10 and are included in the integrated analysis.

The Applicant included an analysis of baseline medical characteristics and risk factors for cardiac disease in their TSP in the Summary of Clinical Safety. The rate of subjects in DV2-HBV-23 reporting at least one medical condition was 91.8% in the Heplisav group and 91.1% in the Engerix-B group. In the mTSP without Study DV2-HBV-23, the rate of subjects reporting at least one medical condition was balanced between treatment groups and slightly lower than in DV2-HBV-23 (88.1% in both groups).

The below table summarizes the FDA analysis of cardiac risk factors at baseline in study DV2-HBV-23 and the mTSP without DV2-HBV-23. The reviewer generated analyses for hypertension, which was not provided by the Applicant, and for all the conditions in the mTSP excluding DV2-HBV-23. The results in the mTSP without DV2-HBV-23 are similar to Applicant-provided results for the TSP.

Table 26. FDA analysis of the number and proportion of subjects with medical history and baseline characteristics indicating increases risk for cardiovascular disease, Safety Population for DV2-HBV-23 and for all other studies utilizing the proposed formulation of Heplisav (DV2-HBV-10, -14, 16, and -22)

Condition or characteristic	DV2-HBV-23 Heplisav N=5587 n (%)	DV2-HBV-23 Engerix-B N=2781 n (%)	mTSP without DV2- HBV-23 Heplisav N = 4021 n (%)	mTSP without DV2- HBV-23 Engerix-B N = 1088 n (%)
At least one baseline medical diagnosis of cardiac ischemia*	211 (3.8)	99 (3.6)	63 (1.6%)	17 (1.6%)
Type 2 Diabetes†	762 (13.6)	381 (13.7)	206 (5.1)	44 (4.0)
Hypertension§	2021 (36.2)	978 (35.2)	818 (20.3)	200 (18.4)
Hyperlipidemia¶	1757 (31.4)	879 (31.6)	768 (19.1)	199 (18.3)
Sex and Age: Male ≥ 46 years	1879 (33.6)	919 (33.0)	1106 (27.5)	271 (24.9)
Sex and Age: Female ≥ 56 years	1028 (18.4)	537 (19.3)	459 (11.4)	92 (8.5)
Smoking within 1 year	1843 (33.0)	909 (32.7)	1134 (28.2)	342 (31.4)
Obesity: BMI ≥ 30	2724 (48.8)	1285 (46.2)	1405 (34.9)	372 (34.2)

Source: Adapted from BLA STN 125428/0.42; Module 2.7.4, Summary of Clinical Safety; Table 2.7.4-27, p. 84-86

N number of subjects in each treatment group

n number of subjects reporting medical history item or characteristic

* 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 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

DV2-HBV-23 enrolled higher proportions of subjects reporting all risk factors for cardiovascular disease examined and baseline history of cardiac ischemia. In the mTSP excluding DV2-HBV-23, the rate of subjects reporting cardiac ischemic medical history at baseline was balanced between treatment groups. There were small differences between groups in baseline risk factors for cardiovascular disease. The greatest differences between treatment groups were in female ≥ 56 years of age (11.4% Heplisav, 8.5% Engerix-B), smoking (28.2% Heplisav, 31.4% Engerix-B), male ≥ 46 years of age (27.5% Heplisav, 24.9% Engerix-B), and hypertension (20.4% Heplisav, 18.6% Engerix-B). Please see 6.3.10.1.2 for a discussion of these medical conditions and baseline characteristics in DV2-HBV-23.

Reviewer comment: While the differences between treatment groups are relatively small in the mTSP excluding DV2-HBV-23, they are greater than the differences noted in DV2-HBV-23. In the mTSP without DV2-HBV-23, more subjects in the Heplisav group reported more type 2 diabetes, hypertension, hyperlipidemia, and sex and age risk factor. More subjects in the Engerix-B group reported smoking. Notably, studies other than DV2-HBV-23 did not demonstrate an imbalance in MI. Each risk factor may not contribute equally to an increased risk of coronary artery disease, as may be supported by the similar number of subjects with a history of cardiac ischemic disease despite small imbalances in risk factors.

8.2.3 Categorization of Adverse Events

All verbatim terms for spontaneously reported AE were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0 and the resulting system

organ class (SOC) and preferred terms (PTs) were used for tabulation of incidence rates.

Reviewer comment: MedDRA tends to “split” closely related events leading to greater specificity but less sensitivity (for example, abdominal pain is split into upper abdominal pain, lower abdominal pain, etc.). For the purposes of this review and analysis of events, “split” events were “lumped” and assessed for trends.

8.3 Caveats Introduced by Pooling of Data across Studies/Clinical Trials

The following limitations of the ISS are introduced by pooling data from several studies:

- Monitoring of SAEs for varying lengths of time
- Varying randomization ratios
- Varying methods of identification and evaluation of AESIs

Reviewer comment: FDA’s three-part ISS analysis addresses the limitation regarding varying monitoring times for SAEs as much as possible. Only studies evaluating the proposed formulation have been included in this ISS, in order to address limitations introduced by using other processes of manufacture. The clinical review of the original BLA included an ISS of all studies evaluating all formulations of Heplisav.

8.4 Safety Results

8.4.1 Deaths

In addition to the 32 deaths reported in DV2-HBV-23 (See section 6.3.12.3), there were two deaths in DV2-HBV-16. One 45 year-old male Heplisav-recipient with no relevant past medical history died of pulmonary embolus^{(b) (6)} days after the second study injection. One 64 year-old male Engerix-B recipient died secondary to a PT of cardiac failure^{(b) (6)} days after the second dose. As per the clinical review of the initial BLA submission, this death occurred following a heart attack. All deaths were determined to be unrelated by the investigators.

Table 27. FDA analysis of all deaths and deaths due to causes other than accident, injury, or overdose, Integrated Safety Populations

	6 mo PSP Heplisav N = 9376 n (%)	6 mo PSP Engerix-B N = 3869 n (%)	1 yr PSP Heplisav N = 7555 n (%)	1 yr PSP Engerix-B N = 3262 n (%)	mTSP 6 mo Heplisav N = 9608 n (%)	mTSP 6 mo Engerix- B N = 3869 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

The Applicant considers nine deaths in the Heplisav group and three deaths in the Engerix-B group in study DV2-HBV-23, clearly due to overdose or injury (deaths with an SOC of injury, poisoning, or procedural complications and the death with a PT of hypoxic ischemic encephalopathy). Excluding overdoses and injuries, the rates of death in Heplisav groups ranged from 0.09% to 0.23%, and in Engerix-B groups from 0.08% to 0.15% (see Table 27 above).

Reviewer comment: As discussed in section 6.3.12.3, in the opinion of the clinical reviewer, the exclusion of those 12 deaths is reasonable. Even after the exclusion of those deaths, the imbalance in deaths in the 1 year PSP still persists, driven by the deaths in Study DV2-HBV-23. The imbalance is less apparent in the six month PSP and mTSP.

One explanation for a greater frequency of deaths being observed in Study DV2-HBV-23 is a population with more medical problems enrolled in Study DV2-HBV-23 compared to the previous studies. However, one would still expect a similar distribution of deaths between the treatment groups in each study.

8.4.2 Nonfatal 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 the table below.

Table 28. FDA analysis of number and percentage of subjects with serious adverse events by treatment group, Integrated Safety Populations

Event	6 mo PSP Heplisav N = 9376 n (%)	6 mo PSP Engerix-B N = 3869 n (%)	1 yr PSP Heplisav N = 7555 n (%)	1 yr PSP Engerix- B N = 3262 n (%)	mTSP 6 mo Heplisav N = 9608 n (%)	mTSP 6 mo Engerix-B N = 3869 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 (2.77)	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 mTSP was the most inclusive population evaluated by FDA in the ISS and the 1-year PSP included monitoring for the longest time period. The most common SAEs reported in the Heplisav group in the mTSP were: acute myocardial infarction, non-cardiac chest pain, pneumonia, osteoarthritis, cellulitis, asthma, cholecystitis, cerebrovascular accident, chronic obstructive pulmonary disease, and hypertension. The most common SAEs reported in the Heplisav group in the 1-year PSP were: acute myocardial infarction, pneumonia, osteoarthritis, non-cardiac chest pain, chronic

obstructive pulmonary disease, coronary artery disease, atrial fibrillation, small intestinal obstruction, cellulitis, cerebrovascular accident, and asthma. These SAEs were balanced between groups or were reported more frequently in the Engerix-B group with the following exceptions: acute myocardial infarction (mTSP 6 month: Heplisav 0.08%, Engerix-B 0.03%; 1-year PSP: 0.21% Heplisav, 0.06% Engerix-B) and asthma (mTSP 6 month: Heplisav 0.06%, Engerix-B 0.05%; 1-year PSP: 0.09% Heplisav, 0.03% Engerix-B). The imbalance in asthma SAEs in the 1-year PSP is slightly greater than the imbalance noted in Study DV2-HBV-23; however, there is no imbalance in asthma SAEs in the mTSP, which is based on all subjects receiving the proposed formulation reporting events within six months following vaccination.

Cardiac SAEs

The table below show the SAEs likely to be acute ischemic cardiac events and all cardiac SAEs in the ISS.

Table 29. FDA analysis of number and percentage of subjects with cardiac serious adverse events and events of myocardial infarction (MedDRA SMQ narrow) by treatment group, Integrated Safety Populations

Event	6 mo PSP Heplisav N = 9376 n (%)		6 mo PSP Engerix-B N = 3869 n (%)		1 yr PSP Heplisav N = 7555 n (%)		1 yr PSP Engerix-B N = 3262 n (%)		mTSP 6 mo Heplisav N = 9608 n (%)		mTSP 6 mo Engerix-B N = 3869 n (%)	
At least one SAE in SOC CARDIAC DISORDERS	29 (0.31)		16 (0.41)		58 (0.77)		19 (0.58)		29 (0.30)		16 (0.41)	
At least one SAE of myocardial infarct*	12	0.13	2	0.05	21	0.28	5	0.15	12	0.12	2	0.05
Acute coronary syndrome	1	0.01	0	0.00	1	0.01	0	0.00	1	0.01	0	0.00
Acute myocardial infarction	8	0.09	1	0.03	16	0.21	2	0.06	8	0.08	1	0.03
Angina unstable	1	0.01	1	0.03	1	0.01	1	0.03	1	0.01	1	0.03
Coronary artery occlusion	1	0.01	0	0.00	8	0.01	1	0.03	1	0.01	0	0.00
Myocardial infarction	1	0.01	1	0.03	4	0.03	1	0.03	1	0.01	1	0.03

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

* Defined as the MedDRA SMQ Narrow for myocardial infarct.

In addition to the above events, as per the clinical review of the initial BLA, subject 92-638 in Study DV2-HBV-16 who received Engerix-B and died of “cardiac failure”, actually experienced pulmonary arrest and ventricular fibrillation following a heart attack occurring (b) (6) days after the second study injection. Including this event, rates of myocardial infarction in the Engerix-B group are: 0.08% 6 month PSP and mTSP, and 0.18% 1 year PSP.

In contrast to Study DV2-HBV-23 alone, all cardiac SAEs were more frequent in the Engerix-B groups in the integrated safety populations over the first six months. All cardiac SAEs were slightly higher in the Heplisav group in the one year integrated safety

population. An imbalance in myocardial infarction (MedDRA narrow SMQ) was still observed in the integrated populations, driven by the events in Study DV2-HBV-23. One subject in the Engerix-B group in Study DV2-HBV-16 had two SAEs, unstable angina and AMI, which start on the same day, and are considered by the reviewer as one event.

In addition, in prior studies which used a different formulation of Hepelisav other than the one proposed for licensure, two additional subjects reported an SAE in the MedDRA SMQ Narrow for myocardial infarction – one subject who received Hepelisav in Study DV2-HBV-05 and reported an acute myocardial infarction 121 days following last active injection (3 prior active injections), and one subject who received Engerix-B in DV2-HBV-04 and reported unstable angina (preferred term “suspected unstable angina”) 14 days after the last active injection.

Reviewer comment: *The imbalance in MI persists in the integrated safety populations, with a relative risk of $RR = 1.61-1.81$ in the Hepelisav groups compared to the Engerix-B groups. These numbers may be revised following further review of cardiac SAE narratives in Study DV2-HBV-23.*

8.4.3 Study Dropouts/Discontinuations

The Applicant provided an analysis of subjects who discontinued from study treatment following an AE. These numbers were small and similar between study groups.

8.4.4 Common Adverse Events

Adverse events that were not medically attended are not evaluated in this submission because they were not monitored in Study DV2-HBV-23. Please see the clinical review of the original BLA.

8.4.5 Clinical Test Results

The Applicant does not provide an integrated analysis of clinical laboratory test results that includes results from Studies DV2-HBV-23 or DV2-HBV-22. In their Clinical Summary of Safety, the Applicant describes the results of testing for renal function and thrombotic disease on a subset of subjects in Study DV2-HBV-23, and testing of chemistry and hematology in Study DV2-HBV-16, separately. They also include a presentation of testing for autoantibodies conducted in studies included in the initial BLA submission. Review of the clinical laboratory testing from Study DV2-HBV-16 and autoantibody testing was included in the clinical review of the initial BLA. Results of the laboratory sub-study in Study DV2-HBV-23 are discussed in section 6.3.12.6.

8.4.6 Systemic Adverse Events

Solicited adverse events, including systemic AEs, were not evaluated in this submission, with the exception of information submitted in response to the Complete Response Letter. Please see the clinical review of the original BLA for discussion of other events. The 22 February 2013 Complete Response Letter (item 2) requested additional information regarding subjects with events that either may be considered systemic adverse events or AESIs; thus, the Applicant's responses, submitted in STN 125428/0.34 and 0.35 regarding subjects with systemic adverse events are reviewed here and responses regarding AESIs are reviewed in Section 8.4.8.

In the initial BLA review, five Hepelisav subjects were identified that reported PE; the CR Letter requested clotting disorder evaluations and any serologic markers of autoimmune

disease on three of these subjects. The Applicant submitted additional information for these subjects in STN 125428/0.34 (subjects 21-047, 22-070, 22-602) and 125428/0.35 (subject 22-070).

21-047 (Study DV2-HBV-10) was a 32 year old female with a medical history that included obesity, smoking, and use of an etonogestrel ethinyl vaginal ring. She reported pain in her right arm 38 days after her second study injection. The pain worsened and she was admitted and was diagnosed with pulmonary embolism, pleuritis, pneumonia and cystitis 44 days following her second study injection. The clinical review of the initial submission states that “a thrombophilia diagnostic study was negative, but antiphospholipid antibodies were elevated.” An ultrasound examination of the legs was limited due to the subject’s obesity but no sign of deep vein thrombosis was found on this limited exam. The investigator assessed the event as severe and probably not related to study treatment. The Applicant submitted results of ANCA testing of study samples, which were all negative, CRP testing of study samples (1.88 – 3.06 mg/dL, no normal range provided), and results of hospital laboratory tests were consistent with those reported above and also noted elevated CRP.

22-070 (Study DV2-HBV-10) was a 26 year old male with a medical history of asthma, had a traumatic rupture of the anterior cruciate ligament of the right knee one month after his second study injection. He was treated with prophylactic dalteparin, but developed phlebothrombosis of the complete right leg and subsequent pulmonary embolism. He was discontinued from the study due to this SAE. The investigator assessed the event as severe in intensity and not related to study treatment. At the time of discontinuation, an evaluation of hereditary causes of thrombosis was pending. In response to FDA’s request, the Applicant submitted results of ANCA and CRP testing of study samples (all negative), results of the thrombophilia work-up, and follow-up information on subject status. A test for lupus inhibiting bodies was positive and factor VIII was significantly elevated. As per the subject’s discharge summary, “thrombophilia was diagnosed on an outpatient basis prior to the initiation of therapy with Marcumar. A test for lupus inhibiting bodies was positive; this may be a temporary phenomenon. We believe that the increased Factor VIII activity is most likely related to a reactive elevation.” Tests for hereditary thrombophilias were negative. Follow-up evaluation of the abnormalities was recommended in two months; these results were not provided. However, in a follow-up contact with the subject, he reported another event of left leg DVT six months after the first event in the setting of right knee surgery and despite prophylaxis. Lifelong anticoagulation therapy was recommended.

22-602 (Study DV2-HBV-16) was a 62 year old male with a past medical history that included hyperlipidemia, hypertension, sleep apnea treated with continuous positive airway pressure and hand tendonitis, who was admitted eight months after the last active study injection an extensive bilateral pulmonary emboli with a clot at the bifurcation of both main pulmonary arteries and an extensive clot extending into the upper and lower lobes of both lungs and ultrasound evaluation showing an extensive deep venous thrombosis on the left leg in the main femoral vein, popliteal, posterior tibial and peroneal veins. An evaluation for an underlying clotting disorder was planned and results were pending at the time of the initial review. He had a history of frequent traveling and had recently taken an interstate road trip. The investigator assessed the events as severe and not related to study treatment. The Applicant submitted records from the PCP approximately two years later. These laboratory results performed while

the subject was on anticoagulation indicate the subject has a factor V Leiden mutation, a Protein C and Protein S deficiency, and prothrombin variant. The PCP note also indicates the subject had a history of factor V Leiden, discontinued anticoagulation for a dental procedure, and went on a car trip, resulting in a DVT and PE. It is not entirely clear if this refers to the event on-study, though it seems to describe it. Of note, this subject appears to be incorrectly identified as 22-601 in the previous clinical review and the CR letter.

Reviewer comment: *Subject 22-602 appears to have clear hereditary and circumstantial risk factors for thrombophilia and the event is more likely due to these factors than vaccine. Subjects 21-047 and 22-070 clearly had clinical risk factors for thrombophilia. However, they also have both reported VTE events approximately one month following the second dose of Heplisav, with reports of positive antiphospholipid antibodies. This is at approximately the same time that a small increase in subjects in the laboratory sub-study of DV2-HBV-23 had increases in some anti-phospholipid antibodies. Notably, no subjects in DV2-HBV-23 who reported VTE had increases in anti-beta2 glycoprotein 1 antibodies when assessed.*

Hospital records and neurological outpatient follow-up information for subject 06-174 (study DV2-HBV-10), a Heplisav recipient, were requested by the FDA because of an unclear diagnosis of an SAE that included multiple neurologic complaints. The Applicant submitted records from hospitalization and outpatient follow-up, which was reviewed. The exact diagnosis is still unclear. The subject was admitted with facial numbness, dysphasia, and unilateral hand numbness. The hand numbness was suspected to be secondary to carpal tunnel syndrome. The leading diagnosis by the neurologist was small left cerebral infarct. Head CT and MRI were normal. On outpatient follow-up, the neurologist noted that he had “no symptoms suggestive of recurrent cerebral ischemia” and that “it is somewhat surprising that his MRI was completely normal.”

Reviewer comment: *Based upon the evaluations of the treating physician, an SAE of resolved cerebral ischemia, as the event appears in the integrated ADAE, appears to be a reasonable way to report the event.*

Medical records regarding evaluation of a rash and facial swelling in subject 42-320 (Study DV2-HBV-16) were requested by the FDA. Study progress notes were submitted as the subject declined to release records. The following summary is from the previous clinical review, the additional progress notes, and information in the datasets. The subject was a 57 year-old female Heplisav recipient with a medical history that included osteoarthritis, pain in legs and feet and allergic rhinitis, who developed a rash on her stomach of unknown cause on the day of the first study injection, which resolved within hours. She received her second vaccination as scheduled. At approximately the same time she began tramadol, amitriptyline and naproxen for bilateral hand and foot pain, which is reported as pre-existing. Six weeks after her second injection, she developed swelling of the face of unknown cause for which she received diphenhydramine and an eight day course of oral prednisone. Nine days after the facial swelling, she developed a “skin rash” of unknown cause. Further vaccinations were not administered due to the unknown nature of the rash. The investigator assessed the event as mild in intensity and possibly related to the study treatment. The additional progress notes reviewed revealed that the subject was evaluated by a dermatologist. As per the subject the rash did not recur following tramadol discontinuation. However, it is noted that the first rash

was reported prior to tramadol use and, as no other cause is known, the first rash is assessed as possibly related to vaccine. No further information is provided regarding the facial swelling, with the possible exception of one note that says “Subject confirms no history of swelling or itching since 2010 incident.”

Reviewer comment: *Though information is limited, events appear to be recorded adequately. It is unlikely that an event of facial swelling six weeks following the last vaccination is related to Heplisav.*

8.4.7 Local Reactogenicity

Not evaluated in this submission. Please see the clinical review of the initial BLA submission.

8.4.8 Adverse Events of Special Interest

AESIs were collected prospectively only in Studies DV2-HBV-16 and -23, in which potential AESIs were referred to a SEAC for evaluation. In their Clinical Summary of Safety, AESIs were identified retrospectively by PT search for terms on the AESI list, excluding verbatim terms that indicated worsening of a pre-existing condition.

Reviewer comment: *Because the Applicant identifies AESIs in their Clinical Summary of Safety by PT search, some events that were referred to the SEAC, potentially adjudicated as autoimmune or AESIs, but for which the preferred term was not updated to reflect the final diagnosis, are not included in their analysis. For example, they note that two subjects with AEs of hypothyroidism, instead of autoimmune thyroiditis, are not included. For this reason, some of the numbers presented in the Applicant’s Clinical Summary of Safety are not accurate.*

Please see section 6.3.12.5, where AESIs identified in Study DV2-HBV-23 are described in detail. Briefly, the following events were reported in Study DV2-HBV-23 in the Heplisav group and adjudicated as AESIs without an alternative plausible cause: Bell’s palsy (n = 5), alopecia areata, polymyalgia rheumatica, and ulcerative colitis. One Engerix-B subject reported Bell’s palsy. In addition, this analysis does not include a subject diagnosed with granulomatous dermatitis who did not receive an evaluation for sarcoidosis as was recommended by treating physicians. No events were determined to be related by the SEAC.

Please see the clinical review of the initial BLA for a full discussion of the AESIs that were identified prospectively in Study DV2-HBV-16 and retrospectively in the initial integrated safety summary. Briefly, the SEAC in DV2-HBV-16 adjudicated five events as new-onset AESIs or AIAEs, all occurring in the Heplisav group – hypothyroidism (n = 2), vitiligo (n = 1), Bell’s palsy (n = 1), and erythema nodosum (n = 1). Please also see the discussion below of a possible new-onset AESI of narcolepsy in Study DV2-HBV-16. Only one event, erythema nodosum, reported by a subject who received Heplisav, was determined by the SEAC to be related to vaccination, but not autoimmune in nature. In this submission, the Applicant also includes two additional events in subjects who received Heplisav, in Study DV2-HBV-16, that were not identified during the trial or in the initial ISS. One event of “cavernous sinus thrombosis” that was initially evaluated by treating physicians and also by FDA consultants as Tolosa-Hunt syndrome is discussed in section 5.4. One event of dermatitis herpetiformis was identified, for which the site

sent a follow-up communication noting that the subject and her PCP denied that the subject was ever diagnosed with the condition.

In addition to the AESIs described above, the 22 February 2013 Complete Response Letter (items 2) requested additional information regarding the below subjects enrolled in DV2-HBV-16 with events that may be considered AESIs. The Applicant's responses, submitted in STN 125428/0.34 and 0.35 regarding subjects with AESIs are reviewed here.

Briefly, subject 32-018 (Study DV2-HBV-16) was a 43 year-old female who was diagnosed with narcolepsy 13 days following her second study injection. She was treated with armodafinil and sodium oxybate. The adverse event was graded as mild in intensity and was deemed unrelated to study vaccine by the investigator. No action was taken with regard to further study treatments. Additional information submitted included the source document in which the narcolepsy was first submitted to the site and a note dated three years later (2013) stating that the subject declines to allow the site to contact her previous PCP for more information, that the subject is not currently being treated due to insurance reasons, and she is not currently experiencing symptoms.

Reviewer comment: *The Applicant is unable to provide further information. Narcolepsy was not included in the list of AESIs for Study DV2-HBV-16, but has since been added to the FDA list due to an evolution in understanding of the disease. This subject reports receiving a diagnosis of narcolepsy approximately six weeks following her first vaccination. A diagnosis at such a brief interval following vaccination may suggest symptoms were present prior to vaccination, but no information is available to corroborate this. In a study of 37 children with narcolepsy in Sweden, 28 of which developed symptoms of narcolepsy following vaccination with another vaccine, the median time from the first dose of the vaccine to the onset of symptoms was 9.5 weeks (range 2 to 40 weeks).¹³ This diagnosis is within that range. In the opinion of the clinical reviewer, this event is suspicious for an AESI.*

Briefly, subject 21-640 (Study DV2-HBV-16) was a 68 year-old female Heplisav recipient with a past medical history that included cervical stenosis, laminoplasty and hypertension who developed moderate left hand swelling and aching three days following her first and only study injection. Over the next two months, she also reported general body aches, left foot swelling and bruising, mild pain in her right upper shin. Other symptoms were treated and/or resolved, but her left hand swelling and left hand aching were ongoing at the end of the study. The hand aching, swelling and general aches were assessed by the investigator as possibly related to the study treatment; injections were discontinued due to these events. Additional information submitted 10 April 2013 and 26 April 2013 included the rheumatologist's note, in which he assessed the subject as having a severe degenerative osteoarthritis of her left thumb with acute symptoms brought about by minor trauma. There was no laboratory evidence of autoimmune disease.

Reviewer comment: *The specialist's assessment that this is not an autoimmune event appears reasonable.*

In the two studies that utilized review of potential AESIs by an expert panel, both demonstrated that a small number of new-onset confirmed AESIs or AIAEs were

reported almost exclusively in the Heplisav groups. Per SEAC adjudication and including the subject with Tolosa-Hunt syndrome as determined by FDA-consultants, in DV2-HBV-16 and -23, the one-year PSP, 14 subjects who received Heplisav (0.19%) and one subject who received Engerix-B (0.03%) reported new-onset AESIs. This does not include two additional subjects in the Heplisav group with suspected, but unconfirmed AESIs: narcolepsy in DV2-HBV-16 and granulomatous dermatitis in DV2-HBV-23. As noted in the initial ISS, the overall incidence of AESIs was low and limitations of sample size and safety follow-up periods, the relatively low background incidence of autoimmune events, and the indolent nature of many of these diseases make accurate assessment of risk of autoimmune disease with Heplisav difficult. However, two studies utilizing a blinded panel with relatively strict criteria for diagnosing these events have both shown an imbalance in AESIs, with the Heplisav group reporting approximately 6.3 times as many AESIs as the Engerix-B group.

In the Summary of Clinical Safety, the Applicant identifies the following AESIs in Study DV2-HBV-10 through retrospective review: Guillain-Barre syndrome, Basedow's disease (Grave's disease), lichen planus, and granulomatosis with polyangiitis in the Heplisav group and Bell's palsy, scleroderma, Basedow's disease, Raynaud's phenomenon, and p-ANCA positive vasculitis in the Engerix-B group. Subjects in DV2-HBV-10 were monitored for 28 weeks following first vaccination, were not referred for SEAC evaluation, and did not undergo further testing to determine whether AESIs were pre-existing or autoimmune. No other AESIs were identified in studies DV2-HBV14 or -22, which make up the remainder of the FDA mTSP. In the Summary of Clinical Safety, the Applicant identifies the following AESIs through retrospective review of supportive studies: Bell's palsy and uveitis in the Heplisav group and rheumatoid arthritis in the Engerix-B group. All three events were reported in Study DV2-HBV-04. Of note, the initial clinical review of the ISS did not identify the subject with lichen planus and included three subjects that are now excluded from the above summary. Upon review of the datasets, the clinical reviewer concludes that these subjects are two Heplisav recipients in DV2-HBV-10 with worsening disease (one with rheumatoid arthritis and one with SLE) and one Heplisav recipient in DV2-HBV-0001 with rheumatoid arthritis diagnosed on study day 556.

Based upon the previously stated evaluation of SEAC adjudicated AESIs in DV2-HBV-16 and -23 and the Applicant's retrospective review including AESIs identified in DV2-HBV-10, in the FDA mTSP, 18 subjects in the Heplisav group (0.24%) and six subjects in the Engerix-B group (0.16%) reported new onset AESIs. This does not include an additional event of narcolepsy in DV2-HBV-16 and granulomatous dermatitis, for which sarcoidosis was not ruled out, in DV2-HBV-23. Integration of AESIs in these studies is limited by different follow-up times and methods of assessment of events.

Bell's palsy was the most commonly reported new-onset AESI. Bell's palsy was reported in four Heplisav recipients and two Engerix-B recipients in the six month PSP and mTSP (6 months), and in six Heplisav recipients and two Engerix-B recipients in the one-year PSP. An additional Heplisav recipient reported Bell's palsy in study DV2-HBV-004. Please see section 6.3.12.5 for the events that occurred in Study DV2-HBV-23. Subjects in the other studies included a 53 year-old woman who reported Bell's palsy 16 days following dose 1 of Heplisav (DV2-HBV-004), a 59 year-old man who reported Bell's palsy 217 days after dose 2 of Heplisav (DV2-HBV-016), and a 34 year-old man who reported Bell's palsy 122 days after Engerix-B (DV2-HBV-010).

Reviewer comment: *The ISS shows a diminished imbalance in events of Bell's palsy between the two study groups. No subjects that were identified in the ISS reported Bell's palsy with an onset following vaccination in the 30-60 day range that has previously been identified as the risk window with another vaccine that was strongly associated with Bell's palsy.¹⁴ Of note, Bell's palsy is listed in the Engerix-B package insert as occurring following vaccination in post-marketing safety reports.*

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Please see the review of the initial BLA submission.

8.5.2 Time Dependency for Adverse Events

Please see discussions of individual events.

8.5.3 Product-Demographic Interactions

The Applicant did provide an integrated analysis of safety outcomes based upon their safety populations. However, the integration of safety data in these populations is problematic for the reasons stated above. Consequently, we will ask for an analysis of safety based on integrated safety populations that the FDA has identified.

8.5.4 Product-Disease Interactions

The population enrolled in Study DV2-HBV-23 was different from the populations enrolled in previous studies, particularly in cardiac disease risk factors. Study DV2-HBV-23 was the only study in which an imbalance in cardiac events, in particular acute myocardial infarction, was observed.

Reviewer comment: *The proposed indication for Heplisav in this CR is immunization against all known subtypes of hepatitis B virus in adults 18 years of age and older. An adjuvanted vaccine might be targeted to populations that tend to demonstrate higher rates of non-response to approved hepatitis B vaccines (for example, older individuals, obese individuals, smokers) or to subjects on dialysis who require a higher dose of approved vaccines yearly confirmation of anti-HBsAg levels. A true safety signal in cardiac events in populations with cardiac risk factors would be concerning, as those populations might targeted for vaccination with Heplisav.*

8.5.5 Product-Product Interactions

Not applicable.

8.5.6 Human Carcinogenicity

Not applicable.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.5.8 Immunogenicity (Safety)

Please see safety conclusions (section 8.6).

8.5.9 Person-to-Person Transmission, Shedding

Not applicable.

8.6 Safety Conclusions

The ISS conducted by the FDA focused on SAEs and AESIs, as these safety outcomes were collected in DV2-HBV-23, the major trial submitted in response to the complete response, and overlapped with previous trials. The FDA ISS was based on the following three populations: 1) a six-month primary safety population (PSP), including all three pivotal studies; 2) a one-year PSP, including the two pivotal trials that monitored SAEs and AESIs for one year; and 3) a six-month modified total safety population (mTSP), including all studies that used the proposed formulation of Heplisav. The subject population in the mTSP was a similar age and gender composition as the largest pivotal study, DV2-HBV-23. The mTSP was slightly less diverse than DV2-HBV-23 and subjects had fewer cardiac risk factors than those enrolled in DV2-HBV-23.

Deaths were balanced between treatment groups in the six month safety populations, but a slight imbalance was observed in the one-year PSP, driven by the deaths reported in Study DV2-HBV-23. Excluding deaths due to overdose and injury, there were 17 deaths in the subjects who received at least one dose of Heplisav (0.23%) and five deaths in subjects who received at least one dose of Engerix-B (0.15%). SAEs and non-fatal SAEs occurred at similar rates in the Heplisav and Engerix-B treatment groups in the integrated safety populations. SAEs in the cardiac system organ class were slightly more frequent in subjects who received Engerix-B in the six-month ISS populations, but more frequent in subjects receiving Heplisav in the one-year ISS population. However, when considering events that are likely to be acute cardiac ischemic events, a smaller imbalance than that observed in Study DV2-HBV-23 was seen in all three FDA safety populations. Given the seriousness of the events of AMI and deaths and the degree of the imbalance observed in one of the pivotal trials, further assessment of all cardiac SAEs is required in order to assess the risk benefit profile of the Heplisav.

In the two studies that utilized review of potential AESIs by an expert panel, both demonstrated that a small number of new-onset confirmed AESIs or AIAEs were reported almost exclusively in the Heplisav groups. Per SEAC adjudication and including the subject with Tolosa-Hunt syndrome, in DV2-HBV-16 and -23, the one-year PSP, 14 subjects who received Heplisav (0.19%) and 1 subject who received Engerix-B (0.03%) reported new-onset AESIs. This does not include two additional subjects in the Heplisav group with suspected, but unconfirmed AESIs: narcolepsy in DV2-HBV-16 and granulomatous dermatitis in DV2-HBV-23.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No trials were conducted specifically to assess the safety of HEPLSIAV in pregnancy and pregnancy was an exclusion criterion for all clinical trials of Heplisav. Limited data are available from subjects who became pregnant after receiving Heplisav.

The clinical review of the initial BLA submission contains a discussion of pregnancies reported in the clinical trials conducted prior to submission of the BLA.

In Study DV2-HBV-23, 41 pregnancies were reported in 40 subjects (26 pregnancies in 26 subjects in Heplisav, 15 pregnancies in 14 subjects in Engerix-B). The pregnancy outcomes in the Heplisav group were as follows: healthy term delivery (n = 12), spontaneous abortion (n = 3), induced abortion (n = 2), premature delivery (n = 1), congenital Ebstein's anomaly (n = 1), and unknown (n = 7). One subject reported gestational diabetes in the mother with a healthy term delivery. The pregnancy outcomes in the Engerix-B group were as follows: healthy term delivery (n = 8), spontaneous abortion (n = 2), induced abortion (n = 2), fetal complication (n = 1), congenital Ebstein's anomaly (n = 1), and unknown (n = 1). There were no pregnancies reported in Study DV2-HBV-22.

Subject 106-213 was a 35 year-old woman with medical history of diabetes type 2, morbid obesity, post-traumatic stress disorder, anxiety, depression, irritable bowel syndrome, and one prior spontaneous abortion. She reported concomitant medication of metformin, Levemir (insulin detemir), Bydureon (exenatide), Zoloft (sertraline hydrochloride), Lamictal (lamotrigine), Abilify (aripiprazole), prazosin, and amitriptyline. She had a positive urine pregnancy test 21 days following her second dose of Heplisav, 26 days after her last menstrual period (LMP). She reportedly discontinued all medications at this time. Sixteen days later, 42 days after her LMP, she had a spontaneous abortion.

Subject 129-154 was a 30 year-old woman with “three prior pregnancies and one induced abortion.” At the Week 24 study visit, a positive urine pregnancy test was obtained. The subject reported bleeding had started the previous day, assumed to be her LMP. Ultrasound demonstrated an empty uterus. No treatment for the spontaneous abortion was given.

Subject 134-047 was a 41 year-old woman with a medical history of headaches, migraines, hypertension, hyperlipidemia, asthma, and uterine fibroids with two prior pregnancies. She had a positive serum pregnancy test approximately nine months after the second dose of Heplisav. Approximately one month later no fetal pole was seen on ultrasound and three weeks after that a spontaneous abortion was reported.

Subject 139-119 was a 31 year-old woman taking Effexor (venlafaxine hydrochloride) for depression with two prior pregnancies and one spontaneous abortion. She reported a pregnancy while on study, with an estimated date of conception 45 days after the second dose of Heplisav. Placenta previa was diagnosed and she delivered a female infant via C-section at 31 weeks gestation. At study conclusion, the subject and her infant were reported to be doing well.

Subject 120-019 was a 25-year-old African-American woman with a past medical history of two prior pregnancies (one spontaneous abortion and one prior C-section), urinary tract infection, and morbid obesity. Approximately six months after the second dose of Heplisav, the subject had a positive urine pregnancy test. LMP was estimated approximately 4.5 months following dose 2. A first trimester ultrasound revealed a dichorionic/diamniotic pregnancy with intrauterine growth restriction (IUGR) for each fetus and a congenital cardiac anomaly in one fetus. At approximately 36 weeks of gestation, she was admitted to the hospital. An ultrasound at that time revealed both babies with less than the 5th growth percentile and one baby with Ebstein's anomaly.

The subject underwent a C-section and delivered a viable male and female infant. No birthweights are reported, but the female infant was noted to be small for gestational age and with a systolic murmur.

In the Total Safety Population, the Applicant reports that there were 40 pregnancies reported in Heplisav recipients with the following outcomes: healthy term delivery (n = 21), spontaneous abortion (n = 3), induced abortion (n = 4), healthy premature delivery (n = 2), stillbirth (n = 1), congenital Ebstein's anomaly (n = 1), pending at the time of the submission (n = 3), and unknown (n = 5).

Reviewer comment: *Data are insufficient to assess Heplisav in pregnancy. There is no evidence that Heplisav contributed to the adverse outcome of any pregnancy listed above. We will ask the Applicant to submit updated narratives for any pregnancies that were ongoing. Review of any information they have submitted following the 9 September IR is deferred until the next review cycle.*

9.1.2 Use During Lactation

No clinical data are available to address the use of Heplisav during lactation.

9.1.3 Pediatric Use and PREA Considerations

Not applicable. Please see the clinical review of the initial BLA submission for a discussion of the Pediatric Research Committee meeting regarding this product.

9.1.4 Immunocompromised Patients

No data have been submitted regarding the safety and immunogenicity of this product in immunocompromised subjects.

9.1.5 Geriatric Use

Not applicable.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not applicable.

10. CONCLUSIONS

The complete response letter issued in February 2013, noted concerns with the size of the safety database for Heplisav and the occurrence of two potential events of vasculitis in Heplisav recipients. In response, the Applicant has submitted Study DV2-HBV-23, a large safety study in which 5587 subjects received Heplisav and 2781 subjects received Engerix-B and were monitored for one year following second vaccination.

Immunogenicity was comparable to previous studies, although immunogenicity results from those studies were revised by the Applicant in their Complete Response and cannot yet be verified. Safety review identified notable imbalances, not observed in previous studies, in deaths and cardiac SAEs, in particular acute myocardial infarction, with Heplisav recipients reporting more events. The clinical significance of the cardiac events cannot be fully assessed as narratives for all events and all Applicant analyses were not submitted with the March 2016 complete response. Approval is not recommended at this time as further evaluation of these imbalances is underway.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

We are unable to assess risk-benefit of this vaccine at the time of this review. We will review the corrected immunogenicity data for Studies DV2-HBV-10 and -16, responses to questions regarding such study conduct issues as determination of protocol deviations in Study DV2-HBV-23 and additional requested safety information to fully evaluate the safety and overall risk-benefit profile of Heplisav.

11.2 Risk-Benefit Summary and Assessment

Not able to be assessed at this time.

11.3 Discussion of Regulatory Options

The information submitted in the CR is insufficient to recommend approval of Heplisav at this time for the reasons previously stated.

11.4 Recommendations on Regulatory Actions

The data available prior to the 9 September 2016 IR are not sufficient to adequately determine the safety of the product. In addition to review of the data submitted in response to the September 9 2016 IR, the following comments will be communicated to the Applicant:

The following questions refer to study HBV-23:

1. Subject 128-042 reported an MAE of MI 112 days following the first injection of HEPLISAV of one day duration. In the CSR, on page 106, you report that this was a history of MI and not an acute treatment-emergent event. However, this event was coded as treatment-emergent in the ADAE datasets. Please explain this discrepancy. Please describe for this event, and in general, how you reconcile discrepant reporting and provide any other information you have regarding this event.
2. In the CSR, on page 106, you note that two subjects, 122-308 and 122-448, received Engerix-B and reported a medically attended adverse event (MAE) of troponin increased, and that these events “were non-serious MAEs without myocardial infarction.” Both subjects reported serious adverse events coincident with the MAEs of troponin increased, “diabetes mellitus inadequate control” and urosepsis. Please provide the narratives of these events, CRFs, lab results, and any other information available relevant to determining the diagnosis and severity of the MAEs of troponin increased for these subjects.
3. Please provide the CRFs and the narratives for any subjects reporting the following:
 - a. an SAE of chest pain or non-cardiac chest pain
 - b. an SAE of cerebrovascular accident, transient ischemic attack, or other preferred term indicative of one of these events.
4. In our analysis of your ADAE dataset, we note the following events for which the rate in the HEPLISAV group exceeded that in the Engerix-B group. Please provide your assessment of these imbalances, including any explanation for the

differences noted between study groups, an exploration of the potential relationship between HEPLISAV and the events, and a discussion of any biologically plausible mechanism.

- a. MAEs of herpes zoster
 - b. MAEs of atrial fibrillation
 - c. MAEs and SAEs of bipolar and bipolar 1 and SAEs of depression and depression suicidal
 - d. MAEs of drug hypersensitivity
 - e. SAEs of sepsis
 - f. SAEs of diabetic ketoacidosis
5. We note in section 16.1.4 of the complete study report, *List and Description of Investigators and Sites*, it appears that 24 subjects transferred from one study site to another. However, we cannot locate the reason subjects transferred from one site to another. Please specify where in the submission the explanation is located or provide an explanation for why subjects transferred from one site to another and how you ensured seamless follow-up and capture of safety information.
 6. As per the Safety Evaluation and Adjudication Committee (SEAC) Charter, Version 5, dated May 21, 2015, section 6.0 g, subjects with newly discovered potentially autoimmune hypothyroid disease entered the SEAC adjudication process but had baseline laboratory specimens examined. "Subjects with a documented diagnosis of hypothyroidism prior to enrollment in the study, or by laboratory examination of specimens obtained at baseline prior to the first administration of study vaccine [did] not require expert consultation or SEAC evaluation." We note that this was added in version 4 in November 18, 2014. Given that this represents a change in the procedures for adjudicating thyroid disease, and in order to assess all events of hypothyroidism similarly, please provide a list of all subjects, and their treatment assignment, who had thyroid assessments performed on their pre-vaccination laboratory draw, the results of that assessment, and whether those subjects were referred to the SEAC for evaluation.
 7. As per the HBV-23 CSR, page 87, you report 61 subjects with 65 diagnoses of potential new-onset AESIs or AIAEs evaluated by the SEAC. The datasets and the Adverse Events Listings Table 16.12.6.1 show 61 subjects with 68 events evaluated by the SEAC; thirty-nine subjects who received HEPLISAV reporting 41 events and 22 subjects who received Engerix-B reporting 27 events. Please clarify this apparent discrepancy.
 8. Subject 136-149 received HEPLISAV and was diagnosed with new-onset Hashimoto's thyroiditis and papillary thyroid cancer. In regard to the Week 28 elevated anti-thyroglobulin (anti-TG) level, the narrative notes that "the panel [SEAC] noted that this result was written in the case narrative as being taken from serum collected at baseline; however the date of the sample was 28 weeks

after the subject received the first dose of blinded study vaccine.” Please describe the events that led to erroneous information in the narrative prepared for the SEAC, other subjects and laboratory results that may have been erroneously reported, and the procedures that were put in place following this event in order to prevent other similar events from occurring.

9. Incomplete or inconsistent information was provided for several subjects who reported potential adverse events of special interest. Please provide the following information:
 - a. Subject 103-108 received HEPLISAV and was diagnosed with hypothyroidism, by her primary care physician, based on one slightly elevated thyroid stimulating hormone (TSH). Analysis of the subject's banked study baseline serum demonstrated a normal TSH. The investigator and the SEAC questioned the diagnosis. The subject declined further laboratory testing for hypothyroidism and evaluation by a specialist. As the diagnosis of this potential autoimmune event appears to be in question, please provide the results of testing of the banked Week 28 (approximately two months prior to diagnosis) serum for TSH and thyroid autoantibodies and the banked study baseline serum for thyroid autoantibodies, if autoantibodies are found at Week 28.
 - b. Subject 112-326, who received HEPLISAV and was diagnosed with hypothyroidism with negative testing for anti-thyroperoxidase (anti-TPO) and anti-TG antibodies. The subject was evaluated by an endocrinologist but the results of the endocrinologist's assessment of the subject, following the negative thyroid autoantibody testing, were not provided in the narrative. Please provide the endocrinologist's assessment of the etiology of the subject's hypothyroidism.
 - c. Regarding subject 118-111, who was diagnosed with hypothyroidism following vaccination with Engerix-B, the narrative states the subject had a history of “inflammatory bowel disease (IBS).” Please clarify if this subject had a history of inflammatory bowel disease or irritable bowel syndrome and if inflammatory bowel disease, please comment on the subject's eligibility prior to study enrollment.
 - d. Subject 114-027 was diagnosed with Graves' disease following vaccination with HEPLISAV based upon low TSH and elevated thyroid stimulating immunoglobulin (TSI). This event was assessed by the SEAC as a pre-existing autoimmune event based upon the endocrinologist's assessment of low-normal TSHs over the eight years prior to study enrollment. As the subject had clear evidence of persistent abnormal TSH and elevated TSI following, but not prior to, vaccination, based upon the information available, The FDA considers this a new-onset adverse event of special interest (AESI). A pre-vaccination elevated TSI would likely provide evidence that the AESI was pre-existing.
 - e. Subject 133-107 received HEPLISAV and was initially diagnosed with hypothyroidism by their primary care physician. The subject was also evaluated by an endocrinologist for hypothyroidism and further testing

was performed. The investigator and the SEAC later determined that this diagnosis was an error. Please provide the endocrinologist's ultimate assessment of the subject following the laboratory and ultrasound evaluations. The subject had laboratory results that were consistent with subclinical hyperthyroidism, yet this does not appear to be reported as an adverse event. Please clarify if the subject's subclinical hyperthyroidism was evaluated by an endocrinologist or considered as a potential immune-mediated condition.

10. Subject 105-238 received HEPLISAV and reported an MAE with a preferred term of phlebitis superficial 245 days following the second dose. This event was not flagged as a VTE in the datasets, nor does it appear to be reported as such in the CSR. Please explain. Please provide the narrative and CRFs for this subject. Did this subject have thrombophilia testing performed? If so, please provide the results.
11. In study HBV-23, subjects who reported MAEs of VTE were to return to the study site to have laboratory evaluations for thrombophilia. Please provide a summary of these evaluations and your interpretation of any abnormalities, or provide the location within the submission that contains this information.
12. In the CSR on page 82, you report that "all subjects in both vaccine treatment groups who had a new-onset thrombotic/thromboembolic event had at least one pre-disposing risk factor for thrombosis with the exception of "one Engerix-B subject". Please clarify the pre-disposing risk factor for subject 140-099.
13. Incomplete information was provided for several subjects who experienced adverse events. Please provide the following information:
 - a. For subject 108-065, who reported granuloma annulare, please provide any other information available regarding the event, evaluation of the subject, and whether the event may be potentially immune-mediated.
 - b. For subject 113-016, who reported pyoderma gangrenosum, please provide any other information available regarding the event, its assessment, associated symptoms or diagnoses, an update on the subject's condition and new diagnoses, and whether the event may be potentially immune-mediated.
 - c. For subject 123-049, who reported "anaphylaxis reaction secondary to allergy serum" on the same day the subject received dose 2 of HEPLISAV, please provide further information describing this event and why it was not attributed to vaccination.
 - d. For subject 117-125, who reported abnormal serum protein electrophoresis, please provide the laboratory records as there appear to be inconsistencies in the narrative in describing laboratory evaluation dates. Please provide an update for this subject, as the narrative states he was to be evaluated January 2016.

- e. For subjects 102-063 and 112-237, who reported multiple myeloma, please provide narratives and CRFs for these events and subjects, respectively.
 - f. Subject 102-046, received HEPLISAV and had one reported MAE, diaphragmatic paralysis, 226 days after the second dose that was also serious. Please provide a brief narrative which includes the investigator's assessment of the etiology of the event (for example trauma, cardiac surgery, ALS, myopathy, MS, Guillain Barré syndrome).
14. For subjects who reported a pregnancy that was ongoing at the conclusion of the study, please submit updated information regarding the outcome of those pregnancies, or identify the location within previously submitted material.
15. Please provide an analysis of safety events, including deaths, MAEs, SAEs, and AESIs, reported in study HBV-23 by age, gender, race, and ethnicity.
16. Please provide a complete list of all subjects in study DV2-HBV-23 who were lost to follow-up (LTFU) and who were subsequently reengaged. This request is based on the incomplete information obtained during the BIMO inspections. The inspections noted that sites did not accurately capture the LTFU subjects and those who were subsequently reengaged. For example, two subjects whose records were reviewed during the inspection were LTFU and reengaged but neither were identified on a site list of LTFU and reengaged subjects. With an incomplete list of potentially affected subjects we are unable to determine the full scope of number of LTFU subjects and reengaged in study DV2-HBV-23.
17. A BIMO inspection in study DV2-HBV-23 identified a Protocol Deviation guidance document instructing sites to maintain a protocol deviations log as an Excel spreadsheet. These documents could potentially be changed at any time by any individual without the ability to track who made changes and when they were made. Because the study populations were based upon protocol deviations, please explain how you verified that the information in the logs was complete and accurate.

Regarding your Integrated Safety Analysis:

18. In your Summary of Clinical Safety, you present integrated analyses of safety endpoints based upon a Primary Safety Population (PSP) and a Total Safety Population (TSP). The PSP includes Study DV2-HBV-10, which monitored SAEs for 28 weeks following dose 1, and Studies DV2-HBV-16 and -23, which monitored SAEs for one year or more following dose 1. The TSP includes studies which did not employ the final formulation of HEPLISAV. The FDA's integrated safety analysis will focus on deaths, SAEs, and AESIs because these events were collected in studies DV2-HBV-23 and -22, the studies submitted since the initial BLA review; we will not analyze MAEs and AEs in an integrated fashion. In order to address concerns that studies monitoring AEs for varying lengths of time and studies using distinct formulations of study product are not integratable, the FDA plans to analyze an integrated summary of safety using the following populations:
- a. Primary Safety Population (PSP)

- i. 6 month PSP: DV2-HBV-10, DV2-HBV-16, DV2-HBV-23
SAEs reported from vaccination through Week 28
- ii. 1 year PSP: DV2-HBV-16, DV2-HBV-23
SAEs reported from vaccination through study end (Week 52-56)

b. Modified Total Safety Population (mTSP):

- i. DV2-HBV-10, DV2-HBV-14, DV2-HBV-16, DV2-HBV-22, DV2-HBV-23

SAEs reported from vaccination through Week 28

Please provide an addendum to the Summary of Clinical Safety, analyzing important safety outcomes based upon these populations. At a minimum, this should include deaths, SAEs, cardiac SAEs, myocardial infarction, cerebrovascular disease, venous thromboembolism, acute and chronic renal failure, and AESIs. Please also include an analysis of safety outcomes by age, gender, race, and ethnicity based on these populations.

Regarding the overall submission:

19. Multiple hyperlinks to clinical sections of your submissions are not functional. Please ensure that all hyperlinks are working appropriately.

11.5 Labeling Review and Recommendations

Deferred

11.6 Recommendations on Postmarketing Actions

Deferred

APPENDIX A – EXPERT CONSULTATIONS

Four consults regarding the case of cavernous sinus syndrome, possibly Tolosa-Hunt syndrome, reported in Study DV2-HBV-16, and two consults regarding the case of Takayasu's arteritis reported in Study DV2-HBV-23 appear below.

Dr. Patricia Coyle, Neurology Department, Stony Brook Medicine

1

I have reviewed the provided data, including the January 23, 2013 memorandum, as well as the July 18, 2009 consultation regarding the Wegener's granulomatosis case.

In summary, I do feel this patient meets the criteria for Tolosa-Hunt syndrome (THS) as we currently apply it. These patients can have negative MRI scans. The clear-cut response to steroids is really highly suggestive, and not expected with cavernous sinus syndrome. The etiology of THS is not known for sure, but the presumption is that it is immune mediated. Certainly there is nonspecific inflammation pathologically, and excellent response to steroids, both of which support an etiologic term immune-mediated etiology. This etiologic term (immune mediate) seems more appropriate than autoimmune, which implies an auto-antigen target. THS is generally considered under orbital inflammatory diseases, and within the spectrum of idiopathic orbital inflammation.

Questions for the consultant

1. Based on the information provided, is this case consistent with THS?

The most up-to-date diagnostic criteria for THS are from the 2004 International Headache Society. Diagnostic criteria are:

- a) One or more episodes of unilateral orbital pain persisting for weeks if untreated
- b) Paresis of one or more of the third, fourth and/or sixth cranial nerves and/or demonstration of granuloma by MRI or biopsy
- c) Paresis coincides with pain onset, or follows within 2 weeks
- d) Pain and paresis resolve within 72 hours of adequate corticosteroids
- e) Other causes have been excluded by appropriate investigations

There has been debate about whether MRI inflammatory changes should be required for diagnosis. In one review of 124 cases, only 35% showed MRI inflammation or biopsy evidence of granuloma; 33% had normal neuroimaging; and 31% turned out to have a specific lesion with a secondary syndrome (Lamantia et al, 2006). In a series of 126 consecutive cavernous sinus syndrome patients, the most common cause (in 64%) turned out to be a tumor (Fernandez et al, 2007). However pain at onset of the syndrome, and cranial nerve III involvement, were independently associated with THS.

Although this patient never showed MRI evidence of cavernous sinus inflammation/granulomatous tissue, I believe they do meet all the diagnostic requirements: episodes of unilateral orbital pain; involvement of the third nerve; onset of diplopia within a short period of the left orbit pain (December 31, 2010 pain onset to early January 2011 intermittent diplopia onset, to January 31, 2011 persistent diplopia); excellent pain resolution with steroids (confirmed on multiple occasions); and other causes excluded. Cranial nerve III is most commonly affected in THS (85%), with 30% showing involvement of cranial nerve V (first division), as did this gentleman. There was no evidence for tumor, stroke, sarcoidosis, or infection. Therefore I do think this patient would qualify for THS, even though having a normal MRI is unusual. In a 2008 literature search that reviewed the diagnosis in 62 patients; 92.1% had a positive MRI which normalized after clinical resolution (Colnaghi et al, 2008).

2. Is there any overlap between THS and Wegener's granulomatosis?

Granulomatosis with polyangiitis (Wegener's granulomatosis), according to the 1990 American College of Rheumatology Criteria, requires two of four criteria: 1. Nasal or oral inflammation (painful or painless oral ulcers, or purulent/bloody nasal discharge). 2. Abnormal chest x-ray (nodules, fixed infiltrates, or cavities). 3. Urine microhematuria (>5 RBCs per HPF), or RBC casts in the urine sediment. 4. Granulomatous inflammation on biopsy in the arterial wall or perivascular/extravascular area around arteries or arterioles. This is a rare multisystem presumptive autoimmune disorder with necrotizing granulomatous inflammation and vasculitis involving small and medium sized blood vessels. It is an ANCA-associated vasculitis, with a predilection for the upper and lower respiratory tracts, and the kidney. Generally there are diffusely staining antibodies against cytoplasmic ANCA (C-ANCA) directed against serine proteinase 3 antigen.

Clearly THS is not Wegener's. However, there are limited forms of Wegener's relatively confined to the respiratory tract region. There has been speculation that THS may be a limited form of Wegener's (Montecucco et al, 1993; Thajeb et al, 2000). Patients described in this category were C-ANCA positive however. Wegener's was reported to involve the cavernous sinus, but this was associated with significant sinus disease (Fadil et al, 2007).

The pathology is similar but not identical. I believe the data does not strongly support true overlap. Clearly they are both inflammatory disorders, which can involve the cavernous sinus.

3. If you determine that this is a case of THS, please comment on the likelihood of identifying a case of Wegener's granulomatosis and a case of THS in a database of 4,000 otherwise healthy individuals between the ages of 18 and 70 years old followed for six and twelve months in their respective studies.

Both THS and Wegener's are rare disorders. The annual incidence of Wegener's in the United States is estimated at 10 per million, while the incidence of THS is estimated at 1 per million. Therefore the likelihood of finding one case of each in 4,000 individuals over a year is extraordinarily unlikely, and does raise concern about a possible link to immune-mediated inflammatory diseases. Of note, the THS case was eight months after the last vaccination however.

4. If there is overlap, do you think there is any basis for etiologic relatedness between this case and the case of Wegner's granulomatosis in the clinical trial DV2-HBV-10? Details of the case of Wegener's granulomatosis are included in the appendix.

As noted above, the link between Wegener's and THS is questionable. THS is not a limited Wegener's. That being said, both are likely immune mediated. Wegener's can rarely produce local involvement that mimics THS, and it would be difficult to rule out that there might not be some etiologic links promoting similar immune-mediated processes, given the relative rarity of both these disorders. However, it is clear that Wegener's and THS are not the same.

5. In your opinion, is it plausible mechanistically, that a Hepatitis B recombinant protein with a TLR-9 agonist adjuvant could be involved in the pathogenesis of this adverse event? What role, if any, do you think the TLR-9 agonist adjuvant played?

There has been an ongoing but low level concern about the Hepatitis B vaccine and immune-mediated events. This was reviewed in the July 18, 2009 commentary, question 3.

The current test vaccine is using a unique adjuvant; there is very limited experience with it. The adjuvant clearly works by activating toll like receptor-9 (TLR-9). TLR-9 has been implicated in the pathogenesis of immune-mediated disease such as systemic lupus erythematosus. Therefore there is a concern that this particular vaccine and adjuvant could be involved. However, multiple autoimmune disorders are not being seen. The THS case, following the issue of the Wegener's case, is a clear concern. However, the data is not sufficient currently to prevent this vaccine development. In my opinion, they are two distinct disorders.

6. Is this case consistent with any other etiology, autoimmune or non-autoimmune that has not been ruled out?

THS is a diagnosis of exclusion. You need to rule out primary tumor, lymphoma or metastatic tumor; aneurysm; carotid cavernous sinus fistula; carotid dissection; cavernous sinus thrombosis; infection; sarcoidosis; diabetic cranial neuropathy; giant cell arteritis or vasculitis; I believe basically these were ruled out. The highly

suggestive clinical syndrome, along with the very clear steroid response, made me comfortable that this is the correct diagnosis.

7. What other clinical test or information, if any, would be useful in establishing a definitive diagnosis in his case?

I do not see any clinical test or information that was missed to make a more definitive diagnosis. Biopsy is not indicated. I do not believe angiography or MR venogram were necessary. I do not understand why the diagnosis was changed to cavernous sinus syndrome, although of course that is technically correct (THS is a cavernous sinus syndrome).

8. What additional safety monitoring or exclusion criteria, if any, do you suggest in designing clinical trials involving vaccines with CpG adjuvant?

None additional. Individuals with a history of autoimmune disease or significant auto-antibody titers should not be entered. It may be worthwhile noting eosinophilia, to see if there is any relationship to predicting issues.

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Consultative Review and Evaluation of Clinical Data

Subject: Request for Neurology consultation regarding HEPLISAV (BLA 125428)

From: Devanand Jillapalli, MD (Reviewer) Devanand Jillapalli
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To: Lorie B. Smith, MD, MHS and Alexandra S. Worobec, MD
Medical Officers
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Material Reviewed: Consult request, possible Tolosa-Hunt syndrome case summary and source documents, and relevant literature.

Date Received: January 2, 2013

Date Reviewed: February 28, 2013

The Division of Vaccines and Related Products Applications (DVRPA) from the Center for Biologics and Evaluation (CBER) has requested the Division of Neurology Products (DNP) to provide responses to the following questions:

1. Based on the information provided, is this case consistent with Tolosa-Hunt syndrome?
2. Is there any overlap between Tolosa-Hunt syndrome and Wegener's granulomatosis?
3. If you determine that this is a case of Tolosa-Hunt syndrome, please comment on the likelihood of identifying a case of Wegener's granulomatosis and a case of Tolosa-Hunt syndrome in a database of 4,000 otherwise healthy individuals between the ages of 18 and 70 years old followed for six and twelve months in their respective studies.
4. If there is overlap, do you think there is any basis for etiologic relatedness between this case and the case of Wegener's granulomatosis in the clinical trial DV2-HBV-10? Details of the case of Wegener's granulomatosis are included in the appendix.
5. In your opinion, is it plausible mechanistically, that a Hepatitis B recombinant protein with a TLR-9 agonist adjuvant could be involved in the pathogenesis of this adverse event? What role, if any do you think the TLR-9 agonist adjuvant played?

6. Is this case consistent with any other etiology, autoimmune or non-autoimmune that has not been ruled out?
7. What other clinical test or information, if any, would be useful in establishing a definitive diagnosis in this case?
8. What additional safety monitoring or exclusion criteria, if any, do you suggest in designing clinical trials involving vaccines with CpG adjuvant?

Background

In 2012, Dynavax Technologies Corporation (Sponsor) submitted a Biologics Licensing Application for HEPLISAV – a new vaccine for adult hepatitis B. The Agency issued a Complete Response letter on February 24, 2013 citing the need for further clinical evaluation and noting a concern that the vaccine's novel adjuvant may cause rare autoimmune events. In the consult request, DVRPA has provided the following background information.

HEPLISAV is comprised of recombinant hepatitis B surface antigen (rHBsAg) combined with a new cytosine phosphoguanine (CpG) enriched oligodeoxynucleotide (ODN) phosphorothioate immunostimulatory adjuvant. The proposed indication for this new vaccine is for active immunization against all subtypes of hepatitis B virus infection in adults 18-70 years of age. Each 0.5 mL dose contains 20 mcg of rHBsAg and 3000 mcg of the 1018 ISS adjuvant. The proposed dosing regimen is two 0.5 mL doses administered 1 month apart.

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 vertebral (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). HEPLISAV is proposed to act by using an adjuvant that activates TLR9 which combined with HBsAg, leads to production of HBsAg-specific antibodies.

While TLR activation is critical for initiation of the innate and adaptive immune response to invading pathogens, the inappropriate activation of the innate immune system may, in principle, induce autoimmune responses and chronic inflammatory diseases. In light of the theoretical potential for TLR-agonist adjuvants, such as CpG, to induce or exacerbate autoimmune disease in humans, 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.

Two randomized, controlled Phase 3 trials, study DV2-HBV-10 and DV2-HBV-16, compared the safety and immunogenicity of HEPLISAV to that of the active comparator, ENGERIX-B. ENGERIX-B is a licensed vaccine against hepatitis B comprised of recombinant antigen adsorbed to aluminum hydroxide. The Phase 3 trials were conducted in 4,864 subjects (HEPLISAV: N=3777, ENGERIX-B: N=1087) followed for adverse events and for serious adverse events for 28 weeks in study DV2-HBV-10 and 52 weeks in DV2-HBV-16. Additionally, there were 7 other supportive trials conducted in a total of 981 subjects

(HEPLISAV: N=648, ENGERIX-B: N=333) followed for safety events for various time periods. The total safety database included 5845 subjects (HEPLISAV: N=4425, ENGERIX-B: N=1420). The results of the safety evaluation will be briefly summarized here.

Two deaths occurred in study DV2-HBV-16 – one each in HEPLISAV group (46 year old previously healthy male recipient died of a pulmonary embolus (b) (6) days after the second study injection) and ENGERIX-B group (64 year old male with multiple comorbidities died of cardiac arrest after having a myocardial infarction (b) (6) days after the second study injection). There was a numerical imbalance between the incidence of pulmonary embolus in HEPLISAV [5 (0.1%)] and ENGERIX-B recipients [0]. All five events occurred in individuals with underlying predisposition to thrombosis. Non-serious thrombotic events occurred with similar incidence between groups.

Because of the nature of the adjuvant, efforts were made to identify clinical cases of autoimmunity and evaluate biomarkers of autoimmunity, such as ANA, anti-dsDNA, and ESR in individuals enrolled in studies of HEPLISAV. DVRPA review notes that there were no clinically significant differences in autoimmune laboratory parameters between groups.

A previously healthy HEPLISAV recipient from study DV2-HBV-10 developed granulomatosis with polyangiitis (Wegener's granulomatosis) in 2008. The clinical development program was placed on clinical hold because of this event. The Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) was consulted on 7/18/2009. In September 2009, the clinical hold was lifted allowing the Sponsor to resume Phase III studies with additional monitoring.

In addition to the healthy patient who developed granulomatosis with polyangiitis, another ENGERIX-B recipient with a history of mixed connective tissue disease from study DV2-HBV-10 developed p-ANCA positive vasculitis. Based on the occurrence of these two events, the Sponsor conducted additional retrospective evaluations of serum specimens from trial subjects, and further analyses of adverse events were performed in an attempt to assess possible cases of autoimmunity. A retrospective analysis of adverse events that required immunosuppressive therapy (excluding asthma exacerbations and those on immunosuppressive therapy at baseline) was performed. This analysis showed a case of possible Tolosa-Hunt syndrome which is of interest because of its potential vasculitic or other autoimmune etiology. Reports in the literature suggest that this condition could be a limited form or initial presentation of Wegener's granulomatosis, and ANCA testing is often negative in this possible limited form of Wegener's granulomatosis. Because of the possibility of the occurrence of what may be a second vaccine-related case of granulomatous inflammatory disease in HEPLISAV trial subjects, DVRPA seeks the consultant's opinion regarding whether this case fulfills the criteria for diagnosis of Tolosa-Hunt syndrome.

DNP Response

The following are DNP responses to each of the questions in the consult request.

1. Based on the information provided, is this case consistent with Tolosa-Hunt syndrome?

Case Narrative: Subject #40-416 was a 69-year-old white male with no pertinent medical or surgical history other than recurrent rashes of uncertain etiology who received two HEPLISAV injections on 3/22/10 and 4/19/10 (and a saline placebo injection on 9/8/10). About 3 weeks after the first study injection, he experienced pruritic erythematous rash on elbows bilaterally which resolved with a course of topical steroids, and about 3 months after the second study injection experienced recurrent bouts of osteoarthritis of the right hand treated with oral and intramuscular injections of steroids. Subject reportedly developed "amblyopia" about 6 months after the second study injection which "failed to improve with corrective lenses". Severe headaches began more than 7 months after the second study injection. Three weeks after onset of these headaches, he sought evaluation in an emergency room for complaints of frontal headaches on the left. CT of the head and maxillofacial region showed minimal mucosal thickening of the ethmoid air cells bilaterally. He was discharged on antibiotics and hydrocodone for pain, but returned three days later with a left sided headache, pain around the left eye and numbness of the left forehead. He was given methylprednisolone in the ER (pain resolved while in the ER) but it is not clear if he was given a course of steroids. Shortly thereafter (more than 8 months after the second study injection), he was evaluated by an ophthalmologist for intermittent diplopia associated with headaches and was given a course of steroids. Symptoms significantly improved but headache returned after steroids were discontinued.

About one month after he was evaluated by the ophthalmologist (more than 9 months after the second study injection), he was hospitalized on (b) (6) for severe headache on the left, persistent double vision x 5 days, numbness on the left side of the face (forehead to upper lip), worsening of left eye droop, and worsening of vision. Physical examination showed that he was afebrile with ptosis on the left, slight adduction deficit on the left eye with deviation to the left on primary position, pupils equally reactive to light and left V1 deficit. Consulting ophthalmologist at admission noted that there was no jaw claudication or scalp tenderness, that "headache improved tremendously the next day" after starting oral steroids in the previous month and in addition, noted visual acuity of 20/50 left eye, severe ptosis with no edema or redness, abducens palsy on the left, and essentially unremarkable fundus. The ophthalmologist concluded that there was a high suspicion for cavernous sinus syndrome (inflammatory/tumor /vascular), likely inflammatory etiology considering tremendous improvement of symptoms with systemic steroids in the previous month. Prednisone 60 mg daily was initiated at admission. MRI of brain (with contrast) and CT angiography of the head were unremarkable. MRA of the circle of Willis was normal. Cerebrospinal fluid analyses (CSF) were normal; CSF bacterial culture were negative and VDRL non-reactive. The Attending Physician noted on 2/5/11 that imaging did not reveal evidence of cavernous sinus inflammation and the plan was to continue steroid and obtain MRI of orbits to rule out Tolosa-Hunt syndrome. MRI of the orbits with contrast showed normal globes and retrobulbar soft tissue, ophthalmologic veins, optic nerve and chiasm, and no abnormal signal or enhancement. Chest X-ray showed blunting of the left costophrenic angle and otherwise was normal. Serologic workup including TSH, angiotensin converting enzyme, erythrocyte sedimentation rate (16 mm), random blood glucose, c-reactive protein and ANA all of which were normal. Antibodies to myeloperoxidase, serine protease 3, Smith antigen, SSA, SSB and RNP were not detected. Headache, left eye pain and numbness of the face had resolved 3 days later, and he was discharged on oral prednisone with a diagnosis of Tolosa-Hunt

syndrome. About 6 weeks after discharge, physical examination was noted to be normal with the exception of a faint blanching rash limited to the upper extremities. Subsequent discussions between the sponsor and attending neurologist took place, and via an email (4/1/11), the neurologist changed the diagnosis from Tolosa-Hunt syndrome to cavernous sinus syndrome, noting that “.... he was diagnosed of Tolosa-Hunt syndrome. His workup was negative. So I think the more appropriate diagnosis in this context would be cavernous sinus syndrome.”

DNP response:

Diagnosis of neurological disorders typically begins with anatomic localization of the lesion followed by generation of differential diagnoses taking into consideration the potential pathological processes and etiologies as suggested by the clinical history/features and site of the lesion. The diagnosis of the above case will be discussed in that order.

The important clinical signs that this patient exhibited at hospital admission were severe ptosis (sympathetic fiber involvement from cavernous plexus), cranial 3, 5 (ophthalmologic branch) and 6 neuropathies, and to a lesser extent optic neuropathy, all on the left, localizing the anatomic site of the lesion to the superior orbital fissure, apex and/or the anterior cavernous sinus. The pertinent clinical features were those of severe headaches on the left for about 2 months which were “improved tremendously the next day” to oral steroids and which recurred after cessation of steroid therapy. Thus, the clinical presentation was that of a subacute painful unilateral ophthalmoplegia which is usually traceable to one of the several potential underlying pathophysiological processes – aneurysm, tumor or inflammatory/ granulomatous process, in the anterior portion of the cavernous sinus or the adjacent superior orbital fissure¹.

After reasonably excluding intracranial aneurysms or tumor in or near the vicinity of the site of interest by MRI of the brain (with contrast), CT angiography and MRA of the brain (these images which were provided by CBER on a DVD disc were also reviewed), an idiopathic inflammatory/granulomatous condition, termed Tolosa-Hunt syndrome¹, is most likely present. Some authorities on the subject state that the inflammatory changes in Tolosa-Hunt syndrome are limited to the superior orbital fissure¹; however, others think that the inflammation is in the cavernous sinus²⁻⁴, while still others opine that it affects the cavernous sinus, superior orbital fissure and the apex of the orbit⁵⁻⁷. The superior orbital fissure and the anterior cavernous sinus are contiguous structures; therefore, it is not surprising, that the inflammation in Tolosa-Hunt syndrome can localize to the superior orbital fissure and/or the anterior cavernous sinus. Inflammatory changes in any of these contiguous structures can result in similar clinical presentation and cranial deficits. It is for this reason, perhaps, that there is confusion in nosology: Tolosa-Hunt syndrome is sometimes used synonymously with cavernous sinus syndrome when inflammation is thought to be the underlying process (we prefer to use the term ‘Tolosa-Hunt syndrome’). Of note, cavernous sinus syndrome can also result from other pathophysiological processes such as trauma or neoplastic invasion¹, carotid-cavernous fistulas, compression from an intracavernous internal artery aneurysm, thrombophlebitis, or rare but life-threatening infections (bacterial, or fungal – aspergillosis, mucormycosis in diabetic or immunosuppressed patients)²⁻³. In this patient, the clinical features, investigations and clinical response as described above have reasonably excluded these alternate pathological processes that can potentially affect the cavernous sinus.

A marked response with reduction in pain and improved ophthalmoplegia in one or two days of treatment with corticosteroids is confirmatory of the diagnosis of Tolosa-Hunt syndrome¹. In this patient, the dramatic improvement to oral steroids, followed by relapse after cessation of steroid therapy, and during hospitalization one month later, resolution of headache, left eye pain and numbness of the face and improvement of ophthalmoplegia within a few days after starting high prednisone (60 mg/day) is strongly supportive of the diagnosis of Tolosa-Hunt syndrome. Other inflammatory conditions such as orbital pseudotumor (inflammatory enlargement of the extraocular muscles often accompanied by injection of the conjunctiva and lid and proptosis), sarcoidosis, lymphomatous infiltration, temporal arteritis or tumors of the parasellar region can also respond to steroid therapy. In this patient, normal MRI of the orbits and brain (both with contrast), chest X-ray, normal angiotensin converting enzyme levels, normal erythrocyte sedimentation rate, unremarkable cerebrospinal fluid analyses, the presenting clinical features including the absence of symptoms of jaw claudication or scalp tenderness, reasonably exclude these alternate etiologies.

The International Classification of Headache Disorders (ICHD)-II criteria for Tolosa-Hunt syndrome (see below) are essentially clinical and do not mandate the demonstration of granulomas by MRI or biopsy⁸. MRI of brain/orbits is essential to exclude alternate diagnoses but the demonstration of granulomas by MRI is not necessary for diagnosis of Tolosa-Hunt syndrome. Several authors argue that MRI demonstration of granulomas should play a pivotal role in the diagnosis because it was positive in 92.1% of cases (based on retrospective review of literature) and normalized after treatment⁵⁻⁶. Despite these assertions, the diagnosis of Tolosa-Hunt syndrome remains largely clinical, relying on clinical presentation, response to steroids and exclusion of alternate diagnoses^{1,2,8,9}. Biopsy is considered only in patients with rapidly progressive neurological impairment, high risk for malignant diseases, lack of response to steroids or other unusual findings in MRI⁹. Applying the ICHD-II criteria further supports the diagnosis of Tolosa-Hunt syndrome in this patient.

Diagnostic criteria:

- A. One or more episodes of unilateral orbital pain persisting for weeks if untreated
- B. Paresis of one or more of the third, fourth and/or sixth cranial nerves and/or demonstration of granulomas by MRI or biopsy
- C. Paresis coincides with the onset of pain or follows it within 2 weeks
- D. Pain and paresis resolve within 72 h when treated adequately with corticosteroids
- E. Other causes have been excluded by appropriate investigations¹

Note:

- 1. Other causes of painful ophthalmoplegia include tumours, vasculitis, basal meningitis, sarcoid, diabetes mellitus and ophthalmoplegic 'migraine'.

Comments:

Some reported cases of Tolosa-Hunt syndrome had additional involvement of the trigeminal nerve (commonly the first division) or optic, facial or acoustic nerves. Sympathetic innervation of the pupil is occasionally affected. The syndrome has been caused by granulomatous material in the cavernous sinus, superior orbital fissure or orbit in some biopsied cases. Careful follow-up is required to exclude other possible causes of painful ophthalmoplegia.

2. Is there any overlap between Tolosa-Hunt syndrome and Wegener's granulomatosis?

In 1954, Tolosa described a male patient who died a few days after an exploratory surgery of the sella turcica for left retro-orbital pain and ophthalmoplegia; the histopathological findings at post-mortem showed granulomatous tissue wrapped around the intracavernous portion of the carotid artery and without endoarteritic or mesoarteritic lesions¹⁰. In 1961, Hunt described a new syndrome on the basis of six patients with similar symptoms that improved with corticosteroids, and despite the lack of histopathological data postulated that this syndrome was caused by an inflammation of the cavernous sinus⁴. Biopsy is not routinely obtained in patients with Tolosa-Hunt syndrome, and consequentially, there is little data on histopathology^{9,11}.

Wegener's granulomatosis has a special predilection for orbital tissue, and eye involvement (in 52% of patients) may range from a mild conjunctivitis to dacryocystitis, episcleritis, scleritis, granulomatous sclerouveitis, ciliary vessel vasculitis, and retroorbital mass lesions leading to proptosis¹²⁻¹³. Some authors have reported cases of patients with Tolosa-Hunt syndrome with the presence of c-ANCA but without obvious systemic vasculitis, and another case with negative ANCA, and argue that it could be consistent with a localized form of Wegener's granulomatosis¹⁴⁻¹⁵. Others have reported a case of a woman with multiple cranial deficits related to a mass lesion in the orbit and cavernous sinus, epidural mass with thickened dura and positive c-ANCA and favorable response to steroids and another immunosuppressant¹⁶.

Several authors consider Wegener's granulomatosis as a secondary cause or one of the clinical differential diagnoses of steroid-responsive painful ophthalmoplegia^{1,9}, implying that Tolosa-Hunt syndrome and Wegener's granulomatosis are separate entities.

We are uncertain whether Tolosa-Hunt syndrome is a limited form of Wegener's granulomatosis, or an independent entity with or without an overlap between it and Wegener's granulomatosis. You may wish to consult others with expertise in autoimmune disorders in this regard.

3. If you determine that this is a case of Tolosa-Hunt syndrome, please comment on the likelihood of identifying a case of Wegener's granulomatosis and a case of Tolosa-Hunt syndrome in a database of 4,000 otherwise healthy individuals between the ages of 18 and 70 years old followed for six and twelve months in their respective studies.

Iaconetta et al estimate the incidence of Tolosa-Hunt syndrome to be approximately one to two cases per million but it is not clear on what basis this estimate was made as they do not cite supporting epidemiological data⁷. The lack of epidemiological data makes it difficult to estimate the incidence of Tolosa-Hunt syndrome reliably. Given this limitation, a case of Tolosa-Hunt syndrome in a database of 4,000 otherwise healthy individuals appears to be higher than what would be expected to occur spontaneously.

You may wish to consult others with expertise in autoimmune disorders with regard to the likelihood of identifying a case of Wegener's granulomatosis in this database.

4. If there is overlap, do you think there is any basis for etiologic relatedness between this case and the case of Wegener's granulomatosis in the clinical trial DV2-HBV-10? Details of the case of Wegener's granulomatosis are included in the appendix.

Please our response to Question 2.

5. In your opinion, is it plausible mechanistically, that a Hepatitis B recombinant protein with a TLR-9 agonist adjuvant could be involved in the pathogenesis of this adverse event? What role, if any, do you think the TLR-9 agonist adjuvant played?

We are unable to provide a response to this question as we lack the necessary expertise.

6. Is this case consistent with any other etiology, autoimmune or non-autoimmune that has not been ruled out?

No. As discussed in our response to Question 1, we believe that this case is consistent with Tolosa-Hunt syndrome.

7. What other clinical test or information, if any, would be useful in establishing a definitive diagnosis in this case?

Please our response to Question 1.

8. What additional safety monitoring or exclusion criteria, if any, do you suggest in designing clinical trials involving vaccines with CpG adjuvant?

There are no subject characteristics or risk factors that we are aware of that might predispose subjects to developing Tolosa-Hunt syndrome. We do not have any particular recommendations for additional safety monitoring for clinical trials involving vaccines with CpG adjuvant.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Memorandum

Date: May 6, 2013

/s/

From: Michael C. Sneller, M.D.
Laboratory of Immunoregulation, NIAID/NIH

To: Lorie B. Smith, M.D., M.H.S., Division of Vaccines and Related Products
Applications, Office of Vaccines Research and Review Center for Biologics and
Evaluation

Subject: Request for consultation regarding HEPLISAV (rHBsAg-1018 ISS)

I have reviewed the material (summary documents, neurologic consultant notes, laboratory results, and radiology reports) you sent me as part of the above consultation request. Below are my responses to the questions posed in the Consultation Request.

Questions for the consultant

1. Based on the information provided, is this case consistent with Tolosa-Hunt syndrome?

I am not an expert in Tolosa-Hunt syndrome, but based on the information provided, this patient's illness sounds most consistent with that diagnosis.

2. Is there any overlap between Tolosa-Hunt syndrome and Wegener's granulomatosis?

With regards to a possible association between Tolosa-Hunt syndrome and Granulomatous with polyangiitis (GPA; formerly Wegener's granulomatosis), I do not think there is convincing evidence that the two disorders are in anyway associated with regards to clinical-pathologic features or pathogenesis. I was only able to find 2 reports in the English language literature that suggest a possible association with GPA and Tolosa-Hunt. The report by Montecucco et. al (reference 14 in your summary document) describes 2 patients with (what seems to me) typical Tolosa-

Hunt syndrome. Both patients are reported to have c-ANCA detected by indirect immunofluorescence (not confirmed by anti-Pr3 EIA-this assay was not available in 1992). Relying on immunofluorescence (IF) testing alone for c-ANCA is not adequate for diagnostic purposes, as there are false positives, especially in laboratories that are not experienced in performing IF assays. Testing for c-ANCA by IF has largely been abandoned and has been replaced by anti-Pr3 EIAs, which are less susceptible to observe interpretation. Testing for c-ANCA (by any method) has a high positive predictive value for the diagnosis of GPA only in patients with a clinical syndrome suggestive of GPA (i.e. sinusitis, glomerulonephritis, pulmonary nodules and/or infiltrates where infection has been excluded). In patients who do not have a clinical syndrome suggestive of GPA (such as the patients in the report by Montecucco et al.) the positive predictive value of c-ANCA for the diagnosis of GPA is poor. Contrary to popular practice, ANCA is not a good screening test for GPA or any kind of vasculitis. This was demonstrated many years ago in a paper from Duke (see Rao et. al Lancet 346:926-931, 1995). Thus, the finding of a positive c-ANCA (by IF only), in 2 patients with Tolosa-Hunt syndrome who do not have clinical features suggestive of GPA, is most likely a false positive IF and does not constitute evidence for a pathophysiologic association between the two disorders.

The second paper by Thajeb (reference 13) describes a patient who actually had multiple features suggestive of GPA. In addition to painful ophthalmoplegia, this patient had otitis media with hearing loss that was refractory to surgical/antibiotic therapy, sinusitis, mastoiditis, mononeuritis multiplex and pachymeningitis (MRI showing meningeal enhancement, CSF pleocytosis with elevated protein). These are all known manifestations of GPA and occasionally can be the presenting features. The patient in this report had a positive c-ANCA and likely had GPA, not Tolosa-Hunt syndrome.

- 3. If you determine that this is a case of Tolosa-Hunt syndrome, please comment on the likelihood of identifying a case of Wegener's granulomatosis and a case of Tolosa-Hunt syndrome in a database of 4,000 otherwise healthy individuals between the ages of 18 and 70 years old followed for six and twelve months in their respective studies.**

I'm not sure all the patients in your database can be classified as "otherwise healthy". The patient in this report had multiple other health problems including presbyopia, bilateral hearing deficit, seasonal allergic rhinitis, hypertension, gastroesophageal reflux disease, esophageal ulcer,

benign prostatic hyperplasia, osteoarthritis. That being said, I would think that finding single cases of 2 rare, unrelated diseases out of 4,000 individuals could occur by chance alone.

4. **If there is overlap, do you think there is any basis for etiologic relatedness between this case and the case of Wegener's granulomatosis in the clinical trial DV2-HBV-10? Details of the case of Wegener's granulomatosis are included in the appendix.**

I do not think GPA and Tolosa-Hunt syndrome are related (see response to #2)

5. **In your opinion, is it plausible mechanistically, that a Hepatitis B recombinant protein with a TLR-9 agonist adjuvant could be involved in the pathogenesis of this adverse event? What role, if any do you think the TLR-9 agonist adjuvant played?**

I 'm not an expert in TLR-9 immunobiology, but it seems to me that a localized injection of a small amount of TLR-9 agonist would be unlikely to produce organ specific autoimmunity at a distant site (Tolosa-Hunt) or a systemic autoimmune disease (GPA).

6. **Is this case consistent with any other etiology, autoimmune or non-autoimmune that has not been ruled out?**

Not that I can think of.

7. **What other clinical test or information, if any, would be useful in establishing a definitive diagnosis in this case?**

Nothing I can suggest based at this point

8. **What additional safety monitoring or exclusion criteria, if any, do you suggest in designing clinical trials involving vaccines with CpG adjuvant?**

None I can think of.



Walter Reed
National Military
Medical Center

Dr. Eric D Weber, MC, MAJ, USA

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Walter Reed National Military Medical Center
8901 Wisconsin Ave., Bethesda, MD 20889-5600
(301) 285-1339

May 8, 2013

To Whom it May Concern,

I have reviewed the consultation regarding the HEPLISAV vaccine and its possible linkage to one case of Tolosa-Hunt syndrome (THS). Based on the information provided, I believe this case is consistent with Tolosa-Hunt. I understand that the diagnosis was changed to "cavernous sinus syndrome," (CSS) but this is a very vague description under which THS is just one of the causes. Since this patient was very responsive to steroids, this implies that the cause of his CSS had to be inflammatory; one of the more common causes of inflammatory CSS is THS or granulomatous disease. Unfortunately, the MRI was non-diagnostic for this, and there is no tissue biopsy to give a definitive diagnosis. Therefore, this case could also be the result of many other causes of cavernous sinus inflammation, to include pseudotumor, sarcoidosis, or TB. As best I can tell, these entities were worked up and there is no evidence that would suggest any of those as possible causes, but nothing is 100%.

There can be some overlap between THS and Wegener's granulomatosis. However, I would expect more orbital changes on his MRI or CT, and potentially more paranasal sinus disease. Furthermore, I believe the lab workup was entirely normal, which is not consistent with Wegener's. In addition, there were no systemic findings consistent with Wegener's to include arthritis, skin, nervous system or renal involvement. With that being said, there is no way to link a case of Wegener's with a case of THS, other than to say both are inflammatory and both are granulomatous in nature.

There is no way to link this case to the vaccine. The prevalence of Wegener's is approximately 3 per 100,000 with undetermined incidence, while THS carries an incidence of 1 case per million per year. Based on this study's small numbers, it would be highly unlikely to see either in your cohort of approximately 4000 patients. While it is theoretically possible for this vaccine with the TLR-9 antagonist to incite some forms of inflammation, I have no way of linking it definitively to these cases of inflammation. I think the only way to do this would be via a biopsy of the cavernous sinus that demonstrated some deposition of this recombinant protein.



In conclusion, I cannot definitively or even remotely link this case of cavernous sinus disease with your vaccine. In the future, I recommend monitoring all patients for any signs of granulomatous disease, but this is a very broad category and requires surveillance of all major organ systems.

Please contact my office with any questions or concerns.

Sincerely,

/s/

Eric D. Weber, MD
MAJ, MC, USA
Pediatrics, Neuro-ophthalmology & Orbit
Associate Program Director
Ophthalmology Service
Walter Reed National Military Medical Center





DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Pulmonary, Allergy, and
Rheumatology Products, HFD-570
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: April 27, 2016

From: Sarah Yim, M.D. /s/
Supervisory Associate Director
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Through: Badrul Chowdhury, M.D., Ph.D. /s/
Director, DPARP

To: Division of Vaccines and Related Products Applications (DVRPA), Office of
Vaccines Research and Review (OVRP), Center for Biologics Evaluation and
Research (CBER)

Subject: Consult dated 4/6/16, HEPLISAV Safety Concern: Autoimmunity

I. Executive Summary

The 49 year-old hispanic man from the safety study HBV-23 with an incidental finding of aortic abnormalities consistent with Takayasu arteritis (TA), is a likely case of subclinical TA that predated the subject's exposure to HEPLISAV. Acknowledging that TA, granulomatosis with polyangiitis (GPA), and Tolosa-hunt syndrome are each associated with granulomatous inflammation, granulomatous inflammation itself is a nonspecific finding, and I am not otherwise aware of any pathophysiological relationships between these disorders that could unify the pathogenesis or explain their occurrence in the HEPLISAV clinical development program.

II. Background

HEPLISAV is a vaccine comprised of recombinant hepatitis B surface antigen (rHBsAg) combined with a cytosine phosphoguanine (CpG) enriched phosphorothioate oligodeoxynucleotide (ODN) adjuvant. In 2012, Dynavax Technologies Corporation submitted a Biologics Licensing Application (BLA) for HEPLISAV, which was discussed at the Vaccines and Related Biological Products Advisory Committee (VRBPAC) on November 15, 2012. The original BLA contained 2 randomized, controlled phase 3 trials, Study HBV-10 and Study HBV-16, which compared HEPLISAV to an active comparator, the licensed hepatitis B vaccine,

ENGERIX-B. The phase 3 trials included 4864 subjects (HEPLISAV n=3777; ENGERIX-B n=1087), followed for 28 weeks in Study HBV-10 and for 52 weeks in Study HBV-16. Additionally there were seven other supportive trials in 981 subjects (HEPLISAV n=648; ENGERIX-B n=333)

At the time of that review, the existing safety database had similar rates of autoimmune and inflammatory laboratory abnormalities and adverse events requiring immunosuppressive medications in the HEPLISAV group and the ENGERIX-B control group. However, three autoimmune disease cases were identified:

- A previously healthy 55 year old female who received HEPLISAV in Study HBV-10 was diagnosed with granulomatosis with polyangiitis (GPA, a.k.a. Wegener's granulomatosis) approximately 7 months after her first injection of HEPLISAV. The subject developed widespread urticaria 18 days after the first injection, but received the second injection approximately 1 month later. She developed recurrent sinusitis starting 1.5 months after the second injection, followed by pulmonary infiltrates, pleural effusions, and glomerulonephritis along with a positive c-ANCA. Serologic testing of banked samples revealed her to be ANCA negative at baseline, weakly positive at 4 weeks after the first injection, positive by 12 weeks after the first injection, and strongly positive 23 to 28 weeks after the first injection.
- A 44-year old female with a history of mixed connective tissue disease who received ENGERIX-B in Study HBV-10 developed a p-ANCA positive vasculitis. She developed fever and malaise 3 months after her second injection of ENGERIX-B. Approximately 4 months after the second injection, she developed pulmonary hemorrhage and a positive p-ANCA. At baseline, she was ANA positive (>1 :5120) but ANCA negative until the time of her vasculitis diagnosis.
- A 69 year old male with multiple medical problems who received HEPLISAV, developed "amblyopia" approximately 6 months after the second injection of HEPLISAV followed by severe headaches, diplopia, a severe ptosis and a left cranial nerve VI palsy. His symptoms were acutely responsive to steroids, but returned whenever steroids were discontinued. Ultimately, he was diagnosed with Tolosa-Hunt syndrome or cavernous sinus syndrome.

Based on these concerns, the VRBPAC voted 8 to 5 that the safety data available for HEPLISAV was not adequate to support licensure. The BLA received a complete response. The sponsor subsequently conducted a randomized safety study (Study HBV-23) in 8368 subjects comparing HEPLISAV (n=5587) to ENGERIX-B (n=2781), which is currently under review. In this additional data, 65 subjects reported adverse events (AE) that were considered potential immune-mediated events that were evaluated for adjudication, and there does not appear to be an imbalance in these [HEPLISAV, n=41 (0.73%), and ENGERIX-B, n=24 (0.86%)]. However, there was one case of possible Takayasu arteritis (TA) in a subject who received HEPLISAV. DVRPA has consulted DPARP about this additional case.

Before delving into the particulars of this case, in light of the CBER questions, it should be noted that the American College of Rheumatology (ACR) no longer endorses diagnostic criteria, and the ACR-endorsed classification criteria are not designed for use as diagnostic criteria. Classification criteria are standardized definitions that are primarily intended to enable clinical

studies to have uniform cohorts for research, and are intended to define a relatively homogeneous group that can be compared across studies and geographic regions. Such criteria are expected to have very high specificity, even if there is some loss in sensitivity. In contrast, diagnostic criteria need to reflect and capture the heterogeneity of a disease, but should have both high specificity and sensitivity in order to be useful in making clinical decisions for an individual patient.¹

Regarding the 1990 ACR criteria for the classification of TA, these were developed by comparing 63 patients with clinically diagnosed TA with 744 control patients with other forms of vasculitis.² In this original exercise, the vasculitis most misclassified by these criteria (occurring in 11 of the 744 control patients) was giant cell arteritis (GCA), which can also include aortic, carotid, and subclavian artery involvement. In fact, due to similarities in histopathology, distribution of arterial lesions, and female predominance, it has been hypothesized that TA and GCA could represent a spectrum within the same disease, with the main difference being age of onset (above 50 years for GCA and below 50 years for TA).³

Table 1: The 1990 American College of Rheumatology Classification Criteria for Takayasu Arteritis (TA)

Criteria	Definition
Age at disease onset <40 years	Development of symptoms or findings related to TA at age <40 years
Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of 1 or more extremity while in use, especially the upper extremities
Decreased brachial artery pulse	Decreased pulsation of 1 or both brachial arteries
Blood pressure difference >10 mmHg	Difference of >10 mmHg in systolic blood pressure between arms
Bruit over subclavian arteries or aorta	Bruit audible on auscultation over 1 or both subclavian arteries or abdominal aorta
Arteriogram abnormality	Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental

For purposes of classification, a patient shall be said to have TA if at least 3 of these 6 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 90.5% and a specificity of 97.8%

Although not endorsed by the ACR, diagnostic criteria for TA have been proposed and are summarized in Table 2 below. Based on testing in 96 Japanese patients with TA and 12 patients with other aortic disease, the Ishikawa criteria had 84% sensitivity, and no patients with other aortic disease fulfilled the criteria. Based on testing in 106 Indian patients with angiographically proven TA and 20 control subjects, the Sharma modification of the Ishikawa criteria had 92.5% sensitivity and 95% specificity (compared to a sensitivity of 60.4% and specificity of 95% for Ishikawa's criteria, and 77.4% sensitivity and 95% specificity for the ACR classification criteria, in the same population). When tested in 79 Japanese patients with TA and 79 control subjects, the Sharma modified criteria had a 96% sensitivity and 96% specificity. However, the Diagnostic and Classification Criteria in Vasculitis Study (DCVAS) is an international study that is ongoing and aims to include 2000 patients with systemic vasculitis and 1500 patients presenting with conditions that mimic vasculitis to revise classification and diagnostic criteria.⁴

¹ Aggarwal R et al. Distinctions between diagnostic and classification criteria? *Arthritis Care & Research*, July 2015, 67(7):891-897

² Arend WP et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. *Arthritis and Rheumatism*, August 1990, 33(8):1129-1134.

³ De Souza AWS and JF de Carvalho. Diagnostic and classification criteria of Takayasu arteritis. *J Autoimm*, 2014, 48-49:79-83

⁴ Luqmani RA et al. Nomenclature and classification of vasculitis—update on the ACR/EULAR diagnosis and classification of vasculitis study (DCVAS). *Clin Exp Immunol*. 2011; 164:11-13.

Table 2: Diagnostic Criteria for Takayasu Arteritis (TA)

Ishikawa Diagnostic Criteria ⁵		Sharma Modification of Ishikawa Criteria ⁶	
Criteria	Definition	Criteria	Definition
<i>Obligatory criterion</i>		<i>Three major criteria</i>	
Age ≤40 years	Age <40 years at diagnosis or onset of characteristics signs and symptoms* of 1 month duration	Characteristic signs and symptoms of ≥1 month duration	Includes limb claudication, pulselessness or pulse differences in limbs, unobtainable or significant blood pressure difference (>10mmHg SBP), fever, neck pain, transient amaurosis, blurred vision, syncope, dyspnea, palpitations
<i>Two major criteria</i>			
Left mid-subclavian artery lesion	Most severe stenosis or occlusion present in mid-portion from 1 cm proximal to left vertebral art. orifice to 3 cm distal to the orifice, determined by angiography	Left mid-subclavian artery lesion	Most severe stenosis or occlusion present in mid-portion from 1 cm proximal to left vertebral art. orifice to 3 cm distal to the orifice, determined by angiography
Right mid-subclavian artery lesion	Most severe stenosis or occlusion present in mid-portion from right vertebral art. orifice to 3 cm distal to the orifice, determined by angiography	Right mid-subclavian artery lesion	Most severe stenosis or occlusion present in mid-portion from right vertebral art. orifice to 3 cm distal to the orifice, determined by angiography
<i>Nine minor criteria</i>		<i>Ten minor criteria</i>	
High ESR	Unexplained persistent high ESR ≥20mm/hr (Westergren) at diagnosis or documented history	High ESR	Unexplained persistent high ESR ≥20mm/hr (Westergren) at diagnosis or documented history
Carotid artery tenderness	Unilateral or bilateral tenderness of common carotid arteries by palpation; not neck muscles	Carotid artery tenderness	Unilateral or bilateral tenderness of common carotid arteries by palpation; not neck muscles
Hypertension	Persistent BP ≥140/90 mmHg brachial or ≥160/90 popliteal at age <40 yrs or history of at <40	Hypertension	Persistent BP ≥140/90 mmHg brachial or ≥160/90 popliteal
Aortic regurgitation or annuloaortic ectasia	By auscultation or echo, or angiography	Aortic regurgitation or annuloaortic ectasia	By auscultation or echo, or angiography
Pulmonary art. lesion	Lobar or segmental art. occlusion or equiv, determined by angiography or perfusion scintigraphy ; or presence of stenosis, aneurysm, luminal irregularity or any combination in pulmonary trunk or unilateral or bilateral pulm art.	Pulmonary art. lesion	Lobar or segmental art. occlusion or equiv, determined by angiography or perfusion scintigraphy ; or presence of stenosis, aneurysm, luminal irregularity or any combination in pulmonary trunk or unilateral or bilateral pulm art.
Left mid common carotid lesion	Most severe stenosis or occlusion in the mid portion of 5 cm in length from the point 2 cm distal to its orifice, by angiography	Left mid common carotid lesion	Most severe stenosis or occlusion in the mid portion of 5 cm in length from the point 2 cm distal to its orifice, by angiography
Distal brachiocephalic	Most severe stenosis or occlusion	Distal brachiocephalic	Most severe stenosis or occlusion

⁵ Ishikawa K. Diagnostic approach and proposed criteria for the clinical diagnosis of Takayasu's arteriopathy. J Am Coll Cardiol 1988; 12:964-72

⁶ Sharma BK et al. Diagnostic criteria for Takayasu arteritis. Int J Cardiol 1996; 54:S141-7

trunk lesion	in distal third by angiography	trunk lesion	in distal third by angiography
Descending thoracic aorta	Narrowing, dilation or aneurysm, luminal irregularity or any combination, by angiography; tortuosity alone is unacceptable	Descending thoracic aorta	Narrowing, dilation or aneurysm, luminal irregularity or any combination, by angiography; tortuosity alone is unacceptable
Abdominal aorta lesion	Narrowing, dilation or aneurysm, luminal irreg or any combo and absence of lesion in aorto-iliac region consisting of 2 cm of terminal aorta and bilat common iliac art., by angiography; tortuosity alone is unacceptable	Abdominal aorta lesion	Narrowing, dilation or aneurysm, luminal irreg or any combo and absence of lesion in aorto-iliac region consisting of 2 cm of terminal aorta and bilat common iliac art., by angiography; tortuosity alone is unacceptable
		Coronary artery lesion	Documented on angiography below age 30 in absence of risk factors like hyperlipidemia or diabetes mellitus

*Characteristic signs and symptoms include: cardinal limb signs or symptoms—pulselessness, differences in pulses in the arms, obtainable blood pressure, significant blood pressure differences in the arms, easy limb fatigability or pain—and minor signs or symptoms, including unexplained fever or high ESR or both, neck pain, transient amaurosis or blurred vision or syncope, dyspnea or palpitations or both, or hypertension, or aortic regurgitation. Ishikawa Criteria high probability of TA: Obligatory criterion plus two major criteria or one major criterion and two or more minor criteria, or ≥ 4 minor criteria. Sharma modification: same as Ishikawa without obligatory criterion.

TA generally has an indolent early course with constitutional features (fever, malaise, anorexia, and weight loss), extremity pain/ Claudication, and light headedness. Absent or diminished pulses, loss of blood pressure, and presence of bruits may follow, depending on vessel involvement.⁷ Because of the nonspecific nature of the clinical symptoms, this disease is often not diagnosed for years. The pathological change begins with granulomatous inflammation of the vascular adventitia and outer part of the media. Severe inflammation of the vasa vasorum is typical. The inflammation eventually extends to all layers of the aortic wall.⁸ Unfortunately, there are no reliable measures to determine disease activity vs chronicity, including inflammatory markers and angiography. However, 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) has shown promise in identifying clinically active vasculitis.⁹

III. Review

As per the consult, the case summary is as follows:

Subject 131-109, was a 49 year-old U.S. Hispanic man with a history of type 2 diabetes (1998), cerebrovascular disease (2005, see below), cardiovascular disease (2006), hypertension (2010), morbid obesity, gastric bypass (2010), fatty liver disease (2010), gastroesophageal reflux disease, degenerative joint disease, gout, low back pain, occasional headaches (2004), bulimia nervosa, insomnia (2014), shattered patella (1979), skull fracture (1966), and hernia (1974). He was a former smoker (quit 2003) and current alcohol user (few times a month). Following gastric bypass surgery in 2010, the subject's BMI decreased from 45 kg/m² to 34.1 kg/m² at study enrollment and he was able to control his hyperglycemia with diet and exercise instead of metformin, which he was previously taking. Family history included Crohn's disease. Concomitant medications at study enrollment were ibuprofen, unisom, and amlodipine.

7 Alibaz-Oner F and H Direskeneli. Update on Takayasu's arteritis. Presse Med. 2015; 44:e259-e265

8 Isobe M. Takayasu arteritis revisited: current diagnosis and treatment. International J Cardiol 2013 168:3-10.

9 Direskeneli H et al. Assessment of disease activity and progression in Takayasu's arteritis. Clin Exp Rheumatol. 2011; 29:S86-S91

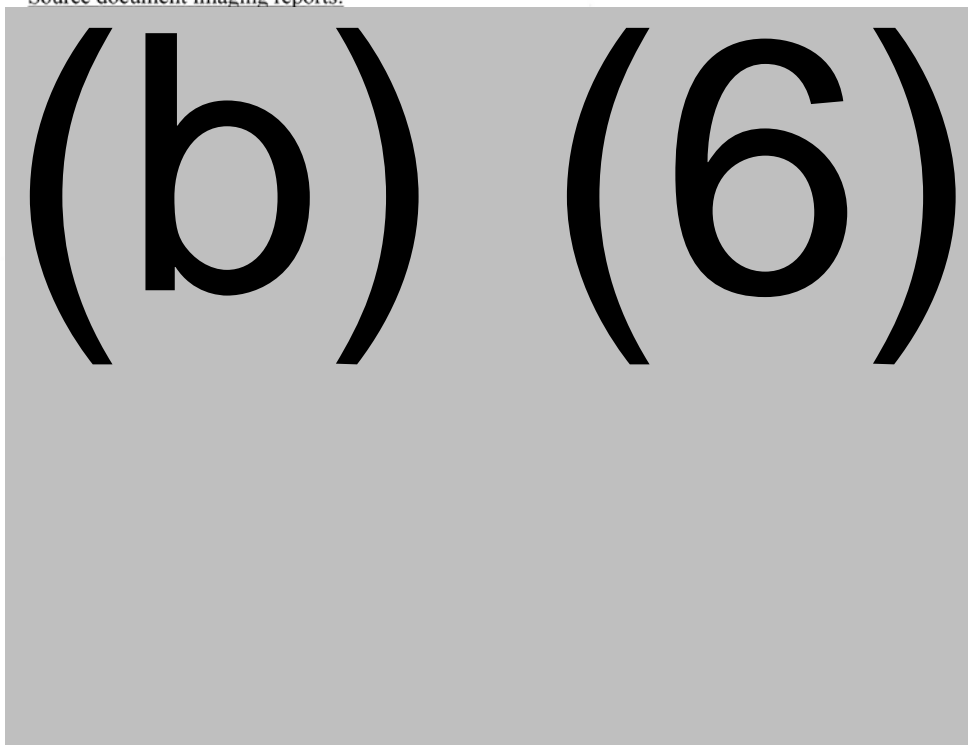
With the exception of a 2010 chest x-ray, which was reported by the Applicant as normal, there are no known prior imaging studies of the subject's chest. In May of 2005, the subject was evaluated in the ER by a neurologist for slurred speech, and right-sided numbness. A computerized tomography (CT) scan of the brain, with and without contrast, showed a 5 mm hypodensity within the left thalamus, felt to represent an age-indeterminate infarct. He declined admission and was discharged with the diagnoses of transient ischemic attack (TIA) versus lacunar infarct, age-indeterminate left thalamic infarct, and renal insufficiency.

A timeline of study events, adverse events, and associated evaluations is summarized below.

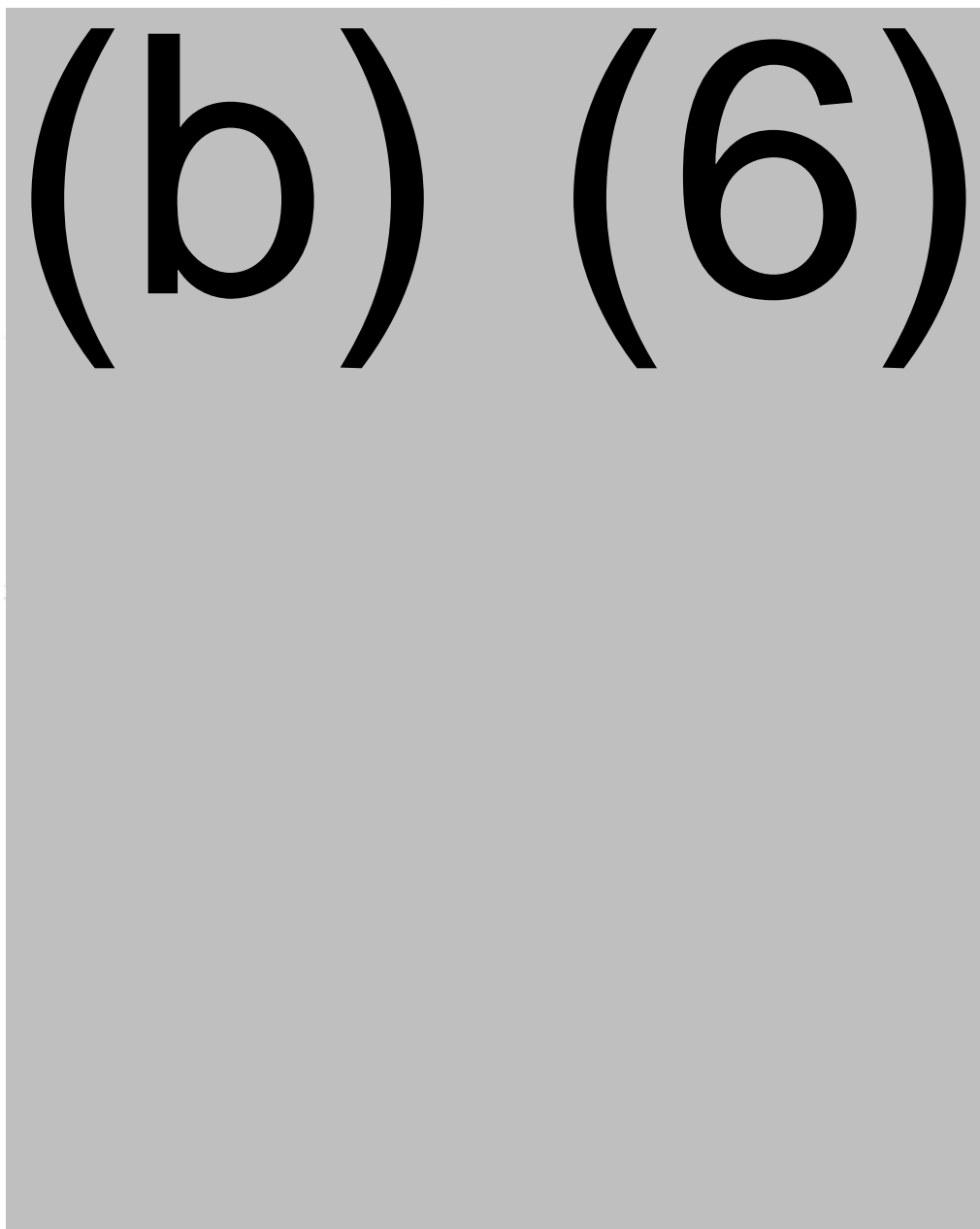
- July 1, 2014: Received the first dose of blinded study vaccine (HEPLISAV).
- July 29, 2014: Received the second dose of blinded study vaccine (HEPLISAV).
- (b) (6) Hospitalized for an acute thalamic infarct after experiencing unilateral arm and facial numbness and tingling. A magnetic resonance imaging (MRI) showed an acute right thalamic infarct and chronic left thalamic infarct and moderate chronic microvascular disease. CTA of the head and neck and chest (to evaluate the incidental findings noted on the head and neck studies) were performed (88 days after first study vaccination and 60 days after second study vaccination). In addition to the cerebrovascular findings above, imaging demonstrated "smooth, concentric mural thickening of the aortic arch." He was discharged on aspirin daily, simvastatin, and amlodipine. Erythrocyte sedimentation rate (ESR) was 33 mm/hr (normal 0-20) and a high-sensitivity C-reactive protein (CRP) was 2.8 mg/L (no normal range provided) on September 27th. According to the Applicant, "no ESR or CRP testing results are available prior to enrollment."
- (b) (6) Hospitalized for a gastrointestinal bleed due to anastomotic gastric ulcers. He was transfused four units of blood for hemoglobin of 4.5 mg/dL. The gastroenterologist noted he had been taking aspirin twice daily and ibuprofen 100 mg every few hours for intermittent pain. Esophagogastroduodenoscopy showed multiple anastomotic ulcers, one of which was clipped, and a suspicion for Barrett's esophagus. He was discharged on aspirin daily and a higher dose of amlodipine for hypertension during the hospitalization.
- October 17 and October 31, 2014: Established care with a primary care physician (PCP).
- January 7, 2015: Received the third dose of blinded study vaccine (placebo).
- On January 19, 2015: CTA of the chest at the Sponsor's request to assess if there was any progression of the findings noted on the September CTA. This study showed "abnormal circumferential wall thickening of the aortic arch" with "extension to a small degree into the right brachiocephalic and left common carotid arteries." No aortic stenosis, dilation, or dissection was noted. A later re-interpretation of the January 19th chest CTA notes stable (compared to the September 27th CTA) "mural thickening approaching 6-7 mm involving the mid aortic arch as well as the most proximal left common carotid and subclavian arteries."
- February 5, 2015: Laboratory results were significant for ESR 31 mm/hr (normal 0-15) and CRP 3.6 mg/L (normal <0.9). Rheumatologic evaluation was negative, including ANA, dsDNA antibody, SS-A (La) antibody, SS-B (Ro) antibody, RNP antibody, Smith antibody, HLA-B27 antigen, tuberculosis Quantiferon, and coccidioides antibodies. He had a microcytic anemia and an anion gap of 20. Hepatitis B surface antibody was reactive (63.19 mIU/mL), hepatitis B core antibody was non-reactive, and hepatitis C antibody was non-reactive.
- On February 18, 2015: Rheumatologic consult for evaluation of the radiographic findings. The subject reported having headaches in August 2014 and taking a considerable amount of ibuprofen tablets. The rheumatologist noted no symptoms suggestive of vasculitis or rheumatologic disease and no history that would suggest an underlying inflammatory disorder. Physical examination was unremarkable. Pertinent negatives included no murmurs, no subclavian, axillary, abdominal, or iliac bruits, radial artery pulses symmetric and normal, normal femoral, popliteal, dorsalis pedis, and tibial pulses, and no rashes. There is no indication that brachial artery pulses or blood pressure in both upper extremities was assessed. The rheumatologist ordered a CTA of the abdomen and pelvis to evaluate the renal arteries, laboratory evaluations, and re-interpretation of the previous chest CTAs at his facility (results above). Notably, at this time, no ESR or CRP results were available in the outside records.
- On March 11, 2015: CTA of abdomen and pelvis showed normal abdominal aorta, iliac arteries, mesenteric arteries, and renal arteries. Laboratory assessments on March 11, 2015, demonstrated normal inflammatory markers (ESR 20 mm/hr (normal range 0-22), CRP <3.0 mg/L (normal range 3-8)) and a microcytic anemia.

- March 15, 2015: An addendum to the rheumatologist's note states that the rheumatologist had reviewed the chest CTA re-interpretation, the CTA of the abdomen and pelvis, and the laboratory results. This note states, "The diagnosis of Takayasu's arteritis appears correct but the activity level is difficult to know with certainty since inflammatory markers may be normal and arteritis can persist and worsen." The rheumatologist recommended a chest CT scan in 6 months to assess the rate of progression.
- May 12, 2015: MRI angiography of the chest with and without contrast showed left ventricular hypertrophy with an elevated ejection fraction of 86% (normal range 50-70%) and marked thickening of the left ventricular muscle, and findings of "stable aortic arch soft tissue thickening with an additional area of thickening of the descending aorta at the aortic hiatus."
- June 16, 2015: Laboratory test results included IgG (subclass 4) 83.6 mg/dL (normal range 4-86), VDRL nonreactive, and Treponema pallidum antibody-particle agglutination non-reactive. The subject was unable to complete a tuberculin skin test.
- October 22, 2015: CTA of the chest with contrast to assess progression showed the aorta to be "stable in appearance with a stable region of circumferential wall thickening which measur[ed] maximally approximately 5 mm along the left aspect of the aortic arch. There [was] stable slight extension of the wall thickening into the left common carotid artery and left subclavian artery (misidentified as the right brachiocephalic on the previous report). There [were] some minimal mural calcifications of the aortic arch. There [was] no dissection."
- The investigator assessed the event, Takayasu's arteritis, as a non-serious, potential autoimmune disorder of severity grade 1 (mild), and as not related to the study vaccine. An alternative causality was unknown.

Source document imaging reports:



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Source document clinical notes:

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(b) (6)

(b) (6)

IV. CBER Questions for DPARP and DPARP Responses

Question 1: Based on the information provided, is this a case of Takayasu arteritis? Please detail your considerations in making this assessment.

DPARP Response:

Based on the information provided, this appears to be a likely case of TA, but does not appear to be an early/inflammatory stage and thus seems unlikely to be due to the hepatitis B vaccination, which occurred only 2 to 3 months prior to diagnosis. Our conclusion is based on the following considerations:

- The imaging findings are reported by multiple radiologists as consistent with large vessel vasculitis/TA in the characteristic appearance of the smooth, circumferential wall thickening involving the mid aortic arch as well as the most proximal left common carotid and subclavian arteries.
 - The patient has many cardiovascular risk factors, and this lesion could be non-calcified atherosclerotic plaque. However, the smooth concentric nature of vascular involvement was considered less likely to represent atherosclerotic vascular disease and I concur with this thinking.
- Although no inflammatory markers or other evidence of systemic inflammation were available prior to the late September TIA event, the inflammatory markers subsequent to the TIA event were either normal or only mildly elevated. Inflammatory markers are generally high (i.e. >50 mm/h) in TA early disease, but may be normal later.¹⁰ This suggests the patient was not in an early, acute inflammatory stage of TA at the time of diagnosis.
- TA symptoms are nonspecific and therefore the diagnosis may be delayed for years. While the patient did have hypertension, headaches and stroke (all of which can be associated with TA) during the study, the hypertension of TA is related to renovascular involvement, which the patient did not have, and the stroke of TA is related to carotid involvement, which was not the cause of the patient's September 2014 acute thalamic stroke, which is microvascular in etiology and likely related to his longstanding diabetes and hypertension. Therefore the clinical events that occurred since his exposure to HEPLISAV have their precedent in his pre-existing medical conditions and do not appear to reflect new onset TA. It is more likely that the patient had previously undiagnosed TA at study entry and was asymptomatic from the TA at the time of the September-October 2014 medical events.
- While this patient would not fulfill the ACR classification criteria for TA or the Ishikawa or Sharma diagnostic criteria for TA, the ACR classification criteria are not intended to identify all cases of TA, and both the Ishikawa and Sharma diagnostic criteria have had limited testing, especially in North American or Hispanic populations. Therefore, I would not rule out a diagnosis of TA simply because the patient did not meet these criteria.
- It is possible that the diagnosis could be Giant Cell Arteritis (GCA) instead of TA. However, given the age of the patient, the likely chronicity of the findings, and the lack of temporal artery involvement, I believe TA is more likely than GCA in this case.

In summary, I believe the aortic arch/left common carotid/left subclavian artery findings are likely to represent a chronic and subclinical large vessel vasculitis, likely to be Takayasu arteritis.

10 Kerr GS et al. Takayasu arteritis. *Ann Intern Med* 1994 June 1, 120 (11):919-29.
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Question 2: What is the role of the American College of Rheumatology (ACR) 1990 criteria for the classification of Takayasu arteritis in your determination of a diagnosis in this case? Is it sometimes appropriate to make a diagnosis of Takayasu arteritis based upon radiologic findings alone? Please specifically comment on the subject's demographic characteristics and their contribution to determining the diagnosis.

DPARP Response:

See response to question 1. The ACR 1990 criteria are not intended for use as diagnostic criteria and the fact that the patient does not fulfill the criteria does not preclude the diagnosis of Takayasu arteritis. As the disease in question is a large vessel vasculitis, the characteristics and pattern of vascular involvement on angiography are key factors in making the diagnosis. Histology would be definitive but is not feasible.

Regarding demographics, as previously noted, the patient is at the older end of the typical age range of TA. Although predominantly described in the Asian population, there does not appear to be a significant ethnic predisposition to TA. As this patient is a hispanic, it may be relevant that in Mexico the gender predominance of females to males in TA is estimated to be 6.9 to 1.¹¹ Therefore, while this patient would not fit the classical demographics of a TA patient, neither do his demographic characteristics rule him out.

Question 3: Based on the documentation provided, were all critical elements of the ACR criteria evaluated? For example, does evaluation of radial pulses replace evaluation of brachial pulses?

DPARP Response:

Based on the documentation provided, it cannot be determined with certainty that there was not decreased pulses or blood pressure asymmetry. However, given the relatively mild-sounding vascular involvement on angiography, I would not expect decreased pulses or blood pressure asymmetry. As noted in the response to Question 1, I would not overly rely on the ACR criteria or the Ishikawa/Sharma diagnostic criteria to make a determination in this case.

Question 4: Is it mechanistically plausible that a Hepatitis B recombinant protein with a TLR9 agonist adjuvant could be involved in the pathogenesis of the case in question?

DPARP Response:

As previously noted, I do not believe that the patient's TA findings are acute, and therefore I believe the diagnosis of TA is unlikely to be related to his vaccination with HEPLISAV. Regarding the mechanistic plausibility of vaccination promoting or causing vasculitis in general, see the response to Question 8 below.

Question 5: Is this case consistent with any other etiology, autoimmune or non-

¹¹ Richards BL et al. Epidemiology of large-vessel vasculidities. Best Practice & Research Clinical Rheumatology 2010; 24:871-883.
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autoimmune, that has not been considered? How likely are these alternative diagnoses?

DPARP Response:

See response to Question 1. The differential diagnosis for the vascular findings would include atherosclerotic vascular disease, which would be much more common. However, the characteristics and pattern of the vascular findings (i.e., smooth, concentric wall thickening) were more consistent with and characteristic of a large-vessel vasculitis, so I believe that atherosclerosis as the etiology is less likely.

Question 6: What other clinical test or information, if any, would be useful in establishing a definitive diagnosis in this case?

DPARP Response:

As mentioned in the response to Question 2, histology would be very informative, but is not feasible. 18FDG-PET may be helpful in determining whether active vasculitis is present, but if negative would not help the diagnosis.

Question 7: If you determine that this is a case of Takayasu arteritis, please discuss the incidences of Takayasu arteritis, granulomatosis with polyangiitis (Wegener's granulomatosis), and Tolosa-Hunt Syndrome and the likelihood of identifying a case of each in a database of 10,000 individuals between the ages of 18 and 70 years old followed for six to twelve months, in their respective studies.

DPARP Response:

The worldwide incidence rate of TA is estimated to be 1 to 2 per million (0.01 to 0.02 per 10,000). The incidence in Olmsted County, Minnesota is 2.6 per million and in Japan 1 to 2 per million. In Japan, prevalence is estimated to be 40 per million (0.4 per 10,000). However, an autopsy series in Japan suggested that prevalence could be as high as 1 case in 3000 (3.33 cases per 10,000 or 333 per million) due to subclinical disease, which may be missed.¹² The overall incidence rates of ANCA-associated vasculitis (AAV) globally range from 13 to ~20 cases per million (0.13 to 0.2 per 10,000). The prevalence of AAV is estimated to be 46 to 184 cases per million (0.46 to 1.84 per 10,000). The prevalence of granulomatosis with polyangiitis (GPA) ranges regionally from 24 to 160 cases per million (0.24 to 1.60 per 10,000).¹³ Tolosa-Hunt syndrome appears to be even more rare, and I was unable to identify incidence and prevalence estimates. Approximately 208 cases were identified in the medical literature from 1988 to 2002.¹⁴ While the one case of TA in this dataset appears higher than the estimated incidence, based on the possible subclinical prevalence in Japan, up to 3 cases of TA in 10,000 patients would not be out of the ordinary, so the one case in this dataset does not suggest an excessively high incidence. The 1 case of GPA in the 10,000 patient dataset is also higher than expected, but the prevalence of having 1 case in 10,000 would be consistent with expected. I cannot comment

12 Richards BL et al. Epidemiology of large-vessel vasculidities. *Best Practice & Research Clinical Rheumatology*. 2010; 24:871-883.

13 Watts RA et al. Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. *Nephrol Dial Transplant* 2015 30:i14-i22.

14 La Mantia L et al. Tolosa-Hunt syndrome: critical literature review based on IHS 2004 criteria. *Cephalalgia* 2006; 26:772-781.

on the incidence of Tolosa-Hunt syndrome compared to expected because these data are not available. These three diseases are not known to be related pathophysiologically, and their occurrence together in this dataset could be due to random chance. It is difficult to draw any conclusions based on these data.

Question 8: If you determine that this is a case of Takayasu arteritis, please discuss disease overlap, and unifying pathogenic characteristics, if any, among Takayasu arteritis, granulomatosis with polyangiitis (Wegener's granulomatosis), and Tolosa-Hunt Syndrome and their potential relationship to the vaccine.

DPARP Response:

Acknowledging that each disease is associated with granulomatous inflammation, granulomatous inflammation itself is a nonspecific finding, and I am not otherwise aware of any pathophysiological relationships between TA, GPA, and Tolosa-Hunt syndrome. GPA is an ANCA-associated vasculitis, and the anti-neutrophil cytoplasmic antibodies are thought to be pathogenic. Proteinase 3 (PR3) ANCA have been shown to activate primed neutrophils, endothelial cells, and complement.¹⁵ The etiology of TA is unknown, but does not appear to involve autoantibodies. The etiology of Tolosa-Hunt syndrome also appears to be unknown. Therefore it is difficult to postulate a unifying pathogenesis for these three disorders.

Regarding a potential relationship of these disorders to the vaccine, there have been a number of autoimmune manifestations and autoimmune disorders with an onset reported post-vaccination, and both the adjuvant and the vaccine have been implicated.¹⁶ Vasculitis has been reported following hepatitis B vaccination¹⁷. Bacille-Calmette-Guerin (BCG) vaccination¹⁸ as well as influenza vaccination¹⁹ have been implicated as possible etiologies for TA. Therefore it is plausible that vaccination in general, or HEPLISAV specifically, could increase the risk for autoimmune manifestations or autoimmune disease. However, as discussed earlier, I do not believe the case of TA is a new onset case that could be attributable to HEPLISAV exposure. Based on the description of the c-ANCA positive GPA case and the Tolosa-Hunt syndrome case in the HEPLISAV group, and the p-ANCA positive case in the ENGERIX-B group, these other cases were new-onset and temporally associated with the vaccinations, and thus a relationship to vaccination is at least plausible. However, based on the available data and these few cases, it is difficult to conclude an increased risk specific to HEPLISAV.

V. Conclusions

The 49 year-old hispanic man from the safety study HBV-23 with an incidental finding of aortic abnormalities consistent with Takayasu's arteritis, is a likely case of subclinical Takayasu's arteritis that predated the subject's exposure to HEPLISAV. Acknowledging that Takayasu's

15 Kallenberg CGM. Pathophysiology of ANCA-associated small vessel vasculitis. *Curr Rheumatol Rep*. December 2010; 12(6):399-405.

16 Vera-Lastra O et al. Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome): clinical and immunological spectrum. *Exp Rev Clin Imm*. 2013; 9(4):361-373.

17 Zaas A et al. Large artery vasculitis following recombinant hepatitis B vaccination: 2 cases. *J Rheumatol* 2001; 28:1116-20.

18 Kothari SS. Aetiopathogenesis of Takayasu's Arteritis and BCG vaccination: the missing link? *Med Hypothesis*. 1995; 45:227-230.

19 Watanabe T. Transient Takayasu Arteritis after influenza vaccinations. *Ped Inf Dis J*. 2016. 35(5):596.

arteritis, granulomatosis with polyangiitis, and Tolosa-hunt syndrome are each associated with granulomatous inflammation, granulomatous inflammation itself is a nonspecific finding, and I am not otherwise aware of any pathophysiological relationships between these disorders that could unify the pathogenesis or explain their occurrence in the HEPLISAV clinical development program.

Memorandum

Date: May 16, 2016

To: Darcie Everett, MD, M.P.H., Medical Officer, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research

From: Scott Flamm, MD, MBA, Professor of Radiology, Cardiovascular Imaging Laboratory, Imaging Institute, Cleveland Clinic

Subject: Request for consultation regarding HEPLISAV (rHBsAg-1018 ISS)

I have reviewed the volume of materials sent to me, including the multiple laboratory reports, history and physicals, progress notes, discharge summaries, and reports of imaging examinations all dated from September 27, 2014 to October 22, 2015.

In addition, I have closely and individually re-examined each of the imaging studies sent to me, including the CT scan of the Chest and Neck dated September 27, 2014, CT scan of the Chest dated January 19, 2015, CT scan of Abdomen and Pelvis dated March 11, 2015, and CT scan of the Chest dated October 22, 2015. Lastly, I reviewed the MRI/MRA of the Chest dated March 12, 2015. Note that this MRI examination was supposed to have included a cardiac MRI, though these images were not included in the materials sent. Nevertheless, I do not believe that the cardiac MRI evaluation would have contributed in any significant way to my evaluation.

Before I respond to the specific questions posed to me, I would like to summarize the findings noted on the multiple CT scans and MRI scan.

The three CT scans of the chest dated September 27, 2014, January 19, 2015 and October 22, 2015 all demonstrate comparable findings, and without significant change between or among any of these scans. In brief, there is a mild to moderate degree of wall thickening (maximum thickness = 5 mm) involving the aortic arch and extending slightly into the origins of the Left Common Carotid Artery and Left Subclavian Artery. There is no definite enhancement or additional inflammatory changes noted involving the aortic arch wall thickening on any of the CT data sets. There is no wall thickening involving the ascending aorta, descending thoracic-aorta, or aortic root. There is also no involvement of any of the arch branch vessels, including the entire visualized portions of the common carotid arteries, the innominate artery and the full extent of both subclavian arteries (aside from the previously mentioned slight extension of soft tissue thickening into the origins of the left common carotid and left subclavian arteries). There is no significant luminal narrowing of any of the arch branch vessels.

The CT scan of the Abdomen and Pelvis dated March 11, 2015 is entirely normal from a vascular perspective. The abdominal aorta and visualized pelvic arteries, as well as the mesenteric and renal arteries appear widely patent and without signs of abnormal wall thickening.

Lastly, the MRI/MRA of the Chest dated March 12, 2015 demonstrates a thoracic aorta that appears normal in course, caliber and contour. The arch branch vessels appear normal, and widely patent. The detail and quality of the study is insufficient to assess for the previously identified wall thickening involving the aortic arch.

Responses to questions for the consultant:

1. *Based on the information provided, is this a case of Takayasu arteritis? Please detail your considerations in making this assessment.*

It is difficult to provide a definitive answer to this question. It is certainly possible that this is a case of Takayasu arteritis, though it is quite difficult to be definitive about such a diagnosis based on the information available. Takayasu arteritis certainly manifests on cross-sectional, non-invasive imaging studies as a generally smooth thickening, either crescentic or circumferential, of the large arteries and proximal medium sized branch vessels, and has a particular predilection for the aortic arch and proximal arch vessels. In concert, one would expect a variety of systemic symptoms, as well as multiple abnormal laboratory markers, and in particular elevated acute phase reactants. This particular subject has quite modest findings compared to the typical presentation and imaging findings of patients with definitive Takayasu arteritis. From a large vessel vasculitis perspective, the wall thickening present is in the typical location for Takayasu arteritis (namely, involving the arch and proximal arch branch vessels), though the degree of wall thickening is relatively modest, there is only minimal extension into two of the arch branch vessels, and there is no significant luminal narrowing or stenosis, or aneurysm formation. Further, over the almost one-year interval between the first and last CT scans of the chest there has been no interval significant change in the wall thickening present, suggesting that if this were a large vessel vasculitis that it was quiescent, and not active. The laboratory values presented also have only modest abnormalities. The vast majority of the abnormal laboratory values can be explained by the patients' co-morbidities (including diabetes, hypertension, fatty liver disease, and prior morbid obesity). The subject did have an approximately 5 month period where there were modest increases in the erythrocyte sedimentation rate (ESR), as well as of C-reactive protein, both acute phase reactants. However, the degree of abnormality for both of these markers is significantly less than typically seen in patients with Takayasu arteritis. In addition,

such modest increases in acute phase reactants are commonly seen in such relatively minor, and transient, entities such as a common cold or flu.

In sum, the constellation of findings may reflect a case of Takayasu arteritis, though if present, had only a minimal degree of activity or was quiescent.

2. *What is the role of the American College of Rheumatology (ACR) 1990 criteria for the classification of Takayasu arteritis in your determination of a diagnosis in this case? Is it sometimes appropriate to make a diagnosis on the subject's demographic characteristics and their contribution to determining the diagnosis.*

The ACR 1990 criteria for the classification of Takayasu arteritis is a strong framework used by clinicians in determining a diagnosis in this rare disease. In this subject, however, the criteria are not useful in classifying this subject as having Takayasu arteritis. The ACR 1990 criteria included six criteria, three of which needed to be present for a high likelihood of correct classification. These criteria included: onset of age less than 40 years, claudication of an extremity, decreased brachial artery pulse, greater than 10 mmHg difference in systolic blood pressure between arms, a bruit over the subclavian arteries or the aorta, and arteriographic evidence of narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal, upper or lower extremities. Again, this subject would satisfy none of these criteria.

Alternatively, imaging findings such as those found in this subject do contribute to a diagnosis of Takayasu arteritis despite the lack of fulfilling any of the six criteria of the ACR 1990 classification system. Nonetheless, it would be highly unusual for a clinician to use radiographic findings alone to establish a diagnosis of Takayasu arteritis.

The subjects' demographic characteristics are also somewhat unusual for a diagnosis of Takayasu arteritis. Typically, patients are female with a relatively high preponderance, the age of presentation is younger, and Hispanics are only a modest proportion of all patients diagnosed with Takayasu arteritis. Nonetheless, a 49 year old Hispanic male should not be excluded for consideration of the diagnosis. As I am fond of saying to my trainees, "statistics don't apply to individuals."

3. *Is it mechanistically plausible that a Hepatitis B recombinant protein with a TLR9 agonist adjuvant could be involved in the pathogenesis of the case in question?*

The answer to this is a definite yes. However, it not necessarily a terribly useful response. Takayasu arteritis is felt to be an autoimmune disease, though there is so little actually known about its etiology, or stimulating or modifying factors.

Almost any vaccine acts as an immune stimulant, and thus could certainly be involved with or potentially even initiate the development of an autoimmune disease. Again, the potential inciting factors for Takayasu arteritis are so broad that a hepatitis B recombinant protein with a TLR9 agonist adjuvant could surely be considered as a potential inciting factor, though would simply be one possibility within a vast arena of possibilities.

4. *Is this case consistent with any other etiology, autoimmune or non-autoimmune, that has not been considered? How likely are these alternative diagnoses?*

There seems to be little that has not been considered as a possible etiology for this subject's large vessel wall thickening, and a battery of tests have been put into play to exclude a plethora of potential etiologies. The only additional possibilities that I would consider are: atherosclerosis, IgG4 autoimmune disease, and residua from a prior aortic infection.

Atherosclerosis, while a potential etiology, does not seem like a terribly likely possibility considering that no other wall thickening is noted involving any other part of the thoracic or abdominal aorta, or pelvic arteries. Atherosclerosis is known to typically start within the infrarenal abdominal aorta and then gradually worsen or extend to other segments of the aorta. Nonetheless, there are some patients who develop atherosclerosis exclusively in the ascending or descending thoracic aorta, or even in the arch or proximal arch vessels alone. These may be relatively unusual cases, though considering the large number of subjects who participated in these trials, at least a handful of such subjects is likely to be present. IgG4 auto-immune disease I will discuss below in question #5. The other alternative is that the wall thickening represents residua of a prior aortic infection. While this is a possibility, it remains unusual and unlikely as arterial wall infections do not tend to resolve spontaneously and would be expected to be quite symptomatic and require hospitalization.

5. *What other clinical test or information, if any, would be useful in establishing a definitive diagnosis in this case?*

Again, this subject has had a plethora of diagnostic testing employed in order to exclude or establish a diagnosis. The only additional test that I would

recommend as potentially useful would be to determine an IgG4 level, as IgG4 autoimmune disease is a recognized fibro-inflammatory condition that may involve the large arteries. The potential yield for this test is likely quite small, though it is the only additional marker I could recommend.

The final clinical test that could be of benefit in establishing a definitive diagnosis would be direct tissue biopsy of the aortic wall thickening.

While this is impractical, and would certainly not be considered unless there was a clinical need to replace the aortic arch or proximal arch branch vessels, this would be the only way to get direct tissue sampling of the wall thickening. At the same time, tissue analysis may or may not be helpful. If significant giant cell formations were present within the tissue, then a presumptive diagnosis of Takayasu arteritis could be made. Alternatively, if such formations were scant or not present, then no conclusions could be made, and this might simply represent atherosclerosis, or old or “burned out” Takayasu arteritis.

6. *If you determine that this is a case of Takayasu arteritis, please discuss the incidence of the disease and the likelihood of identifying a case in a database of 10,000 individuals between the ages of 18 and 70 years old followed for six to twelve months.*

I will answer this question as if indeed this were a case of Takayasu arteritis. The incidence of Takayasu arteritis in the United States is estimated at 2.6-6.4 newly diagnosed patients per one million individuals each year. The same number is often quoted as the prevalence, yet is incorrect as the diagnosis of Takayasu arteritis lives with the patient for the remainder of their life so the prevalence is substantially larger. If one assumes that the true incidence is approximately four newly diagnosed individuals each per one million people, and that patients live for an additional forty years beyond their initial diagnosis, then there would be approximately 50,000 individuals with Takayasu arteritis in the United States. Considering that the total population is approximately 325 million then there is approximately one patient with Takayasu arteritis for every 5-6 thousand people in the United States. As a result, in a data-base of 10,000 individuals between the ages of 18-70 years, I would expect to see somewhere between 1-3 subjects with Takaysau arteritis.

In sum, based on the information provided, I think that it is possible that this represents a case of Takayasu arteritis, though it not possible to be definitive. An alternative diagnosis could be relatively simple atherosclerosis that

selectively involves the aortic arch, an IgG4 auto-immune aortopathy, or, even less likely, residua from a prior aortic infection. The findings presented on the imaging studies obtained over approximately a one year interval are stable suggesting that whatever has caused the wall thickening of the aortic arch is quiescent, “burned out”, or no longer active.

I hope this evaluation has been useful to the CBER, and if there is any further information or evaluation I might provide, please do not hesitate to ask. I would also be happy to participate in a conversation as needed to clear up any details.

*****Do Not Change Anything Below This Line*****