Pharmacovigilance Review Memorandum
Office of Biostatistics and Epidemiology/Division of Epidemiology (OBE/DE)

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Subject:	Pharmacovigilance Plan Review
Applicant:	Dynavax Technologies Corporation
Product:	Hepatitis B Vaccine (Recombinant), HEPLISAV-B
Proposed Indication:	Immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older
Submission type:	Resubmission of BLA
BLA number/Submission Date:	STN 125428/0, Submitted February 8, 2017
PVP Review Submission Date:	November 7, 2017
Action Due Date:	November 9, 2017

U.S. FOOD & DRUG
ADMINISTRATION

TABLE OF CONTENTS

The OBE/DE reviewer memo concludes after section 11.

ABBREVIATIONS

ADD	Action Due Date
AE	Adverse Event
AESI	Adverse Events of Special Interest
AMI	Acute Myocardial Infarction
BLA	Biologics License Application
BMI	Body Mass Index
CKD	Chronic Kidney Disease
CR	Complete Response
CRL	Complete Response Letter
DMC	Data Monitoring Committee
EMA	European Medicines Agency
ER	Emergency Room
HBsAg	Hepatitis B virus surface antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency virus
HMO	Health Management Organization
ICD-10	International Classification of Diseases 10th Revision
IM	Intramuscular
IPTW	Inverse Probability of Treatment Weighted
ISS	Immunostimulatory sequences
KPNC	Kaiser Permanente Northern California
KPSC	Kaiser Permanente Southern California
MACE	Major Adverse Cardiac Events
MAE	Medically-Attended Adverse Event
OBE/DB	Division of Biostatistics
OBE/DE	Division of Epidemiology
OVRR	Office of Vaccines Research and Review
PMC	Post-marketing Commitment
PMR	Post-marketing Requirement
PS ODN	Phosphorothioate oligodeoxyribonucleotide
PVP	Pharmacovigilance Plan
RMP	Risk Management Plan
SAE	Serious Adverse Event
SMQ	Standardized MedDRA query
TLR9	Toll-like receptor 9
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. OBJECTIVES/SCOPE OF THE REVIEW

The purpose of this review is to assess the adequacy of the Pharmacovigilance Plan (PVP) proposed by the applicant to identify/address potential safety issues with HEPLISAV-B™ through post-marketing safety surveillance.

2. PRODUCT DESCRIPTION

HEPLISAV-B™ (HEPLISAV-B) consists of a recombinant yeast cell-derived hepatitis B virus surface antigen (HBsAg, *adw* subtype, 20 mcg) and a proprietary adjuvant, 1018 ISS (3000 mcg), developed by Dynavax Technologies Corporation (Dynavax). The intended biological activity of HBsAg is to generate antibodies to the alpha determinant of the S protein. The intended biologic activity of 1018, a phosphorothioate oligodeoxyribonucleotide (PS ODN) which uses synthetic immunostimulatory sequences (ISS), is to enhance antibody generation by activating the innate immune system via Toll-like receptor 9 (TLR9), an intracellular, pathogen-associated, molecular pattern (PAMP)-recognition receptor.

Dynavax is seeking approval for HEPLISAV-B for immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older. The proposed dosing regimen of HEPLISAV-B is 20 mcg HBsAg and 3000 mcg 1018 administered by intramuscular (IM) injection at Months 0 and 1.

3. REGULATORY HISTORY

As of the date of this memorandum, HEPLISAV-B has not been approved in any country. This is the first vaccine to use the adjuvant 1018 ISS in humans.

3.1. U.S. Food and Drug Administration

The original Biologics License Application (BLA) for this product was submitted to the Food and Drug Administration (FDA) on April 26, 2012 (STN 125428/00). The proposed indication was for healthy adults aged 18-70 years. Data from two pivotal Phase 3 trials (DV2-HBV-16 and -10) were submitted. The BLA also contained data from eight supportive trials. The Vaccines and Related Biological Products Advisory Committee (VRBPAC) was convened on November 15, 2012. The Committee voted 13 "yes," 1 "no," with one abstention, that the data in the BLA adequately demonstrated the immunogenicity of HEPLISAV-B, and voted 5 "yes," 8 "no," with one abstention, that the safety data were adequate to recommend approval. The Committee noted that (1) the studies were not large enough, (2) did not evaluate HEPLISAV-B in a racially heterogeneous population of subjects who were most likely to benefit from this vaccine, and (3) that concomitant administration studies were not done. The sponsor received a Complete Response letter (CRL) from the FDA, dated February 22, 2013.

In response to the CRL, the Applicant conducted a randomized safety study (DV2-HBV-23). A response to the Complete Response (CR) was submitted to the BLA on March 16, 2016, which included data from the additional pivotal safety study DV2-HBV-23, along with immunogenicity data for the subgroup with type 2 diabetes mellitus, and revised clinical study reports for pivotal phase 3 studies DV2-HBV-16 and -10 (STN 125428/0040). The proposed indication was healthy adults 18 years of age or older. A Major Amendment letter was issued on

April 18, 2016, due to a substantial amount of clinical data not previously reviewed or submitted to the application. FDA issued a second CRL on November 10, 2016.

The applicant submitted a response to the 2nd CR on February 8, 2017. The proposed indication was for healthy adults 18 years of age or older. A VRBPAC meeting was held on July 28, 2017. The committee voted 12 "yes," 1 "no," with 3 abstentions, that the available data was adequate to support the safety of HEPLISAV-B. The Committee commented that the observed imbalance of acute myocardial infarction (AMI) between treatment groups in study DV2-HBV-23 may be due to chance, but strongly emphasized the need for a robust post-marketing study that could provide early detection of an AMI signal. The VRBPAC specifically recommended:

- AMI should be studied separately from Major Adverse Cardiac Events (MACE)
- Given the potential risk, timeliness in both recruitment and evaluation
- Interim results including stopping rules
- Minimization of selection bias
- Prospective study, including the need for collecting specific data from electrocardiography, cardiac imaging techniques, laboratory tests, as well as data on cardiovascular risk factors not frequently recorded in electronic healthcare databases
- Event-driven study
- Appropriate study power
- Oversampling of groups at higher risk for cardiovascular disease

VRBPAC also recommended addressing the potential increased risk of immune-mediated diseases following HEPLISAV-B vaccination through post-marketing. A Major Amendment letter was issued on August 10, 2017, due to a substantial amount of data not previously reviewed or submitted to the application, particularly regarding the proposed pharmacovigilance plan. The Action Due Date is November 9, 2017.

3.2. Other regulatory agencies

Dynavax sought HEPLISAV-B licensure by the European Medicines Agency (EMA). The proposed indication was healthy adults and adults with chronic kidney disease. The applicant presented the results of three pivotal Phase 3 trials, DV2-HBV-10, -16, and -17 (clinical study in adults with chronic kidney disease), and data from nine supportive trials.

The Committee for Medicinal Products for Human Use (CHMP) considered that the way in which the study DV2-HBV-17 had been carried out and documented was not satisfactory. The identified deficiencies also led the inspection team to recommend caution also for the other studies, as the problems appeared to be systemic rather than study specific. As per the EMA, *"A GCP inspection was conducted on study HBV-17. Initially three sites were inspected, and due to the findings, also the sponsor and CRO were inspected. The conclusion of the inspection was: "Due to lack of quality system by the sponsor, the insufficient instruction with regard to IMP handling, storage and keeping the study blind as well as the incorrectness of the clinical study report in a number of fields, the data of trial DV2-HBV-17 are considered non-acceptable and the inspectors recommend not to use the data of trial DV2-HBV-17 in the context of evaluation of the marketing authorization application of Heplisav. The findings related to the inappropriate assurance and quality control system are considered to be process-related, and, therefore, apply for the entire study. Most likely, those findings also impact previous and on-going studies performed by the sponsor."*

The application was withdrawn on February 10, 2014, after the EMA had evaluated the documentation provided by the applicant and formulated lists of questions. The applicant stated that it withdrew the application since it would not be possible to provide the additional safety data needed within the timetable required by the procedure. At the time of the withdrawal, the EMA stated that based on the data presented by the applicant the vaccine was not approvable.

4. MATERIALS REVIEWED

Table 1. Materials reviewed

Materials reviewed		
Pharmacovigilance Plan	Risk Management Plan	Version 2.0. STN 125428/0072 Version 3.0. STN 125428/0093 Version 4.0. STN 125428/102
	Responses to information requests	IR dated May 8, 2017. STN 125428/0084 IR dated May 18, 2017. STN 125428/0088 IR dated Jun 7, 2017. STN 125428/0089 IR dated Jun 23, 2017. STN 125428/0091 IR dated Jul 5, 2017. STN 125428/0093 IR dated Jul 10, 2017. STN 125428/0093 IR dated Jul 19, 2017. STN 125428/0094 IR dated Aug 2, 2017. STN 125428/0096 IR (TC Aug 15, 2017). STN 125428/0098 IR dated Sept 20, 2017. STN 125428/100 IR dated Oct 16, 2017. STN 125428/104
	Teleconferences with the applicant	Aug 15, 2017; Sept 15, 2017; Sept 21, 2017
Licensing application	Summary of clinical safety Clinical Study Report Integrated summary of safety Clinical study report synopsis Integrated summary of safety Summary of clinical safety-addendum,	STN 125428/40 STN 125428/40 STN 125428/72 STN 125428/32 STN 125428/103 STN 125428/103
Input from CBER clinical reviewers	Verbal/email communications; Internal meetings	
Input from CBER statistical reviewers	Verbal/email communications; Internal meetings	
European Medicines Agency (EMA)	Withdrawal assessment report. EMA/186212/2014	February 20, 2014 Accessed on September 29, 2017 at http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/human/002603/WC500167560.pdf
VRBPAC documents	Transcripts	131st Meeting. November 15, 2012 147th Meeting. July 28, 2017. Accessed on October 25, 2017 at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM582024.pdf
	FDA Briefing document	Accessed on October 25, 2017 at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM568492.pdf
	Dynavax Briefing document	Accessed on October 25, 2017 at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM568489.pdf https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm538209.htm

5. DESCRIPTION OF THE SAFETY DATABASE

The comparator used throughout the HEPLISAV-B development program was Engerix-B®, a licensed hepatitis B vaccine manufactured by GlaxoSmithKline Biologicals, in 1-mL dose containing 20 mcg of HBsAg adsorbed on 0.5 mg aluminum hydroxide as adjuvant.

The applicant submitted to this BLA data from three Phase 3 trials and eight supportive trials (Table 2).

Adverse Events (AEs) were reported in all trials except in DV2-HBV-23, in which only medically-attended adverse events (MAEs) were collected. Adverse Events of Special Interest (AESIs), which were pre-specified potentially autoimmune or inflammatory disorders and autoimmune adverse events not defined as AESIs, were AEs considered by the independent study adjudication committee to be autoimmune, and were only collected in trials DV2-HBV-16, -23 (pivotal) and -22 (supportive).

Table 2. Overview of the randomized clinical trials included: Safety data collected and follow-up periods

Pivotal studies								
	DV2-HBV-10	Phase 3	11-55	0-6 days	28 weeks	-	28 weeks	-
	DV2-HBV-16	Phase 3	40-70	0-6 days	28 weeks	-	52 weeks	52 weeks
	DV2-HBV-23	Phase 3	18-70	-	-	56 weeks	56 weeks	56 weeks
Supportive trials								
No comparator vaccine	DV2-HBV-14	Phase 2	11-55	0-6 days	28 weeks	-	28 weeks	-
	DV2-HBV-22	Phase 1	50-70	-	12 weeks	-	56 weeks	56 weeks
Early formulation or different dosing schedule	DV2-HBV0001	Phase 1	18-55	0-6 days	62 weeks	-	62 weeks	-
	DV2-HBV-02	Phase 2	18-65	-	4 weeks	-	52 weeks	-
	DV2-HBV-03	Phase 2	18-28	0-6 days	28 weeks	-	60 weeks	-
	DV2-HBV-04	Phase 3	40-70	0-6 days*	28 weeks	-	50 weeks	-
	DV2-HBV-05	Phase 2	40-70	-	24 weeks	-	50 weeks	-
	DV2-HBV-08	Phase 2	18-39	0-6 days	12 weeks	-	32 weeks	-

*412 subjects excluded from redness and swelling analyses (different grading scale was used) Adapted from Table 2 7 4-1 Summary of clinical safety STN 125428/40

A total of 14,038 individuals (10,038 HEPLISAV-B vaccinees and 4,200 Engerix-B vaccinees) participated in the randomized clinical trials submitted to this BLA (Table 3).

Table 3. Safety analysis populations

	HEPLISAV-B recipients	Engerix-B recipients	Total
DV2-HBV-10	1,810	605	
DV2-HBV-16	1,968	481	
DV2-HBV-23	5,587	2,781	
DV2-HBV-14, DV2-HBV-22	232	-	
DV2-HBV0001, DV2-HBV-02, DV2-HBV-03, DV2-HBV-04, DV2-HBV-05, DV2-HBV-08	441	333	
Total Safety Population	10,038	4,200	14,238

Adapted from Table 2 7 4-1 Summary of clinical safety STN 125428/40

6. APPLICANT'S PHARMACOVIGILANCE PLAN

6.1. Safety issues and action plans

A summary of the safety issues and actions proposed by the applicant are shown in Table 4.

Table 4. Action plan for safety issues

Risk				
Important identified risks	Anaphylaxis	√	√	-
	Bursitis	√	-	-
	Vasovagal syncope	√	-	-
Important potential risks	Acute myocardial infarction	√	√	-
	Immune-mediated diseases	√	√[1]	-
	Herpes zoster	√	√	-
Important missing information	Pregnancy	√	-	√
	Immunosuppression	√	√	-
	Chronic liver disease	√	√	-
	Concomitant vaccination	√	√	-

[1] Selected immune-mediated diseases (see Table 6)

6.1.1. Post-marketing study proposal to assess the risk of acute myocardial infarction following HEPLISAV-B administration

The post-marketing study proposed by the applicant designed to assess the risk of AMI following HEPLISAV-B administration is titled *"Post-marketing observational surveillance study to evaluate the occurrence of acute myocardial infarction in adults 18 years of age and older who receive HEPLISAV-B compared with another hepatitis B vaccine."* The protocol number is DV2-HBV-25.

6.1.1.1. Objectives

Assess the risk of AMI following HEPLISAV-B vaccination.

6.1.1.2. Design and study setting

Retrospective observational cohort study using electronic healthcare databases conducted in one Health Management Organization (HMO), Kaiser Permanente Southern California (KPSC).

6.1.1.3. Study population

The proposed study population will be comprised of adults ages 18 years or older enrolled at KPSC, vaccinated with the first dose of a hepatitis B vaccine in family practice or internal medicine departments during the study period (timelines shown in Table 5). Vaccinated individuals receiving hemodialysis will be excluded. Both cohorts, 25,000 HEPLISAV-B recipients and approximately 25,000 recipients of another hepatitis B vaccine, will be recruited over a period of 10.5 months and followed for 13 months following first dose vaccination.

HEPLISAV-B will be provided exclusively to 7 selected medical centers and their affiliated family practice and internal medicine departments as the sole hepatitis B vaccine for adult use in routine clinical care. The remaining 8 medical centers will continue to use their current hepatitis B vaccine exclusively. The selection is based on clustering of medical centers and logistics.

Based on the information provided by the applicant, the study population may be comprised of individuals ages 49.1±10.9 years, mostly Hispanic (51.1%), white (23.9%) and Asian (10.5%). Approximately 78% of them are anticipated to have diabetes.

6.1.1.4. Exposure assessment

Hepatitis B vaccine administration will be retrospectively captured from electronic medical records.

6.1.1.5. Outcome assessment

AMI events will be retrospectively identified from electronic health care databases through ICD-10 codes from databases of hospital discharge records and billing claims, and internal Kaiser Permanente coding. AMI will be captured from clinic or medical visits, emergency room (ER) visits and hospitalizations. Information on deaths in the Kaiser databases will also be collected.

AMI events will be confirmed by two trained physician reviewers using electronic medical records and standardized criteria from the Atherosclerosis Risk in Communities (ARIC) study.[1] In case of disagreement, cases will be reviewed by a third physician. It is important to note that, in 2015, approximately 45% of AMI cases were attended outside of KPSC facilities. As per the applicant, completeness and data quality for those episodes may be variable.

6.1.1.6. Covariates

Data on sex, age, race, dose, duration of membership, diabetes status, other cardiovascular disease risk factors including, but not limited to hypertension and smoking status, and other comorbidities will be retrospectively collected from medical records.

6.1.1.7. Interim analyses

Aggregate vaccine accrual and number of unconfirmed AMI events will be reported to the applicant monthly beginning three months after the administration of the first dose of HEPLISAV-B.

Three interim analyses will compare the incidence rates of **unconfirmed** (non-chart confirmed) AMI events in HEPLISAV-B vaccinees with those in concurrent recipients of another hepatitis B vaccine:

1. After 41 events have occurred (≈12 months after study starts*)
2. After 68 events have occurred (≈18 months after study starts*)
*Assuming no difference in the risk of AMI between the two groups

A futility analysis based on the conditional power will be performed at each interim analysis.

3. After the end of follow-up

Quarterly vaccine accrual and aggregated number of unconfirmed AMI events and results of the pre-specified interim analyses will be reviewed by a Data Monitoring Committee (DMC). If in any of the interim analyses the hazard ratio is ≥2.5, a formal comparison of confirmed AMIs will be conducted and the applicant will suspend administration of HEPLISAV-B in this study, if applicable (i.e. if the participants have not received yet the second dose). Data collection will continue until end of follow-up. Commercial use following the study will be determined by discussions with the FDA.

6.1.1.8. Statistical analyses

The analyses will compare the incidence rates of **confirmed** AMI events in 25,000 HEPLISAV-B vaccinees with those in approximately 25,000 concurrent recipients of another hepatitis B vaccine.

Primary analysis: Cox proportional hazard model employing inverse probability of treatment weighted (IPTW)

Sensitivity analyses:
1. Cox proportional hazard model adjusted for and/or stratified by propensity scores
2. Traditional multivariable Cox proportional hazards regression model

A secondary analysis, as per the applicant "if feasible based on demographic and clinical characteristics," will be conducted to compare the incidence rates of **unconfirmed** AMI in 25,000 HEPLISAV-B vaccinees compared with those in 25,000 recipients of another hepatitis B vaccine in 2016 (historical cohort) using an adjusted Cox proportional hazards regression model.

6.1.1.9. Sample size

At the end of the study, 25,000 vaccinees per group will provide approximately 86.5% power to exclude a hazard ratio of ≥2.0 using a non-inferiority analysis and one-sided test at a level of significance of 0.025 if the background incidence rate is 1.5 per 1,000 person-years.

6.1.1.10. Timelines

Table 5. Study period and milestones in study DV2-HBV-25

Milestone	
Protocol submission	December 31, 2017
Start of data collection	June 1, 2018
End of recruitment	April 15, 2019
Interim report 1	August 31, 2019
Interim report 2	February 29, 2020
End of data collection	May 31, 2020
Interim report 3	September 30, 2020
Final report	June 30, 2021

6.1.2. Post-marketing study proposal to assess the risk of immune-mediated diseases, herpes zoster and anaphylaxis following HEPLISAV-B administration

The post-marketing study proposed by the applicant designed to assess the risk of immune-mediated diseases, herpes zoster and anaphylaxis following HEPLISAV-B administration is titled *"Post-marketing observational surveillance of the safety of HEPLISAV-B in adults 18 years of age and older to evaluate the incidence of new onset immune-mediated diseases, herpes zoster and anaphylaxis."* The protocol number is DV2-HBV-26.

6.1.2.1. Objectives

Assess the risk of new onset immune-mediated diseases, herpes zoster and anaphylaxis following HEPLISAV-B vaccination.

6.1.2.2. Design and study setting

Retrospective observational cohort study using electronic healthcare databases conducted in two HMOs, Kaiser

Permanente Southern California (KPSC) and Kaiser Permanente Northern California (KPNC).

6.1.2.3. Study population

The study population will be adults ages 18 years or older enrolled at KPSC or KPCN and vaccinated with the first dose of a hepatitis B vaccine during the study period. Both cohorts, 30,000 HEPLISAV-B recipients and 30,000 recipients of another hepatitis B vaccine, will be recruited in a period of approximately 12 months and followed for 13 months following first dose vaccination.

6.1.2.4. Exposure assessment

Hepatitis B vaccine administration will be retrospectively captured from electronic medical records.

6.1.2.5. Outcome assessment

Outcomes will be retrospectively identified from electronic health care databases through ICD-10 codes, and internal Kaiser Permanente coding. Events will be captured from clinic or other medical visits, including emergency room (ER) visits and hospitalizations.

The pre-specified immune-mediated events include a total of 19 diseases, as listed in Table 6.

Table 6. Selected immune-mediated diseases and their background rates (as reported in the literature provided by the applicant)

Selected immune-mediated diseases	Background incidence rate (as reported by the applicant)
ANCA-positive vasculitis. Microscopic polyangiitis	Not reported
ANCA-positive vasculitis. Churg-Strauss syndrome	Not reported
ANCA-positive vasculitis. Granulomatosis with polyangiitis	8-10 per 1,000,000 per year [2]
Alopecia areata	Not reported
Basedow's (Graves) disease	13.9 per 100,000 person-years [3]
Bell's palsy	23 per 100,000 person-years [4]
Erythema nodosum	Not reported
Giant cell arteritis	Not reported
Guillain-Barre syndrome	2.4 per 100,000 person-years [5]
Lichen planus	Not reported
Polyarteritis nodosa	Not reported
Polymyalgia rheumatica	58.7 per 100,000 person-years [6]
Rheumatoid arthritis	26.2 per 100,000 person-years [5]
Scleroderma	19.3 per 1,000,000 per year [7]
Systemic lupus erythematosus	6 per 100,000 person-years [5]
Takayasu's arteritis	2.6 per 1,000,000 per year [8]
Ulcerative colitis	2.2-14.3 per 100,000 person-years
Tolosa-Hunt syndrome	1 per 1,000,000 per year [9]
Vitiligo	Not reported

Source: IR dated May 18, 2017. STN 125428/0088

6.1.2.6. Covariates

Data on sex, age, body mass index (BMI), race, ethnicity, diabetes status, comorbidities, smoking status, history of immune-mediated conditions, and history of immunosuppression will be retrospectively collected from medical records.

6.1.2.7. Statistical analyses

The analyses will compare the incidence rates of new onset of 19 selected immune-mediated diseases, herpes zoster, and anaphylaxis in 30,000 HEPLISAV-B vaccinees with those in 30,000 concurrent recipients of another hepatitis B vaccine.

For the analysis of:
- New onset of immune-mediated diseases: adjusted Poisson model
- Herpes zoster: adjusted Cox proportional hazard model
- Anaphylaxis: adjusted logistic regression

6.1.2.8. Sample size

As per the applicant, at the end of the study, 30,000 vaccinees per group will provide approximately:

- 87% power to detect a relative risk of ≥2.5 on the risk of new onset of immune-mediated diseases using a one-sided test at a level of significance of 0.025 if the background incidence rate is 1 per 1,000 person-years
- 99% power to exclude a hazard ratio of ≥1.8 on the risk of herpes zoster assuming a background incidence rate of 4/1,000 person-years using a one-sided test at a level of significance of 0.025 if the background incidence rate is 1 per 1,000 person-years
- <10% power to detect anaphylaxis risk, as the incidence of anaphylaxis is very low.

No further details have been provided.

6.1.2.9. Timelines

Table 7. Study period and milestones of study DV2-HBV-26

Milestone	
Protocol submission	May 31, 2018
Start of data collection	Not reported
End of recruitment	Not reported
End of data collection	August 31, 2020
Final report	February 28, 2022

6.1.3. Pregnancy registry

6.1.3.1. Objectives

Primary objective: Assess the risk of major congenital malformations in the offspring of women exposed to HEPLISAV-B just before or during pregnancy.

Secondary objective: To provide information on outcomes following pregnancy exposure to HEPLISAV-B.

6.1.3.2. Design

Observational prospective study conducted by a contract research organization. The registry will compare rates of the selected outcomes with estimates of background risk in an external population (e.g., CDC's Metropolitan Atlanta Congenital Defects Program).

6.1.3.3. Study population

US pregnant residents ages 18 years or older who would have received HEPLISAV-B just before or during pregnancy and agree to participate in the registry.

6.1.3.4. Outcomes

Primary outcomes: Major congenital malformations, live birth, premature birth, spontaneous abortion, stillbirth, elective termination associated with ectopic pregnancy or molar pregnancy.

Secondary outcomes: pre-eclampsia, thromboembolic events.

6.1.3.5. Sample size

The registry will collect information on at least 250 to 300 pregnant women vaccinated with HEPLISAV-B.

6.1.3.6. Timelines

Table 8. Study period and milestones for the pregnancy registry

Milestone	Planned Date
Protocol submission	February 9, 2018
Start of data collection	August 9, 2018
End of data collection	August 9, 2023
Final report	December 31, 2023

7. ANALYSIS OF APPLICANT'S PHARMACOVIGILANCE PLAN

7.1. Important identified risks

Vasovagal syncope and deltoid bursitis have been considered as important identified risks by the applicant given that they are considered class effects of injectable vaccines. The applicant proposes routine pharmacovigilance to address them.

Anaphylaxis has also been considered an important identified risk by the applicant given the suggested association between hepatitis B vaccination and anaphylaxis in yeast-sensitive individuals.[10] The applicant proposes routine pharmacovigilance and a retrospective observational study using healthcare databases in 60,000 hepatitis B vaccinees (30,000 HEPLISAV-B: 30,000 another hepatitis B vaccine) to address this concern. Nonetheless, the post-marketing study is clearly underpowered to assess the risk of anaphylaxis following HEPLISAV-B vaccination based on the rare occurrence of the event. In addition, the selected comparison group is another hepatitis B vaccine. Therefore, given that a class effect related to yeast is anticipated, it is not expected, even with a larger sample size, that this study would be able to identify potential differences in risk of anaphylaxis, if any, between HEPLISAV-B and Engerix-B. During the clinical trials, there were no attributed cases of anaphylaxis among the 10,038 and 4,200 subjects vaccinated with one or more doses of HEPLISAV-B and Engerix-B, respectively.

The applicant, however, has not included class effects of PS ODNs (other than immune-mediated diseases) in the PVP. A potential increased proportion in anemia events and elevated transaminases within 28 days in subjects who received HEPLISAV-B were noted by the EMA. Liver function tests and routine hematology were not

systematically measured in study DV2-HBV-23. Given the limited experience with the adjuvant and the advice from the EMA, it will be prudent to investigate class effects of PS ODNs, including, but not limited to anemia and liver function tests. These outcomes, particularly when sub-clinical, are not easily detectable through routine pharmacovigilance.

Therefore, this OBE/DE reviewer considers that routine pharmacovigilance is adequate to monitor vasovagal syncope, deltoid bursitis and anaphylaxis, and recommends submitting all anaphylaxis cases collected in the post-marketing study, if any, to the Vaccine Adverse Event Reporting System (VAERS). Class effects of PS ODNs should be included in the PVP as important potential risks, and further investigated through a sufficiently powered observational study.

7.2. Important potential risks

7.2.1. Cardiac events

In study DV2-HBV-23, 51 (0.9%) HEPLISAV-B recipients and 15 (0.5%) Engerix-B recipients presented with at least one serious cardiac disorder during the 13-month follow-up period (Table 9).

Table 9: Treatment-emergent SAEs in the system organ class of cardiac disorders in Study DV2-HBV-23

MedDRA Preferred Term	HEPLISAV-B 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	2 (0.04)	0
Cardiac failure acute	1 (0.02)	0
Cardiac failure congestive	6 (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

Individuals with ≥1 cardiac SAE. Adapted from Table 12-16. Clinical Study Report DV2-HBV-23. STN 125428/40

Among them, 19 (0.34%) HEPLISAV-B recipients and 3 (0.11%) Engerix-B recipients presented with at least

one SAE included in the Standardised MedDRA Query (SMQ) narrow for Myocardial Infarction. More specifically, 14 (0.25%) HEPLISAV-B recipients and 1 (0.11%) Engerix-B recipients were classified as AMI (Table 10).

Table 10: SAEs with PTs in the SMQ Narrow for Myocardial Infarction* in study DV2-HBV-23

MedDRA Preferred Term	HEPLISAV-B 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 unstable	1 (0.02)	0
Coronary artery occlusion	1 (0.02)	1 (0.04)
Myocardial infarction	2 (0.04)	1 (0.04)
Total Subjects	**19 (0.34)**	**3 (0.11)**

*It includes the preferred terms AMI, myocardial infarction, coronary artery occlusion, acute coronary syndrome and angina unstable

A composite Major Adverse Cardiac Events (MACE) endpoint comprising treatment-emergent death due to cardiovascular causes, non-fatal myocardial infarction, and non-fatal stroke (3-point MACE) in the three pivotal trials was analyzed. MACE were confirmed by a post-hoc blinded central adjudication committee (Table 11).

Table 11. Adjudicated AMI and MACE in studies DV2-HBV-23, -16 and -10

	DV2-HBV-23		DV2-HBV-16		DV2-HBV-10	
	HEPLISAV-B	Engerix-B	HEPLISAV-B	Engerix-B	HEPLISAV-B	Engerix-B
N	5,587	2,781	1,968	481	1,810	605
AMI	14 (0.25%)	1 (0.04%)	2 (0.10%)	1 (0.21%)	0	0
MACE	28 (0.50%)	6 (0.22%)	3 (0.15%)	2 (0.42%)	0	0

The Division of Biostatistics (OBE/DB) calculated the 95% CI for AMI, non-fatal stroke, CV death, and MACE in study DV2-HBV-23 using Koopman score intervals instead of the Wald method, which was the one used by the applicant. The reason was that Koopman score intervals perform better with very low event counts (based on literature and simulations) and is better in terms of coverage and power (Table 12).

Table 12: Relative risk and 95% CI of AMI, non-fatal stroke, CV death and MACE following HEPLISAV-B vaccination in study DV2-HBV-23

Study DV2-HBV-23					
AMI	14 (0.25%)	1 (0.04%)	6.97	0.92, 52.97	1.17, 41.44
Non-fatal stroke	11 (0.20%)	4 (0.14%)	1.37	0.44, 4.30	0.46, 4.07
CV death	3 (0.05%)	1 (0.04%)	1.49	0.16, 14.35	0.21, 10.42
MACE	28 (0.50%)	6 (0.22%)	2.32	0.96, 5.60	0.99, 5.46

[A] Wald confidence interval; [B] Koopman score confidence interval

AMI occurred in 14 (0.25%) HEPLISAV-B recipients and 1 (0.04%) Engerix-B recipient. The relative risk was 6.97, with a 95% CI of 0.92-52.97. With the application of Koopman score intervals the 95% CI was statistically significant (Table 12).

OBE/DB also conducted their own analysis of the relative risk of AMI, based on the observations from study DV2-HBV-23, using a Bayesian approach alternatively with or without borrowing from the prior AMI data from DV2-HBV-10 and -16. With "full borrowing" (using Study 10 and 16 data as prior) the probability of the relative risk (RR) of AMI being >1.0 and >2.0 were 94.7% and 65.5% respectively. With no borrowing (using DV2-HBV-23 data only) the probability of the RR of AMI being >1.0 and >2.0 were 98.6% and 85.5%, respectively (Table 13).

Table 13. Posterior probabilities that the RR of AMI following HEPLISAV-B vaccination is greater than 1, 2, 3, or 5

| | Relative Risk (RR) of AMI following HEPLISAV-B vaccination | | | |
	>1.0	>2.0	>3.0	>5.0
Full borrowing	94.7%	65.5%	40.8%	17.3%
Without borrowing	98.6%	85.5%	68.8%	43.3%

Among HEPLISAV-B recipients, one AMI case occurred within 3 days, seven within 28-180 days, and six more than 180 days following any active dose.

The AMI events occurred among HEPLISAV-B recipients with a median age of 63 (IQR:15) years, mostly males (71.4%), with hypertension (92.9%), and non-diabetics (85.7%) (Table 14). All subjects who reported AMI had one or more risk factors for cardiovascular disease.

Table 14: Risk factors for cardiovascular disease among AMI cases

Mean±Standard deviation	59.9 ± 9.2 years	65 years
Max-Min	39-69 years	65-65 years
Male	10 (71.4%)	1 (100%)

As per one member of the VRBPAC, "a causal link between the vaccine and AMI was not out of the question" since the adjuvant 1018 causes an inflammatory response of uncertain duration.[11,12] It is known that inflammation causes atherosclerotic plaques in coronary arteries to rupture, which is the event that triggers most AMIs.[12,13]

The applicant submitted a post-hoc safety analysis on diabetics in response to a FDA request dated September 29, 2017. In study DV2-HBV-23, 22 (2.9%) HEPLISAV-B recipients and 4 (1.1%) Engerix-B recipients presented at least one serious cardiac disorder during the 13-month follow-up period (Table 15).

Table 15: Treatment-emergent SAEs in the system organ class of cardiac disorders for subjects with type 2 diabetes in study DV2-HBV-23

Cardiac events MedDRA Preferred Term	HEPLISAV-B N = 762 n (%)	Engerix-B N = 381 n (%)
Acute myocardial infarction	2 (0.26%)	1 (0.26%)
Angina pectoris	1 (0.13%)	0
Atrial fibrillation	2 (0.26%)	1 (0.26%)
Atrial flutter	1 (0.13%)	0
Cardiac arrest	3 (0.39%)	0
Cardiac failure	1 (0.13%)	0
Cardiac failure congestive	5 (0.66%)	1 (0.26%)
Cardio-respiratory arrest	0	1 (0.26%)
Coronary artery disease	5 (0.66%)	2 (0.52%)
Coronary artery occlusion	1 (0.13%)	0
Hypertensive heart disease	1 (0.13%)	0
Myocardial infarction	1 (0.13%)	0
Pulseless electrical activity	1 (0.13%)	0
Supraventricular tachycardia	1 (0.13%)	0
Ventricular fibrillation	1 (0.13%)	0
Ventricular tachycardia	1 (0.13%)	0

Individuals with ≥1 cardiac SAE. Adapted from Table 29.1. Integrated Summary of Safety. STN 125428/103

The finding of similar rates of AMI among diabetics and non-diabetics vaccinated with HEPLISAV-B in this study (2 cases (0.26%) of AMI among 762 diabetics versus 12 (0.25%) among 4,825 non-diabetics), although it might be coincidental, deserves further investigation, including regarding the possibility of effect modification by diabetes treatment.[14-17] A cardiology consultation was requested by OBE/DE to discuss this matter and the inclusion of additional cardiac events that might deserve further investigation.. Of note, at the time of completion of this review and the Action Due Date (ADD), the request for the consultation had been submitted, but the consult had not occurred. The need for additional endpoints and the possibility of effect modification by diabetes treatment can be further discussed following product approval after receipt of the cardiology consultation. The PMR language describing the study in the approval letter only needs to characterize the major elements of the study.

At the Advisory Committee meeting of July 28, 2017, VRBPAC acknowledged that the imbalance in AMI between treatment groups may be due to chance, but strongly emphasized the need for a well-designed post-marketing prospective study that could provide early verification of the AMI signal associated with HEPLISAV-B. Specific VRBPAC recommendations regarding a post-marketing study on cardiac events are listed in section 3.1. Following the VRBPAC meeting, the applicant submitted an amendment to the PVP to address the limitations highlighted by the Committee. This PVP was not found to be adequate to address the concerns of the VRBPAC and the applicant was asked to revise it. Following several telecons and information requests, the applicant submitted version 4.0 of the PVP that included the final synopsis of study DV2-HBV-25.

Study DV2-HBV-25 aims to assess the risk of AMI (instead of using the MACE composite), following HEPLISAV-B vaccination.

For study DV2-HBV-25, the applicant proposes a "pseudo-cluster" design in which centers will not be randomized, but rather selected based on clustering of medical centers and logistics to either administer HEPLISAV-B (7 centers) or another hepatitis B vaccine (8 centers). Nonetheless, cardiovascular event risk information in the package insert and/or potential media attention over VRBPAC's concerns regarding AMI risk could influence physician likelihood to recommend HEPLISAV-B to patients they may consider at higher risk for cardiovascular disease, even if they belong to a HEPLISAV-B cluster. Also, patients who may want to decrease

their risk of cardiovascular disease could themselves avoid receiving HEPLISAV-B vaccine based on media attention. This selection bias may bias estimates of cardiovascular outcomes towards the null in a study such as the one proposed by the applicant. Thus, this OBE/DE reviewer considers that the best approach to eliminate this potential selection bias is using individual randomization.

The VRBPAC strongly recommended a prospective study given the need for collecting specific data from electrocardiography, cardiac imaging techniques, laboratory tests, as well as data on cardiovascular risk factors not frequently recorded in electronic healthcare databases. The applicant proposes instead a retrospective study using health care databases. In addition, it is important to note that approximately 45% of the AMI cases occurring in KPSC during 2015 were attended outside of KPSC facilities, and, as per the applicant, completeness and data quality for those episodes may be variable. The final primary analysis for study DV2-HBV-25 will be conducted among confirmed cases and case confirmation will be conducted by reviewing medical records. The proportion of individuals who seek care for AMI outside of KPSC may be different by cluster, since the number of proposed clusters is small (15 centers), and they will not be randomized, but selected. Thus, there may be differences in the rates of AMI attended outside of KPSC between HEPLISAV-B vaccinees and the comparison group. This may cause information bias and, as a consecuence, lead to differential outcome misclassification between HEPLISAV-B and the comparison vaccine recipients.

Given the severity of the outcome, in order to verify the signal as soon as possible while the vaccine is in the market and is being administered to the public, the VRBPAC recommended to oversample groups at higher risk for cardiovascular disease. As per the information provided by the applicant on hepatitis B vaccinees in KPSC in 2015, the proposed study population may be comprised of individuals ages 49 ($\pm$ 11) years, being ≈51% of males and ≈79% diabetics. Thus, individuals with risk factors for cardiovascular disease other than diabetes, particularly older age, might not be oversampled as was requested by the VRBPAC. This could delay and make more difficult the finding of AMI risk.

Timeliness depends heavily on the capability to recruit individuals within the planned period. Based on the last information provided by the applicant, approximately 51,668 eligible individuals would be vaccinated with at least one dose of hepatitis B vaccine in KPSC within 10.5 months (STN#125428/0098). If recruitment, particularly among HEPLISAV-B vaccinees, does not occur as well as planned, an extension may be requested by the applicant, extending the duration of the study. Of note, the applicant has increased several times the estimated number of potential eligible individuals to be vaccinated in the study, despite the fact that KPNC ultimately decided to not participate (STN# 125428/0072, STN#125428/0088, STN#125428/0089, STN#125428/0096, STN#125428/0098, and STN#125428/0100). These changes do not help reassure this OBE/DE reviewer that the recruitment may be completed in time.

If recruitment goes as planned (50,000 individuals vaccinated either with HEPLISAV-B or another hepatitis B vaccine in a 1:1 accrual rate within 10.5 months), the final study results (confirmed cases) will be available more than 3.5 years after vaccine approval. Given the observed temporal distribution of AMI cases following HEPLISAV-B vaccination, it is unlikely that passive surveillance will contribute to signal detection in this particular case. Thus, the proposed interim analyses and their accuracy are crucial to allow the FDA a timely and well-informed decision-making regarding this risk. Three interim analyses (unconfirmed cases) will be conducted during the study period. The first and second analyses will be event-driven, i.e., once 41 and 68 events, respectively, have been identified. The last interim analysis will be conducted once the follow-up for the last HEPLISAV-B recipient has ended, regardless of number of events. As per OBE/DB, since the applicant does not plan to stop the study at the interim analyses for non-inferiority given the case distribution observed in study DV2-HBV-23 (will stop vaccination in the study if there are still individuals to vaccinate), the power calculations provided for these analyses are meaningless. Also, it is unclear how the futility analysis in the Cox proportional hazard model will be performed. Thus, the utility of the proposed interim results to inform FDA decision-making is unclear, even if the study were able to provide unbiased results.

As stated above, the applicant's power calculations only apply to the final analysis. Also, the power calculations do not account for the intra-cluster correlation since the applicant claims that the intra-cluster correlation is extremely small (<0.00001) based on sample data of KPSC members vaccinated in 2015, which would result in minimal impact on power. Nonetheless, as per the applicant, clustering by medical center will be addressed through random effects in the final model if the intra-cluster correlation is sufficiently large as calculated from the study data. Thus, the applicant's current power calculations indicate that the study will provide approximately 86.5% power to discard a hazard ratio of ≥2.0 if the background rate for AMI is 1.5 per 1,000 person-years. As per the current FDA Guidance for Industry for antidiabetic drugs and cardiovascular risk, "*if the premarketing application contains clinical data that show that the upper bound of the two-sided 95% CI for the estimated increased risk is between 1.3 and 1.8, and the overall risk-benefit supports approval, a postmarketing trial generally will be necessary to definitely show that the upper bound of the two-sided 95% CI for the estimated risk ratio is less than 1.3*".[18] The proposed study is not designed to meet this recommendation.

Hence, as per the information provided by the applicant, this OBE/DE reviewer considers that the timelines, study design, and setting and population chosen by the applicant are not adequate to verify the AMI signal in a timely and unbiased manner. This OBE/DE reviewer considers appropriate to investigate AMI separately from MACE (as the VRBPAC recommended), but proposes considering the inclusion of additional secondary cardiac outcomes (to be analyzed separately).

7.2.2. Immune-mediated diseases

In study DV2-HBV-10, subjects were monitored for SAEs for 7 months after the first vaccine dose. New-onset immune-mediated adverse events occurred in 4 (0.2%) HEPLISAV-B recipients and 4 (0.7%) Engerix-B recipients (Table 16).

Table 16. New-onset immune-mediated adverse events identified in study DV2-HBV-10

New-onset immune-mediated AEs (DV2-HBV-10)	HEPLISAV-B (n=1,810)	Engerix-B (n=605)
ANCA-positive vasculitis (history of mixed connective tissue disease)	0	1
Bell's palsy	0	1
Granulomatosis with polyangiitis	**1**	**0**
Grave's disease	1	1
Guillain-Barré syndrome	1	0
Lichen planus	1	0
Raynaud's phenomenon	0	1
Overall	4 (0.2%)	4 (0.7%)

In study DV2-HBV-16, subjects were prospectively monitored during 12 months following the first dose administration for the occurrence of potential new-onset immune-mediated adverse events which were subsequently adjudicated by a blinded, independent, external group of experts. New-onset immune-mediated adverse events occurred in 6 (0.3%) HEPLISAV-B recipients. No events occurred in the Engerix-B group (n=481) (Table 17).

Table 17. New-onset immune-mediated adverse events identified in study DV2-HBV-16

New-onset immune-mediated AEs (DV2-HBV-16)		
Bell's palsy	1	0
Erythema nodosum	1	0
Hypothyroidism	2	0
Tolosa Hunt syndrome	**1**	**0**
Vitiligo	1	0
Total	6 (0.3%)	0

In study DV2-HBV-23, subjects were prospectively monitored during 13 months following the first dose administration for the occurrence of potential new-onset immune-mediated adverse events, which were subsequently adjudicated by a blinded, independent, external group of experts. Nine (0.2%) HEPLISAV-B recipients and 1 (0.03%) Engerix-B recipients reported a new-onset AESI (Table 18).

Table 18. New-onset immune-mediated adverse events identified in study DV2-HBV-23

New-onset immune-mediated AEs (DV2-HBV-23)		
Autoimmune thyroiditis (concurrent diagnosis of papillary thyroid carcinoma)	1	0
Alopecia areata	1	0
Bell's palsy	**5**	**1**
Polymyalgia rheumatica	1	0
Ulcerative colitis	1	0
Total	9 (0.2%)	1 (0.03%)

Slightly more HEPLISAV-B recipients reported normal baseline and elevated week 8 anti-beta 2 glycoprotein 1 IgM and lupus anticoagulant screen test levels compared to Engerix-B recipients. As per the clinical reviewer, the significance of this finding is unclear. This deserves further investigation.

The intended biologic activity of 1018 is to enhance antibody generation by activating the innate immune system via Toll-like receptor 9 (TLR9), therefore, it is theoretically possible that 1018 may be associated with the development of immune-mediated diseases. The finding of two serious and very rare events, granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) and Tolosa-Hunt syndrome, with a respective background incidence rate of 0.8-1 per 100,000 and 1 per 1,000,000 per year,[2,9] in studies DV2-HBV-10 and -16, requires attention. There were also 5 (0.09%) cases of Bell's palsy in HEPLISAV-B recipients and one (0.03%) in Engerix-B recipients in study DV2-HBV-23. The background incidence rate of Bell's palsy has been reported as 23 per 100,000 per year.[4]

The applicant proposes a cohort study to assess the risk of 19 selected immune-mediated diseases following HEPLISAV-B vaccination (DV2-HBV-26). As the selected immune-mediated diseases may represent different pathways or etiologies, the analysis will be performed for each disease separately. As per the applicant, the study will provide 87% power to detect a relative risk of ≥2.5 on the risk of new onset of immune-mediated diseases using a one-sided test at a level of significance of 0.0025 if the background incidence rate is 1 per 1,000 person-years. Nonetheless, most of the selected immune-mediated diseases present a background incidence rate clearly lower than 1 per 1,000 person-years (Table 6). Therefore, the proposed sample size (30,000 hepatitis B vaccinees per group) is clearly insufficient to assess the risk of the selected immune-mediated diseases other than alopecia areata, lichen planus, or vitiligo.

As per the applicant, individuals who have a medical history of immune-mediated disease are likely to receive HEPLISAV-B because the prevalence of any type of immune-mediated disease is relatively high. There is a theoretical concern that immune stimulation by adjuvants may exacerbate pre-existing immune-mediated conditions. A total of 129 subjects with pre-existing immune-mediated disorders received HEPLISAV-B. Therefore, persons with pre-existing immune-mediated disorders should be included in the PVP as important missing information for HEPLISAV-B given the insufficient information available. This OBE/DE reviewer proposes to include the lack of information on persons with pre-existing immune-mediated disorders in the label.

7.2.3. Herpes zoster

Herpes zoster (HZ) is a localized, usually painful cutaneous eruption caused by the reactivation of latent varicella zoster virus (VZV). HZ occurs in a dermatomal distribution because the neurons within which it reactivates project to these regions of the skin. VZV, however, also establishes latency in ganglia that do not project to the

skin, including neurons of the sympathetic, parasympathetic, [19] and enteric nervous systems. [20,21] The risk of HZ starts to increase at age 50 years and it is 8 to 10 times higher in persons aged ≥60 years than in younger people. [22] VZV has been recently suggested as a cause of vascular disease.[23] Granulomatous arteritis syndromes (temporal arteritis, intracranial vasculopathy, giant cell arteritis, and Takayasu aortitis) occur more often among persons aged >50 years, which is consistent with the idea that these syndromes may, at least in part, be due to the reactivation of VZV in neurons that project to affected arteries. [24-26] An epidemiologic link has also been found between the occurrence of HZ and AMI. [27]

In study DV2-HBV-23, HZ occurred in 38 (0.7%) HEPLISAV-B recipients and 9 (0.3%) Engerix-B recipients. The relative risk was 2.10, with a 95% CI of 1.02-4.34. The risk, if real, once characterized, may help to better understand the biological plausibility of HZ and related diseases following administration of HEPLISAV-B and its adjuvant.

The mean age of the HZ cases was 52.5 (± 10.2) years and 57.4 (±11.9) years among HEPLISAV-B and Engerix-B recipients, respectively. A total of 13 (34.2%) and 1 (11.1%) HZ cases in the HEPLISAV-B and Engerix-B group respectively, occurred in of individuals aged ≤49 years.

Figure 1. Age distribution of medically-attended herpes zoster cases occurring in study DV2-HBV-23 during the 13-month follow-up
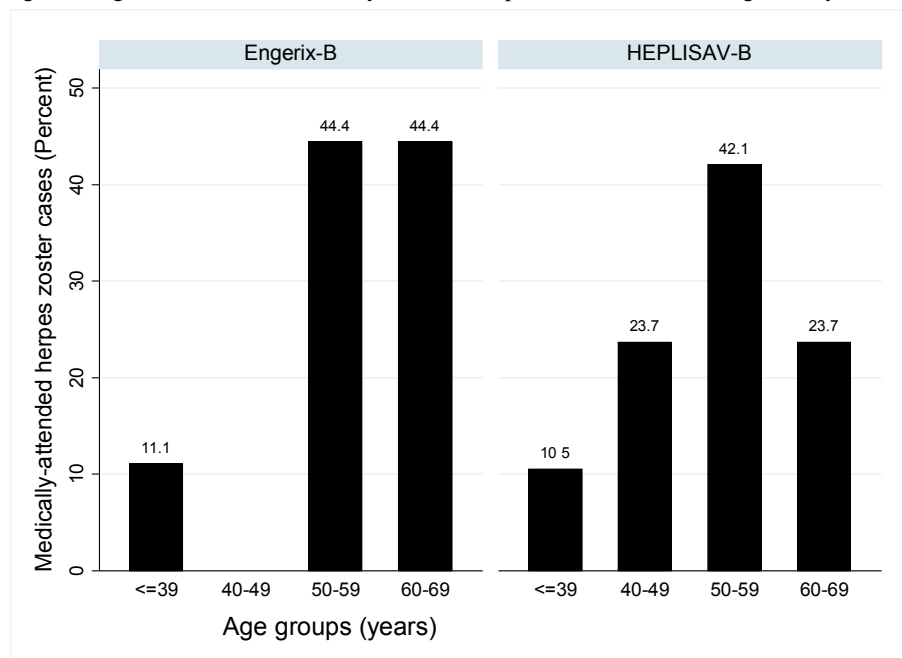
HZ cases following HEPLISAV-B vaccination did not show a clear temporal pattern, they were instead distributed throughout the entire follow-up period. The 2 HZ cases following first HEPLISAV-B administration occurred on days 25 and 116. The 36 HZ cases following second dose of HEPLISAV-B occurred between days 17 and 351 post-vaccination (Figure 2).

Figure 2. Temporal distribution of HZ cases following **HEPLISAV-B** vaccination
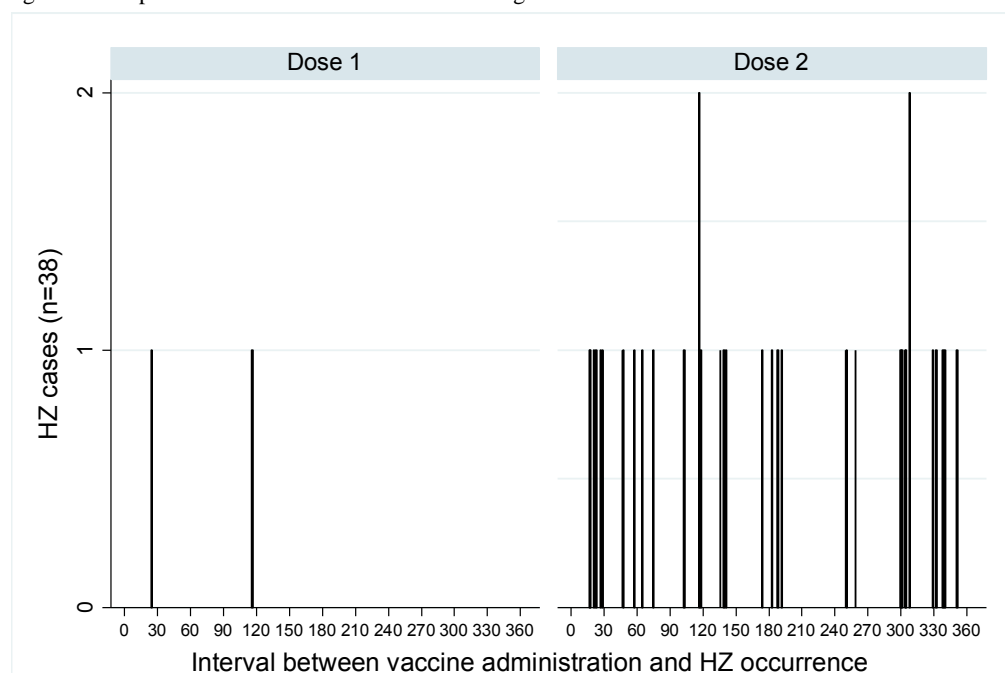
The extended temporal distribution of HZ cases following HEPLISAV-B vaccination in study DV2-HBV-23 strongly suggests the need of using surveillance methods other than passive surveillance to investigate this concern. For the same reason, it is not advisable to use self-controlled case series techniques.

The applicant, as recommended by OBE/DE, proposes a cohort study instead of a self-controlled case series study, to assess the risk of HZ following HEPLISAV-B vaccination (DV2-HBV-26). The proposed sample size (30,000 hepatitis B vaccinees per group) seems adequate to either confirm or discard a 1.8-fold increased risk following vaccination. Very minimal details have been included in the synopsis. However, this reviewer considers it important to highlight the appropriateness of investigating potential differences in risk by vaccine dose and, age group, and properly address any effect modification by prior HZ vaccination among individuals ages ≥50 years.

If the vaccine is approved, this "*important potential risk*" may not be clarified until more than 4 years after approval, when an unknown number of doses of HEPLISAV-B could have already been administered. Thus, this OBE/DE reviewer does not consider the proposed timelines as adequate. The applicant proposes to submit the study protocol more than 6 months after approval, and indicates that 1.5 years will be needed for statistical analyses and preparation of the final report suggest. These timelines could be adjusted to improve timelines.

7.3. Important missing information

7.3.1. Pregnancy

The applicant proposes a pregnancy registry in 250-300 US women to collect information on major congenital malformations, live birth, premature birth, spontaneous abortion, stillbirth, elective termination associated to ectopic pregnancy or molar pregnancy, pre-eclampsia, and thromboembolic events.

The selected outcomes and timelines proposed for the pregnancy registry seem adequate. However, minimal details have been provided since the protocol will be submitted by February 9, 2018 (3 months after approval).

Given the insufficient information available on adverse pregnancy outcomes potentially associated with HEPLISAV-B vaccination in the clinical trials, this OBE/DE reviewer recommends that the registry includes a controlled study comparing rates of the proposed adverse events of pregnancy among pregnant women vaccinated with HEPLISAV-B with pregnant women vaccinated with other hepatitis B vaccines, using standardized case definitions for all study outcomes. The sample size should be based on the outcome of interest with the smallest background rate; also, the applicant should consult the FDA Guidance for Industry current at the time of protocol design. Moreover, this reviewer recommends the inclusion of information in the package insert indicating that there is no sufficient safety data regarding use of HEPLISAV-B in pregnant women.

7.3.2. Immunosuppression, chronic liver disease and concomitant medication

Individuals with a positive test for HIV and/or immunosuppression due to a recent diagnosis of cancer (other than cutaneous) and/or persons on chemotheraphy/immunosuppressive drugs were excluded from the pivotal clinical trials. No specific studies in persons with chronic liver disease have been conducted. Concomitant vaccinations close to HEPLISAV-B vaccination were prohibited in the clinical trials. Therefore, safety data in immunocompromised individuals including HIV infection, individuals with chronic liver disease and those receiving concomitant vaccinations are considered to be important missing information.

Persons with hepatitis C infection (HCV) are not considered by the applicant to be important missing information for HEPLISAV-B. The applicant argues that the 34 individuals with HCV infection included study DV2-HBV-16 showed a similar safety profile compared to the overall safety population. Nonetheless, the applicant states in PVP that individuals with HIV infection and/or chronic liver disease, including those with HCV infection, may be likely to receive HEPLISAV-B vaccination, and it is likely that some adults may receive HEPLISAV-B concomitantly with other vaccines. The applicant has indicated that it will support at least one post-marketing study on immunogenicity and safety in persons who are HIV positive, and that it may conduct or support post-marketing studies on immunogenicity and safety in persons with chronic liver disease and on concomitant use of HEPLISAV-B. No further details have been provided.

This OBE/DE reviewer considers that persons with HCV should also be included in the PVP as important missing information for HEPLISAV-B and recommends the inclusion of information in the package insert indicating that there is no safety data/sufficient safety data in any of these sub-populations, including individuals with HCV infection, and on concomitant use of HEPLISAV-B with other vaccines.

7.3.3. Chronic kidney disease

Hepatitis B vaccination is recommended in individuals with end-stage renal disease, including pre-dialysis, hemodialysis, and peritoneal dialysis. [28] On the other hand, patients with chronic kidney disease (CKD) are at high cardiovascular risk. The applicant has not submitted specific analyses on patients with CKD to this BLA, although, the clinical study report synopsis of the trial DV2-HBV-17, a clinical study in adults with CKD,[29] was submitted. This study had been considered non-acceptable by the EMA, and its inspectors recommended not using the data of this trial in the context of the evaluation of the licensure application (see section 3.2). Ten deaths, most cardiac related, occurred during the study period: 7 (2.8%) in the HEPLISAV-B group and 3 (1.1%) in the Engerix-B group. [29] The applicant did not mention safety data on patients with CKD (receiving dialysis or not) in the PVP.

This OBE/DE reviewer considers that persons with CKD should be included in the PVP as important missing information for HEPLISAV-B. Given that hepatitis B vaccination is recommended in this sub-population, concerns regarding cardiac events, and the imbalance in deaths reported in trial DV2-HBV-17 (although not

statistically significant), further investigation should be performed prior to indicating this vaccine for individuals with CKD (adults ages ≥18 years). Also, this OBE/DE reviewer recommends the inclusion of information in the package insert clearly indicating that there are no sufficient data regarding HEPLISAV-B safety in this sub-population.

7.3.4. Ages >70 years

The pre-marketing clinical trials did not include adults ages >70 years. The proposed indication is for healthy adults 18 years of age or older. However, the applicant has not included the lack of safety data on this sub-population as important missing information and/or has not explained why the lack of safety data on individuals ages >70 (who are at high risk for AMI) should not be included as not important missing information for HEPLISAV-B.

If the vaccine is approved with the indication that the applicant requests, this OBE/DE reviewer recommends the inclusion of information in the package insert indicating clearly that there are no safety data for HEPLISAV-B in this age group.

8. ITEMS OF THE NOVEMBER 10, 2016 CR LETTER

CBER issued a CRL on November 16, 2016, outlining the deficiencies identified in the submitted PVP (STN#125428/0042):

8.1. Question 50

"The Phase 4 Post-Marketing Study Concept (Appendix 1 of the Risk Management Plan, STN 125428/0.42, module 1.16) states that "it is estimated that the study duration will be approximately 8 years in duration including protocol development and study preparation, subject accrual and collection of safety events, data analysis, and report writing." Please provide the number of years that will be needed specifically for subject accrual as well as an explanation and justification for this time estimate. What rate of vaccination uptake are you expecting?"

OBE/DE reviewer comments

The planned periods for subject accrual in studies DV2-HBV-25 ("approximately 10.5 months") and study DV2-HBV-26 ("approximately 1 year") have been provided by the sponsor.
Rate of vaccination uptake was not provided. The applicant provided instead the number of hepatitis B vaccinees in KPNC and KPSC after being requested again by DE/OBE (STN#125428/0088). Of note, the estimated number of potential eligible individuals to vaccinate in KPNC and KPSC within one year changed several times (STN# 125428/0072, STN#125428/0088, STN#125428/0089, STN#125428/0096, STN#125428/0098, and STN#125428/0100).

8.2. Question 51

"The Phase 4 Post-Marketing Study Concept (Appendix 1 of the Risk Management Plan, STN 125428/0.42, module 1.16) states that a sample size of 20,000 subjects per group will achieve 90% power to detect a 2.5 fold increase in the incidence of most immune-mediated diseases. Please describe (1) what is meant by "most immune-mediated diseases"; (2) the calculation used to determine this sample size, including the background incidence rate and the rationale for using this background incidence rate."

OBE/DE reviewer comments

As per the applicant, a sample size of 30,000 subjects per group in study DV2-HBV-26 will provide approximately 97% power to detect a 2.5-fold increase in the risk of individual immune-mediated diseases if the background rate is 1 per 1,000 person-years. No rationale for using a background rate of 1 per 1,000 person-years has been provided. In addition, none of the selected immune-mediated diseases to be included in study DV2-HBV-26, and for which a background incidence rate has been provided, present a background rate of 1 per 1,000 person-years (see section 6.1.2.5, Table 6), but a much lower one.

The background rates for the pre-specified immune-mediated diseases were provided after being requested again by DE/OBE (STN#125428/0088). The last version of study DV2-HBV-26 includes an update on the list of selected immune-mediated diseases (19 instead of 36, although some of the current ones were not included in previous versions). Nonetheless, the applicant has not provided background rates for the added immune-mediated diseases.

8.3. Question 52

"Please submit a revised Pharmacovigilance Plan/Risk Management Plan (submitted with Track Changes) that incorporates any new or changed findings or analyses and is reflective of the most updated safety information. Your responses to items in this CR letter will be incorporated into considerations around a potential post-marketing study. We anticipate that additional discussion and development of a potential post-marketing study will be needed."

OBE/DE reviewer comments

The applicant submitted version 2.0 (STN#125428/0072), version 3.0 (STN#125428/0093) and version 4.0 (STN#125428/0102) of the PVP plan. Version 4.0 did not include track changes.

9. OBE/DE REVIEWER CONCLUSIONS

Based on the review of the materials mentioned in section 2, this OBE/DE reviewer considers that the pre-licensure safety data still present important concerns. These multiple serious safety concerns are not easy to resolve in post-marketing studies in a timely manner.

Per this OBE/DE reviewer, overall, the PVP is not adequate, specifically to address concerns regarding risks of cardiac events and immune-mediated diseases following HEPLISAV-B vaccination. There is important missing safety information on multiple sub-populations at risk, including, but not limited to persons with CKD, chronic liver disease, HCV infection, ages >70 years, with immunocompromising conditions including HIV-positives, and with pre-existing immune-mediated diseases that might still use the vaccine post-marketing. More specifically:

- **Cardiac events**

The finding of 14 (0.25%) cases of AMI among HEPLISAV-B recipients vs. 1 (0.04%) among Engerix-B recipients in study DV2-HBV-23, statistically significant with the application of Koopman score intervals, is a main concern for this reviewer. A total of 51 (0.9%) HEPLISAV-B recipients and 15 (0.5%) Engerix-B recipients presented at least one serious cardiac disorder during the 13-month follow-up period (Table 9).

The post-marketing study on AMI risk, as proposed by the applicant, is not adequate to address in a timely and unbiased manner the potential risk following HEPLISAV-B vaccination, and does not fulfil VRBPAC's

recommendations. Also, even if the study were able to provide unbiased results, the utility of the proposed interim results to inform FDA decision-making is unclear. Moreover, based on the observed distribution of the AMI cases following HEPLISAV-B vaccination we may expect very limited usefulness of passive surveillance to detect this potential signal.

Cardiac events other than AMI should be also included in the PVP as important potential risks. This OBE/DE reviewer considers it appropriate to investigate AMI separately from MACE (as the VRBPAC recommended), but proposes considering the inclusion of additional secondary cardiac outcomes (to be analyzed separately). OBE/DE requested a cardiology consult to obtain advice regarding additional cardiac outcomes that might also deserve further investigation. Of note, at the time of completion of this review and the ADD, the request for the consultation had been submitted, but the consult had not occurred. However, the potential secondary outcomes of interest do not require resolution prior to product approval. The PMR language describing the study in the approval letter only needs to characterize the major elements of the study. Therefore, the need for additional endpoints can be further discussed following product approval after receipt of the cardiology consultation. If the vaccine is approved, the feedback obtained from that consultation will used to inform the review of the study protocol and will be added to the corresponding memorandum.

- **Immune-mediated diseases**

The finding of two serious and very rare events, granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) and Tolosa-Hunt syndrome, with a respective background incidence rate of 0.8-1 per 100,000 and 1 per 1,000,000 per year, in studies DV2-HBV-10 and -16, is concerning. Also, in study DV2-HBV-23, there were 5 (0.09%) cases of Bell's palsy in HEPLISAV-B recipients and one (0.03%) in Engerix-B recipients. The background incidence rate of Bell's palsy has been reported as 23 per 100,000 per year.

As per the applicant, the study DV2-HBV-26 will provide 87% power to detect a relative risk of ≥2.5 on the risk of new onset of immune-mediated diseases using a one-sided test at a level of significance of 0.0025 if the background incidence rate is 1 per 1,000 person-years. Nonetheless, most of the immune-mediated diseases included in study DV2-HBV-26 present a background incidence rate clearly lower than 1 per 1,000 person-years (Table 6). Therefore, the proposed sample size (30,000 hepatitis B vaccinees per group) is clearly insufficient to assess the risk of the selected immune-mediated diseases other than alopecia areata, lichen planus, or vitiligo.

Persons with pre-existing immune-mediated disorders should be included in the PVP as important missing information for HEPLISAV-B given the insufficient information available.

- **Herpes zoster**

The 38 (0.7%) HZ cases found among HEPLISAV-B recipients vs. 9 (0.3%) among Engerix-B recipients, with a relative risk of 2.10 (95% CI of 1.02-4.34) in study DV2-HBV-23 requires further investigation.

The applicant, as recommended by OBE/DE, proposes a cohort study to assess the risk of HZ following HEPLISAV-B vaccination (DV2-HBV-26). The proposed sample size (30,000 hepatitis B vaccinees per group) seems adequate to either confirm or discard a 1.8-fold increased risk following vaccination. Very minimal details have been included in the synopsis. However, this reviewer considers it important to highlight the appropriateness of investigating potential differences in risk by vaccine dose and age group, and properly address any effect modification by prior HZ vaccination among individuals ages ≥50 years. Study timelines could be adjusted to improve timeliness.

- **Anaphylaxis**

During the clinical trials, there were no attributed cases of anaphylaxis among the 10,038 and 4,200 subjects vaccinated with one or more doses of HEPLISAV-B and Engerix-B, respectively.

The proposed sample size (30,000 hepatitis B vaccinees per group) for study DV2-HBV-26 is clearly underpowered to assess the risk of anaphylaxis following HEPLISAV-B vaccination. In addition, the selected comparison group is another hepatitis B vaccine, so, given that a class effect related to yeast is anticipated, it is not expected, even with a larger sample size, that this study would be able to identify potential differences in risk of anaphylaxis, if any, between HEPLISAV-B and Engerix-B. As stated above, timings could be adjusted to improve timeliness.

This OBE/DE reviewer considers that routine pharmacovigilance seems adequate to monitor anaphylaxis and recommends submitting all anaphylaxis cases collected in the post-marketing study, if any, to the Vaccine Adverse Event Reporting System (VAERS).

- **Vasovagal syncope and deltoid bursitis**

This OBE/DE reviewer considers that routine pharmacovigilance seems adequate to monitor vasovagal syncope, and deltoid bursitis.

- **Pregnancy outcomes**

The information on adverse pregnancy outcomes available in the clinical trials is insufficient to confirm or discard such risks. The selected outcomes and timelines proposed for the pregnancy registry seem adequate. However, the study cannot be evaluated at this point since minimal details have been provided.

- **Chronic kidney disease**

The applicant did not mention safety data on patients with CKD with or without dialysis in the PVP. Nonetheless, a clinical study report synopsis of the trial DV2-HBV-17, a clinical study in adults with CKD, was submitted to the BLA and published in an indexed journal. [29] This study had been considered non-acceptable by the EMA, and its inspectors recommended not using the data of this trial in the context of the evaluation of the licensure application (section 3.2). Ten deaths, most cardiac related, occurred during the study period: 7 (2.8%) in the HEPLISAV-B group and 3 (1.1%) in the Engerix-B group. [29]

Persons with CKD should be included in the PVP as important missing information for HEPLISAV-B. Also, it is important to verify whether there is an increased risk of cardiovascular disease and/or death among patients with CKD following use of HEPLISAV-B prior to using it in this population.

- **Immunosuppression (including HIV infection), chronic liver disease, HCV infection, and concomitant medication**

The clinical trials provided no information regarding HEPLISAV-B vaccination of HIV-positives, persons with chronic liver disease, or about concomitant vaccination. Although the applicant has indicated support for at least one post-marketing study on immunogenicity and safety among HIV-positive persons, and that it may conduct or support post-marketing studies on immunogenicity and safety in persons with chronic liver disease and on concomitant use of HEPLISAV-B, no details have been provided.

Persons with HCV infection should be included in the PVP as important missing information for HEPLISAV-B given the insufficient information available.

- **Ages >70 years**

The pre-marketing clinical trials did not include adults ages >70 years. The proposed indication is for healthy adults 18 years of age or older. However, the applicant has not included the lack of safety data on this sub-population as important missing information and has not explained why the lack of safety data on individuals ages >70 (who are at high risk for AMI) is not important missing information for HEPLISAV-B.

- **Class effects of PS ODNs**

Class effects of PS ODNs should be included in the PVP as important potential risks and further investigated through a sufficiently powered observational study.

10. OBE/DE REVIEWER RECOMMENDATIONS

The PVP is not adequate, does not fulfil VRBPAC's recommendations, and should not be considered as the basis for product approval.

Nonetheless, if HEPLISAV-B is approved in adults aged 18 years and older (as the applicant requests), this OBE/DE reviewer recommends:

- A large prospective randomized controlled study to investigate the risk of AMI and other cardiac events following HEPLISAV-B vaccination, overall and by dose and age group, powered to show that the upper bound the 95% CI for the estimated hazard ratio is, at least, less than 1.8. Secondary outcomes may be included based on advice of cardiologists being consulted by OBE/DE. Sub-populations with risk factors for cardiovascular disease other than diabetes should be oversampled, particularly age groups at major risk. As per this OBE/DE reviewer, this study would be the best option to get a definite answer since it would allow addressing potential differential outcome misclassification, selection bias and additional sources of confounding. Given the severity of the outcome, and the risk found, this OBE/DE reviewer considers that it would be essential that this study is completed in a period sufficiently short to minimize the potential risk of AMI among the population vaccinated following licensure.
- Labeling of the AMI risk observed in study DV2-HBV-23 in the Highlights and in "Warning and Precautions" sections until the risk has been adequately either confirmed or discarded.
- A larger observational cohort study designed to investigate new onset of each one of the selected immune-mediated diseases following HEPLISAV-B vaccination with at least 80% power to detect, at least, a 2.5 increased risk if the background rate is 20 per 100,000 person-years.

If HEPLISAV-B is approved with restricted indication, that is, only for adults aged 18-39 years, this restriction per-se would constitute a minimal risk minimization strategy. In that scenario, this OBE/DE reviewer would recommend:

- A sufficiently powered observational study to investigate new onset of each one of the selected immune-mediated diseases following HEPLISAV-B vaccination with at least 80% power to detect, at least, a 2.5 increased risk if the background rate is 20 per 100,000 person-years.
- Even though AMI cases occurred mainly among HEPLISAV-B vaccinees older than 50 years of age (59.9 (± 9.2) years), the potential risk among the (younger) population for which the vaccine is indicated should be evaluated. Thus, this OBE/DE reviewer would also recommend a large post-marketing prospective study aimed to assess the risk of AMI and other cardiac events (secondary outcomes may be included based on advice of cardiologists being consulted by OBE/DE) following HEPLISAV-B vaccination,

overall and by dose, powered to show that the upper bound the 95% CI for the estimated hazard ratio is, at least, less than 1.8.

In addition, regardless of the approved indication, this OBE/DE reviewer recommends:

- Continued routine pharmacovigilance to monitor adverse events as required under 21 CFR 600.80.
- Periodic adverse event reports including details of potential risks and missing information and addressing potential modifications on the frequency of occurrence of the important identified risks.
- A retrospective cohort study to assess the risk of HZ following HEPLISAV-B vaccination, overall, by vaccine dose and age group, powered to discard, at least, an upper bound of a hazard ratio of ≥1.8.
- A pregnancy registry including a group of pregnant women vaccinated with other hepatitis B vaccines as primary comparison group, the use of standardized case definitions for all study outcomes, a sample size based on the outcome of interest with the smallest background rate, and consulting the current FDA Guidance for Industry at the time of protocol design.
- Inclusion of information in the vaccine's package insert clarifying that there is insufficient or no information on HEPLISAV-B safety among pregnant women, persons with chronic kidney and liver disease (including HCV infection), immunocompromised (including HIV-positive individuals), persons older than 70 years of age, with pre-existing immune-mediated disorders and on concomitant vaccination.
- A sufficiently powered observational study to investigate class effects of PS ODNs.
- If any further safety concerns are identified, the FDA may recommend additional pharmacovigilance activities.

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ADDENDUM 1. BRANCH CHIEF RECOMMENDATIONS

As the Branch Chief of the Analytic Epidemiology Branch (AEB), I concur with the conclusions and recommendations of this OBE/DE Reviewer.

ADDENDUM 2. DIVISION RECOMMENDATIONS

As the DE Division Director, I have fully reviewed this memorandum and agree with the limitations to Study DV2-HBV-25 that have been noted by the DE reviewer. However, the proposed study design is consistent with post-market safety studies typically approved by the FDA, and more importantly, FDA is required to use the least burdensome approach to obtaining clinical information as per Section 505(o)(3)(D)(i) of the Federal Food, Drug, and Cosmetic Act, which states that before requiring a post-marketing clinical trial, FDA must first find that a post-marketing study will not be sufficient. Therefore, the critical issue is not whether superior study designs exist, but rather is the proposed study sufficient to address the safety issue. In light of this requirement, I believe that the PMR and PMC study designs that have been agreed to by the FDA and Applicant are acceptable. With regard to the specific issues raised in this review:

- Delay in availability of study results – while the final study results will not be available until approximately 3.5 years after approval, this is a reasonable time frame for completing large post-market safety studies, and multiple interim assessments have been included in the proposed study design in order to detect potential differences in rates of AMI between the study arms in a timely manner.

- Lack of randomization – while individual randomization would be a stronger study design, the more important question is whether it is required to address the safety issue. It should be noted that baseline cardiovascular risk factors will be captured for each participant and used to ensure that the treatment arms are appropriately comparable. In addition, one of the concerns raised by the DE reviewer and VRBPAC was the possibility that patients who are at higher risk of cardiovascular disease may avoid HEPLISAV-B due to the possibility of increased cardiovascular risk, or that physicians may direct their patients to other options due to cardiovascular concerns. However, this may occur regardless of whether randomization is used, and based on my clinical experience, neither patients nor their physicians are generally aware of the specific brand of hepatitis B vaccine that is administered in a given healthcare setting, and are even less likely to have a strong brand preference. In the event that patients do obtain hepatitis B vaccinations outside of their assigned KPSC clinic site, it would be appropriate to capture such events, as well as the occurrence of any subsequent AMIs.

- Lack of prospective study design – a prospective design would likely lead to some improvement in cardiovascular risk factor capture, particularly with respect to smoking. However, other cardiac risk factors are commonly captured in medical records, and while smoking is less reliably captured, this would only impact the results if there was substantive differential ascertainment in smoking across networks based on the hepatitis B product assignment. There is no specific basis for this theoretical concern, and multiple cardiovascular risk factors will be captured and can be reasonably used to determine if there is an important imbalance.

- Potential for incomplete follow-up – while the potential for incomplete follow-up is certainly possible, this is true for all studies. The Applicant has acknowledged this concern, and the finalized protocol will include procedures to be used during the study to capture clinical data when a patient is treated for AMI at a non-KPSC facility. As healthcare for KPSC members is both paid for and coordinated by KPSC, it is reasonable to anticipate that medical information regarding AMI that is generated at outside facilities will be provided to KPSC both for payment and follow-up medical care.

- I agree with the DE reviewer regarding the need to characterize the concern for AMI in the product labeling. In addition, as AMI and MI were both adjudicated to be treatment-emergent events of myocardial infarction during Study DV2-HBV-25, I recommend combining them when presenting this information in product labeling.

Regarding other safety issues unrelated to the PMR, I have the following comments:

- Requiring the use of a control group for the pregnancy registry as recommended by the DE reviewer is not typical. Established historical control rates for birth defects and other adverse pregnancy outcomes are generally used to assess potential effects on pregnancy, and no basis is provided as to why this would not be sufficient for HEPLISAV-B.

- Regarding the PMC for immune-mediated disorders, the DE reviewer is correct that despite including 60,000 individuals, the study is underpowered to detect a number of very rare immune-mediated disorders that this vaccine could conceivably cause. However, powering the study to detect events that may occur in as few as 1 per 1,000,000 person-years is not reasonable, and the proposed 60,000 patient study provides substantial power to characterize the safety of HEPLISAV-B with respect to immune-mediated disorders overall.

- Regarding the DE reviewer's recommendation to investigate PS ODN class effects, the clinical data described in this review do not reasonably support safety concerns for anemia or liver inflammation. If concerns remain regarding class effects for PS ODNs, further discussion with EMA and assessment of other clinical data relating to PS ODNs could be appropriate.

- Regarding the PV plan's listing of identified, potential, and missing information, I generally agree with the DE reviewer's findings, except I would not include "cardiac events other than AMI" as an important potential risk. Such a category is insufficiently specific, and AMI is among the most medically important cardiac adverse events that can occur. Therefore, it is unclear what additional events could be listed that would be informative (i.e., any product that could cause an AMI would be assumed to be able to cause less severe events such as unstable angina).