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Priority Review	No
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Applicant	Dynavax Technologies Corporation
Established Name	Hepatitis B Vaccine (Recombinant), Adjuvanted
(Proposed) Trade Name	HEPLISAV-B, HEPLISAV
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	1018 ISS adjuvant and recombinant HBsAg derived from Hansenula polymorpha yeast cells.
Dosage Form(s) and Route(s) of Administration	Each 0.5 mL dose should be administered by intramuscular injection only.
Dosing Regimen	2 doses administered 1 month apart (1 dose each given at 0, 1 month).
Indication(s) and Intended Population(s)	Immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older.

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GLOSSARY

Abbreviation or Term	Definition/Explanation
AE	adverse event
AESI	adverse event of special interest
AIAE	autoimmune adverse event
ALT	alanine transaminase
ANA	antinuclear antibody
AST	aspartate transaminase
anti-HBc	antibody against hepatitis B core antigen
anti-HBs	antibody against hepatitis B surface antigen
BIMO	Bioresearch Monitoring
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRF	case report form
CT	computerized tomography
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	good clinical practice
GI	gastrointestinal
GMC	geometric mean concentration
GPA	granulomatosis with polyangiitis
HBsAg	recombinant hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IMP	investigational medicinal product
IRB	Institutional Review Board
MAE	medically-attended adverse event
MedDRA	medical dictionary for regulatory activities
mITT	modified Intent-to-Treat
MRI	magnetic resonance imaging
ODN	oligodeoxynucleotide
p-ANCA	perinuclear-staining antineutrophil cytoplasmic antibody

PD	protocol deviation
PEAI	pre-existing autoimmune disorder
PP	Per-Protocol
PS ODN	phosphorothioate oligodeoxynucleotide
PT	Preferred Term
QA	Quality Assurance
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SEAC	Safety Evaluation and Adjudication Committee
SMQ	standardized MedDRA queries
SOC	system organ class
SPR	seroprotection rate
THS	Tolosa Hunt syndrome
TIA	transient ischemic attack
TSH	thyroid stimulating hormone
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. EXECUTIVE SUMMARY

1.1 Introduction

The statistical review of the original BLA 125428/0 for HEPLISAV vaccine was completed more than three years ago. Please refer to the statistical review dated 29 January 2013 of the original license application of HEPLISAV (BLA STN 125428/0). The studies (DV2-HBV-10 and DV2-HBV-16) submitted to the original BLA demonstrated evidence for efficacy based on the primary immunogenicity endpoint of seroprotection against hepatitis B virus infection. The vaccine comprised 1018 ISS adjuvant and recombinant HBsAg derived from *Hansenula polymorpha* yeast cells. HEPLISAV, intended to be administered as two vaccinations at Weeks 0 and 4, was compared to assess non-inferiority to the licensed Engerix-B vaccine (GlaxoSmithKline) administered as three vaccinations at Weeks 0, 4, and 24, in subjects with ages ranging from 11 to 70 years. Regarding safety, the Advisory Committee (VRBPAC meeting held on 15 November 2012) recommended assessment in a larger safety database, due to the concern that the BLA showed occurrence of autoimmune cases (including Guillain-Barre syndrome and Tolosa-Hunt syndrome) in the investigational arm. CBER issued a Complete Response (CR) letter on 22 February 2013. The applicant, Dynavax, conducted a new study, DV2-HBV-23, to address this concern by evaluating safety in an expanded database of about 8,368 new subjects. Dynavax submitted the new study data and the responses to CR items in STN 125428/0/42 on 15 March 2016. On 8 April 2016, the applicant submitted to amendment 45 the revised datasets for the two studies DV2-HBV-10 and DV2-HBV-16 reviewed previously in the original BLA 125428/0. On 11 April

2016, CBER decided that it was a major amendment and therefore, the action due date was changed to December 15, 2016. In the revised data, however, the accuracy of immunogenicity results could not be verified because of discrepancies noted by clinical/medical reviewers (section 3.1). Thus, the related immunogenicity analyses could not be performed and presented in this review. Such analyses can potentially be conducted if these issues get resolved in the next review cycle.

With regard to safety, the new data did not allay concerns about risk imbalances between study arms with regard to new onset of autoimmune diseases and adverse events of special interest. Risk imbalance was evident in acute myocardial infarctions as well (ref. Table 6.1.10). Some of the point estimates of relative risk (RR) and corresponding confidence bounds, although not quite excluding the value 1, nevertheless were suggestive of excess risk with respect to these adverse events.

1.2 Brief Overview of BLA submission

Please refer to the statistical review dated 1 January 2013 for details on the original BLA STN 125428/0, where the two phase 3 studies included safety and immunogenicity data from subjects in the age range 11-70 years. In the new phase 3 study, DV2-HBV-23, safety data are presented from an expanded database comprising 8,368 subjects from 18 to 70 years of age. The new study contained immunogenicity data as well and corroborated efficacy concluded in the original BLA. Regarding safety, the concerns seemed to persist for autoimmune conditions, with likely new concerns added for acute myocardial infarctions.

1.3 Major Statistical Issues and conclusions

With the new safety study DV2-HBV-23 and with the two pivotal studies in the original submission STN 125428/0, the license application contains three pivotal studies. While all of these studies evaluated safety and immunogenicity, the evaluation of pivotal safety in DV2-HBV-23 remains critical, along with the efficacy data from pivotal studies DV2-HBV-10 and DV2-HBV-16. This review, however, does not present immunogenicity results related to the revised data pertinent to DV2-HBV-10 and DV2-HBV-16. The revised data contained discrepancies, which need to be resolved by the next review cycle.

Conclusions related to immunogenicity

The analyses of new study data on immunogenicity (ref. Table 6.1.2) showed no major change from the original conclusion establishing efficacy.

Conclusions related to safety

Please refer to Table 6.1.10 for details. Basically, an estimated relative risk (RR) of 6.97 with 95% exact CI of (1.23, 184.9) indicates that the data are consistent with excess risk for acute myocardial infarctions and new onset of autoimmune diseases including adverse events of special interest (SEC confirmed) associated with HEPLISAV

vaccination. With regard to deaths, the RR point estimate was 1.99 with 95% exact CI: (0.70, 7.62). Although a relative risk of 1 (indicating no difference) is not excluded, the RR point estimate of almost 2-fold along with its upper confidence bound exceeding 7-fold suggests potential excess risk for a hard endpoint like death among the HEPLISAV vaccinees.

2. CLINICAL AND REGULATORY BACKGROUND

The applicant in earlier clinical development found that healthy adult volunteers injected with 1018 ISS- HBsAg achieved protective anti-HBsAg levels earlier than individuals injected with Engerix-B. The purpose of the two pivotal phase 3 studies in the original BLA was to confirm these findings for the candidate vaccine. In the original BLA studies, the seroprotection rate (SPR) induced at Week 12 in the HEPLISAV arm was non-inferior to the SPR induced at Week 28 or at Week 32, as prespecified in study protocols, in the Engerix-B arm. The observation of non-inferiority was supported in the immunogenicity data collected in the expanded safety study (DV2-HBV-23) as well. In this study, the SPR induced at Week 24 in the HEPLISAV arm was non-inferior to the SPR induced at Week 28 in the Engerix-B arm (Table 6.1.2).

2.1 Disease or Health-Related Condition(s) Studied

Immunization against Hepatitis B virus infections of all known subtypes in adults of 18 years of age and older.

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

GSK's Engerix-B vaccine.

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

Please see medical officer's review.

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

A CR letter was issued to the applicant for the original BLA 125428/0 for HEPLISAV vaccine. The VRBPAC recommended further assessment of safety in a larger database, because of occurrences of autoimmune cases (including Guillain-Barre syndrome and Tolosa-Hunt syndrome) in the investigational arm. The new study DV2-HBV-23 was conducted to address this concern, and evaluated safety based on an expanded database of about 8,368 new subjects. The new study was submitted under STN 125428/0/42 on 15 March 2016. The applicant also submitted to amendment 45 on 8 April 2016 the revised datasets for the two studies DV2-HBV-10 and DV2-HBV-16 which were previously reviewed in the original BLA submission. On 11 April 2016, CBER decided that the submission constituted a major Amendment.

2.6 Other Relevant Background Information

None

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The BLA 125428/0/42 was accepted as a resubmission containing complete responses to the CR letter. It was submitted on 15 March 2016. In the submission, the new phase 3 study DV2-HBV-23 is of critical importance because it provided expanded data on safety following recommendations in the CR letter. The submitted materials in the new study included the clinical study report, the SAP, and the SAS data files for safety and immunogenicity information. The SAS programs were not included, however. Additionally, following inspections by another regulatory agency (EMA), not related to this license application, the applicant made additional exclusions and inclusions of subjects in the two pivotal studies DV2-HBV-10 and DV2-HBV-16 of the original BLA 125428/0. The SAS files of these inclusions/ exclusions were not included in the BLA amendment 125428/0/42, but were submitted to amendments 45 (dated 8 April 2016) and 54 (dated 12 July 2016) in response to information request (IR). The medical officer noticed discrepancies between different versions of the datasets with regard to the exclusion/inclusion status. This finding prevented verification of the accuracy of immunogenicity results based on the revised data. In October 2016, the applicant submitted several amendments to explain the revised datasets for these two studies. The time constraint imposed by receipt of this information so close to the action due date, and issues currently not allowing verification of accuracy of immunogenicity data, prevented presentation of revised immunogenicity results for review, until the issues are resolved in the next review cycle. Moreover, expanded evaluation of safety was the most dominant issue in the CR letter.

The completeness of the amendment submission related to study DV2-HBV-23 was satisfactory to enable statistical review, but may be subject to quality assessment by BIMO. However, there were issues regarding the revised materials submitted for studies DV2-HBV-10 and DV2-HBV-16. Of note, the revision was in order to satisfy EMA inspection and queries and was not due to the CR letter. Please refer to the clinical reviewer's report for more on the clinical issues related to discrepancies in the revised data.

3.2 Compliance with Good Clinical Practices and Data Integrity

As per the applicant, data submitted to this BLA amendment were generated by study DV2-HBV-23 conducted in accordance with the Good Clinical Practice (GCP) guidelines and ethical principles.

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

This entire section relates to the CMC issues and assay related matters, including clinical and non-clinical pharmacology/ toxicology and pharmacovigilance, etc., and is not

applicable for statistical review of efficacy and safety. Thus, sections 4.1 through 4.6 are not discussed. Please refer to the relevant reviews by other discipline reviewers.

4.1 Chemistry, Manufacturing, and Controls

Not applicable

4.2 Assay Validation

Not applicable

4.3 Nonclinical Pharmacology/Toxicology

Not applicable

4.4 Clinical Pharmacology

Not applicable

4.5 Clinical

Please see medical officers' reviews.

4.6 Pharmacovigilance

Please see epidemiologist's review.

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

5.1 Review Strategy

The statistical review of this BLA was carried out by the reviewer, and no co-reviewer was involved.

1. The stamped, statistical review dated 29 January 2013 of the original licensing application of HEPLISAV (BLA STN 125428/0) was already uploaded in the EDR and has been referred to in this amendment review.

2. The immunogenicity analyses based on the revised data sets (of DV2-HBV-10 and DV2-HBV-16) were not presented in this review. Clinical/ medical reviewers noticed discrepancies with the data and could not verify accuracy of immunogenicity results. The review and presentation of the revised immunogenicity results are postponed until the discrepancy issues are resolved in the next review cycle.

3. The review of the new study DV2-HBV-23 was carried out as an individual review (section 6.1) and is the only protocol included in this review cycle.

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

The statistical review of the original BLA was based on STN 125428/0. The pivotal studies DV2-HBV-10 and DV2-HBV-16 had a number of additional subject exclusions

and inclusions based on EMA recommendations, which resulted in revision of the efficacy analyses in the current amendment submission, BLA STN 125428/0/42. Because of discrepancies observed with the revised immunogenicity data, the review of revised data in DV2-HBV-10 and DV2-HBV-16 is postponed until the issues are resolved in the next review cycle.

This statistical review of the BLA resubmission is mainly based on the following volumes:

STN125428/0/42 submitted on 15 March 2016

Module 5: The final protocols, SAPs, and clinical study reports for DV2-HBV-23 and revised clinical study reports for DV2-HBV-10 and DV2-HBV-16, with adequate datasets (for DV2-HBV-23). .

Module 1: Administrative information and labeling.

Module 2: Overviews of clinical efficacy and safety.

and

STN125428/0/45 IR response submitted on 8 April 2016

STN125428/0/54 IR response submitted on 12 July 2016.

5.3 Table of Studies/Clinical Trials

After the original BLA was evaluated in 2013, the larger safety study DV2-HBV-23 was listed as the new Phase 3 trial.

5.4 Consultations

Please refer to the medical officer's Report.

5.4.1 Advisory Committee Meeting (if applicable)

The VRBPAC meeting was held on 15 November 2012 to discuss the safety issue in the original BLA. The BLA had the occurrence of autoimmune diseases, including Guillain-Barre syndrome and Tolosa-Hunt syndrome in the investigational arm. The VRBPAC recommended a larger safety data base to allow further assessment of safety. The current Phase 3 study DV2-HBV-23 was in partial fulfillment of that recommendation.

For further details, please refer to the medical officer's and epidemiologist's reviews.

5.4.2 External Consults/Collaborations (if applicable)

Not applicable to this statistical review.

5.5 Literature Reviewed (if applicable)

Not applicable.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

Because of discrepancies noticed by clinical reviewers with the revised immunogenicity data, the review of revised data in DV2-HBV-10 and DV2-HBV-16 is postponed until the issues are resolved in the next review cycle. The review below focuses on the phase 3 study DV2-HBV-23, which is the expanded safety study following the CR letter.

6.1 Trial #1: DV2-HBV-23

Protocol Title of the clinical trial: “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: April 18, 2014 (the first subject visit)

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

Date of Report: March 01, 2016.

Amendment and Reasons: The original BLA STN 125428/0 reported the occurrence of autoimmune diseases including Guillain-Barre syndrome and Tolosa-Hunt syndrome in the experimental arm. To address this safety concern, a larger safety study was recommended in the CR letter. The recommendation has been implemented through a new phase-3 protocol DV2-HBV-23. The protocol studied 8,368 subjects.

6.1.1 Objectives (Primary, Secondary, etc.)

Primary Safety Objectives:

- To evaluate the overall safety of HEPLISAV with respect to clinically significant adverse events (AEs).

Secondary Safety 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.

The current review focuses on the primary safety objective(s). Please refer to the clinical/ medical reviewer’s report for details on the secondary safety objectives.

Immunogenicity Objectives:

The applicant listed a number of immunogenicity evaluations for the type2 diabetes mellitus subgroup, as immunogenicity objectives. These objectives were not a part of the CR letter that served the basis for expanded safety data evaluation, and as such were not a focus of this review addendum. Nevertheless, the reviewer performed analyses of sero-protection rate and GMC, regardless of subgroups, to assess the endpoints' general pattern emerging from all subjects in the expanded data base, DV2-HBV-23. This was in one of the applicant's secondary objectives, as stated below:

- To demonstrate that 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 at Week 24 is non-inferior to the SPR at Week 28 induced by Engerix-B, in all subjects.

In the original BLA, STN 125428/0, the immunogenicity in study DV2-HBV-10 was assessed at Week 12 (i.e., 8 weeks post last dose) for HEPLISAV and at Week 28 (i.e., 4 weeks post last dose) for Engerix-B; in study DV2-HBV-16, the assessments were at Week 12 and Week 32 in the respective arms. I defer to the medical reviewers to interpret the immunogenicity comparisons across the three pivotal studies presenting with three different time points for immunogenicity measurements.

6.1.2 Design Overview

This was an observer-blinded, randomized, phase 3 trial in subjects 18-70 years old. The subjects were randomized 2:1 to HEPLISAV (approximately 5500 subjects) or Engerix-B (approximately 2750 subjects). The HEPLISAV arm was administered a 2-dose series of HEPLISAV at 0 and 4 weeks and placebo at 24 weeks; the Engerix-B group received a 3-dose series of Engerix-B at 0, 4, and 24 weeks. Blood samples for anti-HBs were collected at Week 24 and Week 28 of visits. For safety, the new-onset of auto-immune diseases (AESIs or AIAEs) were determined over the 56 weeks of study period.

6.1.3 Population

The study subjects were 18 to 70 years old, were stated as able to comprehend and follow all required study procedures, and be available for all visits scheduled in the study and able and willing to provide informed consent, and non-pregnant women. Please see the medical officer's review for details on the inclusion and exclusion criteria.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Test Product Dose and Mode of Administration, Batch Number:

The investigational vaccine (HEPLISAV) [20 mcg recombinant HBsAg subtype *adw* with 3000 mcg 1018] was manufactured by Rentschler Biotechnologie GmbH (Germany).

Subjects in the HEPLISAV group received a single intramuscular injection (0.5 mL) into the deltoid muscle at Weeks 0 and 4.

Lot number: 1017098

Reference Vaccine, Dose and Mode of Administration, Batch Number:

The reference vaccine was Engerix-B[®] manufactured by GlaxoSmithKline Biologics (GSK). Each 1.0 mL dose contains 20 mcg of HBsAg adsorbed on 500 mcg aluminum as aluminum hydroxide.

Subjects in the Engerix-B group received a single intramuscular injection (1.0 mL) into the deltoid muscle at Weeks 0, 4, and 24.

Lot Number: 592D3.

Placebo:

The placebo was 0.9% normal saline for injection and was manufactured by APP Pharmaceuticals, LLP.

Subjects assigned to HEPLISAV received placebo administered as an intramuscular injection (0.5 mL) into the deltoid muscle at Week 24.

Lot Number: 6006390.

6.1.6 Sites and Centers

The trial was conducted by 40 investigators at 40 trial centers in the United States.

6.1.7 Surveillance/Monitoring

Not applicable in this review.

6.1.8 Endpoints and Criteria for Study Success

Safety variables

- Medically attended adverse events (MAEs)
- Autoimmune adverse events (AIAEs)
- Serious adverse events (SAEs)
- Deaths

Primary Endpoints

- Proportion of subjects with new-onset MAEs

- Proportion of subjects with new-onset SAEs or deaths
- Proportion of subjects with new-onset AIAEs

6.1.9 Statistical Considerations & Statistical Analysis Plan

Safety

The submission indicated that a specific safety interest in DV2-HBV-23 was the proportion of subjects who developed new-onset of AESIs or AIAEs during the study. The submission considered a background rate of 300/100,000 for such diseases and further stated, “... with a sample size of 5000 HEPLISAV subjects, one 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%.” (DV2-HBV-23, page 6 of 138). The study enrolled approximately 5500 subjects in the HEPLISAV arm and 2750 subjects in the Engerix-B arm. However, the probability that 15 new onset of autoimmune disorders in the HEPLISAV group would occur within 5500 HEPLISAV subjects was only 68% with the background rate assumed above.

Immunogenicity Analysis

Endpoint: SPRs measured at Week 24 and Week 28 in all subjects.

Statistical Hypothesis:

$H_0: \text{SPR}_{\text{HEPLISAV}} - \text{SPR}_{\text{Engerix-B}} < -10\%$ $H_1: \text{SPR}_{\text{HEPLISAV}} - \text{SPR}_{\text{Engerix-B}} \geq -10\%$

Groups: HEPLISAV and Engerix-B.

Analysis Method: The difference between (1) SPR due to HEPLISAV at Week 24 and (2) SPR due to Engerix-B at Week 28, will be used to compute the confidence limits.

Criterion of assessment: HEPLISAV is non-inferior to Engerix-B in seroprotection rates if the lower limit of the 95% CIs of difference from the above analysis is greater than -10%.

6.1.10 Study Population and Disposition

Table 6.1.1: Analysis Populations, 18-70 years, DV2-HBV-23.

Population	HEPLISAV n (%)	Engerix-B n (%)	Total n (%)
Subjects Screened	-	-	12,207
Randomized	5592	2782	8374
Completed study treatment ^{a,b}	5221 (93.4)	2606 (93.7)	7827 (93.5)
Per-Protocol ^a	4537 (81.1)	2289 (82.3)	6826 (81.5)
Safety ^a	5587 (>99.9)	2781 (>99.9)	8368 (> 99.9)

^aDenominator is Randomized Population.

^bSubjects who received 3 injections completed study treatment.

Source: Adapted from CSR DV2-HBV-23, Table 10-1, page 52 and Table 10-3, page 56.

The total subjects randomized following screening (N=12,207) were 8374, with an approximate allocation ratio of 2:1 to HEPLISAV (n=5592) and Engerix-B (n=2781) (Table 6.1.1). The Per-Protocol population consisted of 6826 subjects, which was 81.5% of the randomized population, and where the most common reason for exclusions as stated by the applicant were “no anti-HBs levels obtained at Week 28, did not receive all study injections, received prohibited concomitant medication, anti-HBs serum sample collection obtained outside the specified window, and receiving vaccination outside the visit window at Week 4” (CSR DV2-HBV-23, section 10.1.3, page 54). The Per-Protocol population was used for immunogenicity analyses. The safety population where the subjects received at least one study injection was used for safety analyses.

6.1.10.1 Populations Enrolled/Analyzed

Please refer to Table 6.1.1.

6.1.10.1.1 Demographics

Please refer to Table 6.1.3.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Please see medical officer’s review.

6.1.10.1.3 Subject Disposition

Please refer to Table 6.1.1.

6.1.11 Efficacy Analyses

HEPLISAV’s immunogenicity was not a concern to CBER. The VRBPAC members (15 November 2012) also reached this conclusion. VRBPAC’s concern was related to the size of the safety data base. Thus, the immunogenicity analyses in the submitted amendment were not a required element per CR letter. However, CBER agreed to review the overall immunogenicity data (without breaking into subgroups), which already is a planned secondary objective in the submission. Table 6.1.2 provides these analyses for SPR and GMC.

6.1.11.1 Analyses of Primary Endpoint(s)

The immunogenicity analyses in DV2-HBV-23 consisted of computing SPR (serum concentration of anti-HBs ≥ 10 mIU/mL) and GMC at Week 24 for the HEPLISAV subjects and at Week 28 for the Engerix-B subjects. The SPR was 95.4% (95%CI: 94.8%, 96.0%) in the HEPLISAV arm and 81.3% (95%CI: 79.6%, 82.8%) in the Engerix-B arm, the lower bound of the 95% CI of SPR difference (HEPLISAV-Engerix-B) exceeded -10% and as such met the non-inferiority criterion (Table 6.1.2). This table also showed that the overall GMC in the HEPLISAV arm was higher than in the Engerix-B arm [GMC ratio=1.20 (95% CI: 1.1-1.4)].

Table 6.1.2: Comparison of Seroprotection Rates (SPR) and Geometric Mean Concentrations (GMC) Between HEPLISAV at Week 24 and Engerix-B at Week 28 (Per-Protocol Population), DV2-HBV-23.

SPR

HEPLISAV ^a			Engerix-B ^b			Difference
N	n	SPR (%) (95% CI)	N	n	SPR (%) (95% CI)	(HEPLISAV-Engerix-B) (95% CI)
4376	4176	95.4 (94.8 - 96.0)	2289	1860	81.3 (79.6 - 82.8)	14.2 (12.5 - 15.9)

GMC

HEPLISAV		Engerix-B		GMC Ratio (HEPLISAV / Engerix-B) (95% CI)
N	GMC (95% CI)	N	GMC (95% CI)	
4376	401.0 (380.0 - 423.2)	2289	324.0 (286.6 - 366.2)	1.2 (1.1 - 1.4)

CI = confidence interval; N = number of evaluable subjects; n = number of seroprotected subjects; SPR = seroprotection rate.

^aStudy injections were given at Weeks 0, 4, and 24 (placebo).

^bStudy injections were given at Weeks 0, 4, and 24.

Source: Adapted from CSR DV2-HBV-23, Table 11-2 (for SPR), page 68, and Table 11-10 (for GMC), page 73. Reviewer's generated analyses results are not shown as they were very close to Applicant's.

Sections 6.1.11.2 through 6.1.11.5, being on secondary immunogenicity endpoints, subgroup populations, dropouts and exploratory analyses, are not discussed in this review of responses to the CR letter.

6.1.12 Safety Analyses

Safety population

The study had a planned sample size of 8250 subjects for random allocation in a 2:1 ratio to the HEPLISAV and Engerix-B arms, respectively.

A total of 8374 subjects were enrolled and randomized, of which the safety population comprised 8368 (>99.9%) subjects, with 5587 subjects in the HEPLISAV arm and 2781 subjects in the comparator Engerix-B arm.

Demographics

Table 6.1.3 provides demographic and baseline characteristics of subjects aged 18 and older, including the number of injections received by treatment groups. The individual characteristics, by and large, present balanced distributions across treatments.

Table 6.1.3: Age, Gender, Race, Ethnicity, and number of injections received by Treatment Group, Safety Population, DV2-HBV-23, Age 18-70.

	HEPLISAV (N=5587)	Engerix-B (N=2781)
Men, n (%)	2844 (50.9)	1391 (50.2)
Women, n (%)	2743(49.1)	1390 (50.0)
Age 18-39 Yrs, n (%)	1132 (20.3)	561 (20.2)
Age 40-55 Yrs, n (%)	2356(42.2)	1155 (41.5)

Age 56-70 Yrs, n (%)	2099 (37.6)	1065(38.3)
Age (yrs)		
N	5587	2781
Mean (SD)	50.4 (11.74)	50.4 (11.7)
Median	52.0	52.0
Min, Max	18,71	18,70
BMI ^a < 30 kg/m ² , n(%)	2860 (51.2)	1494 (53.8)
BMI ^a ≥ 30 kg/m ² , n(%)	2724 (48.8)	1285 (46.2)
White, n(%)	3968 (71.6)	2007 (72.2)
Black/Afr American, n(%)	1461(26.2)	696 (25.0)
Asian, n(%)	57(1.0)	38 (1.4)
Other ^a , n(%)	39(0.7)	16(0.6)
Hispanic/Latino ^a	521 (9.3)	239 (8.6)
Not Hispanic/Latino	5062 (90.7)	2541 (91.4)
Subjects receiving 1 injection*	5587 (100.0)	2781 (100.0)
Subjects receiving 2 injections*	5462 (97.8)	2724 (98.0)
Subjects receiving 3 injections*	NA	2606 (93.7)

^a Missing values (n<5) occurred. *Injection information adapted from Table 12-1, CSR, DV2-HBV-23, page 78.

Source: Reviewer's analysis, figures are close to Table 10-5, CSR DV2-HBV-23, page 60.

Overview of Adverse Events

For brief overview of selected safety events (Table 6.1.4), about 46.0% of vaccinees in each of the HEPLISAV and Engerix-B arms had at least 1 medically attended adverse event (MAEs). Serious adverse events (SAEs) happened at a 6.2 % rate in the HEPLISAV arm and at a 5.3% rate in the Engerix-B arm; the relative risk for HEPLISAV vs Engerix-B was RR=1.16 (95% CI: 0.96,1.40; 90% CI: 0.99,1.36). Based on 90% CIs as an additional tool for safety analysis, an excess of clinical risk for SAE cannot clearly be ruled out. The applicant concluded that the risk profiles of the two trial arms were similar.

Table 6.1.4: Overview of Safety Events, Safety Population, DV2-HBV-23.

Subjects ^a with	HEPLISAV (N=5587) n (%)	Engerix-B (N=2781) n (%)
Any AEs	2596 (46.5)	1303 (46.9)
MAEs	2569 (46.0)	1286 (46.2)
SAEs	345 (6.2)	148 (5.3)
Death	25 (0.4)	7 (0.3)

MAE = medically attended adverse event; SAE = serious adverse event.

^aSubjects in each category had at least 1 event.

Source: Adapted from CSR DV2-HBV-23, Table 12-2, page 79.

Deaths

The study reported a total of 32 deaths: 25 in the HEPLISAV arm and 7 in the Engerix-B arm (Table 6.1.5). Twelve deaths (9 in the HEPLISAV arm and 3 in the Engerix-B arm, marked '†'), were excluded from the relative risk (RR) calculations. These deaths were not considered by the clinical reviewer as potentially related to vaccine. After exclusions, resulting in 16 and 4 deaths in the respective arms, the RR point estimate (HEPLISAV vs Engerix-B) was 1.99 (95% CI: 0.70, 5.67; 90% CI: 0.82, 4.85), based on an asymptotic method of calculation. From an exact method of calculation, the 95% CI and 90% CI for the RR were (0.70, 7.62) and (0.81, 6.89), respectively. Although the CIs all include the value 1, suggesting no difference, the point estimate of RR is almost 2 fold.

Table 6.1.5: Deaths, Safety Population, DV2-HBV-23.

	HEPLISAV (N=5587)	Engerix-B (N=2781)	Total (N=8368)
Total Number of deaths	25	7	32
Reported Causes*			
Accident†	1	0	1
Acute Coronary Syndrome	1	0	1
Acute Myocardial Infarction	1	0	1
Acute Respiratory Distress Syndrome	1	0	1
Acute Respiratory Failure	1	0	1
Cardiac Arrest	1	0	1
Cardio-Respiratory Arrest	1	1	2
Craniocerebral Injury†	0	1	1
Death	2	0	2
Gun Shot Wound†	1	0	1
Head Injury†	0	1	1
Hepatic Cirrhosis	1	0	1
Hepatitis C	1	0	1
Hypertensive Heart Disease	3	1	4
Hypoxic-Ischaemic Encephalopathy†	1	0	1
Lung Cancer Metastatic	1	0	1
Myocardial Infarction	1	1	2
Overdose†	1	0	1
Pancreatic Carcinoma Metastatic	0	1	1
Small Cell Lung Cancer Metastatic	1	0	1
Toxicity To Various Agents†	4	1	5
Victim Of Homicide†	1	0	1

*AEDECOD used by the applicant.

†Not included in RR calculations, as these were considered by the clinical reviewer as not potentially related to vaccine.

Source. Reviewer's analysis.

All SAEs

Table 6.1.6 provides a summary of all SAEs occurring to ≥ 4 subjects in either arm, following applicant's cut off of 4 subjects. Overall, 6.2% of HEPLISAV subjects had ≥ 1 SAEs, compared to 5.3% in Engerix-B subjects. As was stated earlier, the RR point estimate was 1.16 (95% CI: 0.96,1.40; 90% CI: 0.99,1.36), showing borderline imbalance if 90% CI is considered.

Table 6.1.6: Serious Adverse Events Occurring to ≥ 4 Subjects in HEPLISAV or Engerix-B Arm, Safety Population, DV2-HBV-23.

AEDECOD Term of AE	AEPTCD code*	HEPLISAV	HEPLISAV	Engerix-B	Engerix-B
		(N=5587)	(n/N,%)	(N=2781)	(n/N,%)
		n	-	n	-
Subjects with at least 1 adverse event:	-	346	6.2	148	5.3
Chronic Obstructive Pulmonary Disease	10009033	16	0.3	4	0.1
Acute Myocardial Infarction	10000891	15	0.3	1	0
Pneumonia	10035664	15	0.3	8	0.3
Cardiac Failure Congestive	10007559	9	0.2	3	0.1
Non-Cardiac Chest Pain	10062501	9	0.2	7	0.3
Asthma	10003553	8	0.1	1	0
Small Intestinal Obstruction	10041101	8	0.1	2	0.1
Cellulitis	10007882	7	0.1	4	0.1
Cerebrovascular Accident	10008190	7	0.1	3	0.1
Osteoarthritis	10031161	7	0.1	3	0.1
Acute Respiratory Failure	10001053	6	0.1	1	0
Atrial Fibrillation	10003658	6	0.1	3	0.1
Coronary Artery Disease	10011078	6	0.1	2	0.1
Bipolar I Disorder	10004939	5	0.1	0	0
Cholecystitis	10008612	5	0.1	2	0.1
Depression	10012378	5	0.1	1	0
Diabetic Ketoacidosis	10012671	5	0.1	1	0
Hypertension	10020772	5	0.1	3	0.1
Sepsis	10040047	5	0.1	1	0
Toxicity To Various Agents	10070863	5	0.1	1	0
Calculus Ureteric	10007025	4	0.1	2	0.1
Cardiac Failure*	10007554	4	0.1	0	0
Cholelithiasis	10008629	4	0.1	4	0.1
Convulsion	10010904	4	0.1	1	0
Deep Vein Thrombosis	10051055	4	0.1	3	0.1
Gastroenteritis	10017888	4	0.1	1	0
Hypertensive Heart Disease	10020823	4	0.1	1	0
Pneumothorax	10035759	4	0.1	1	0
Prostate Cancer	10060862	4	0.1	4	0.1

Renal Failure Acute	10038436	4	0.1	3	0.1
Transient Ischaemic Attack	10044390	4	0.1	2	0.1
Urosepsis	10048709	4	0.1	3	0.1
Syncope	10042772	2	0	4	0.1

Source: Reviewer's analysis. * Not reported in applicant's Table 12-14, CSR, DV2-HBV-23. Otherwise, this table is similar to Applicant's.

Cardiac SAEs

Fifty-two subjects receiving HEPLISAV had at least 1 cardiac SAE, compared to 15 subjects receiving Engerix-B. Table 6.1.7 provides details. The RR point estimate and confidence intervals based on the asymptotic method were 1.73 (95% CI: 0.98, 3.04; 90% CI: 1.07, 2.78). From these confidence intervals, there appears to be borderline excess risk in the HEPLISAV vs Engerix-B arm, since they include or marginally exclude the value 1.0.

Table 6.1.7: Cardiac Serious Adverse Events*(SAEs), Safety Population, DV2-HBV-23.

SAEs	Preferred term code**	HEPLISAV (N=5587) n (100× n/N)	Engerix-B (N=2781) n (100× n/N)
Subjects with SAEs:	-	52(0.9)	15 (0.5)
Acute coronary syndrome	10051592	1 (<0.1)	0
Acute myocardial infarction	10000891	15 (0.3)	1 (<0.1)
Angina pectoris	10002383	2 (<0.1)	1 (<0.1)
Angina unstable	10002388	1 (<0.1)	0
Atrial fibrillation	10003658	6 (0.1)	3 (0.1)
Atrial flutter	10003662	2 (<0.1)	1 (<0.1)
Bradycardia	10006093	2 (<0.1)	0
Cardiac arrest	10007515	3 (0.1)	0
Cardiac failure	10007554	4 (0.1)	0
Cardiac failure acute	10007556	1 (<0.1)	0
Cardiac failure congestive	10007559	9 (0.2)	3 (0.1)
Cardiac ventricular thrombosis	10053994	1 (<0.1)	1 (<0.1)
Cardio-respiratory arrest	10007617	1 (<0.1)	1 (<0.1)
Cardiogenic shock	10007625	1 (<0.1)	0
Cardiomyopathy	10007636	0	1 (<0.1)
Coronary artery disease	10011078	6 (0.1)	2(<0.1)
Coronary artery occlusion	10011086	1 (<0.1)	1 (<0.1)
Coronary artery stenosis	10011089	2 (<0.1)	0
Hypertensive heart disease	10020823	4 (0.1)	1 (<0.1)
Myocardial infarction	10028596	2 (<0.1)	1 (<0.1)
Myocardial ischaemia	10028600	1 (<0.1)	0
Pulseless electrical activity	10058151	1 (<0.1)	0
Supraventricular tachycardia	10042604	1 (<0.1)	0
Ventricular fibrillation	10047290	1 (<0.1)	0
Ventricular tachycardia	10047302	2 (<0.1)	0

*variable name AEDECOD, **variable name AEPTCT, per applicant's data documentations.

Source: Reviewer's analysis. ** Not reported in applicant's Table 12-14, CSR, DV2-HBV-23, page 98 of 138. Otherwise, the table is Is not much different from applicant's.

Acute Myocardial Infarction (AMI)

From Table 6.1.7 above, 15 HEPLISAV vaccinees had acute myocardial infarction compared to 1 such subject receiving Engerix-B. Of these 15 subjects, one had AMI during the "screening period prior to first injection," thus leaving 14 AMIs in the HEPLISAV group. The comparison of 14 vs 1 AMI in the two respective arms, gave rise to an RR of 6.97 (95% CI: 1.23, 184.9; 90% CI: 1.55, 91.31) following an exact statistical method of calculation. The 95% and 90% CIs were, respectively, (1.17, 41.44) and (1.49, 32.65) based on an asymptotic method of calculation. Both methods showed excess risk of AMI in the HEPLISAV arm compared to Engerix-B.

Myocardial Infarction, Acute And Non-Acute (AMI+MI)

Considering AMI and MI together, 16 subjects had the events in the HEPLISAV arm compared to 2 subjects in Engerix-B, and this gave rise to a RR of 3.98 (95% CI: 1.05, 40.71; 90% CI: 1.26, 24.80) by exact method, and RR= 3.98 (95% CI: 1.02, 15.55; 90% CI: 1.24, 12.78) by asymptotic method. These results indicate excess risk of myocardial infarction in HEPLISAV compared to Engerix-B.

New Onset of Autoimmune Diseases and Adverse Events of Special Interest Confirmed by SEAC(Safety Evaluation and Adjudication Committee)

The study reported new onset of autoimmune diseases and adverse events of special interest confirmed by SEAC in 14 subjects receiving HEPLISAV and 1 subject receiving Engerix-B. These cases are listed below in Table 6.1.8. One subject marked '†' in the HEPLISAV arm had two autoimmune events: Raynaud's phenomenon and Sjogren's syndrome. The RR point estimate for HEPLISAV relative to Engerix-B was 6.97 (95% CI: 1.23, 184.9; 90% CI 1.55, 91.31) based on an exact statistical method of calculation, indicating excess risk in HEPLISAV recipients compared to Engerix-B.

Table 6.1.8: New-Onset of Autoimmune Adverse Events and Adverse Events of Special Interest Confirmed by SEAC, Safety Population, DV2-HBV-23.

USUBJID	Site ID	AEDECOD	AETERM	AEAICAT2	AGE	SEX	TRT arm
102146	102	Viith nerve paralysis	bell's palsy	Y	49	F	HEPLISAV
102163	102	Rheumatoid arthritis	New onset Rheumatoid Arthritis	Y	45	F	HEPLISAV
106271	106	Vith nerve paralysis	cranial nerve palsie (right sixth nerve palsy)	Y	43	M	HEPLISAV
108013	108	Alopecia areata	Alopecia areata	Y	52	F	HEPLISAV
116323	116	Viith nerve paralysis	bells palsy, Right	Y	31	F	HEPLISAV
117119	117	Viith nerve paralysis	Bell's Palsy	Y	49	M	HEPLISAV

USUBJID	Site ID	AEDECOD	AETERM	AEAICAT2	AGE	SEX	TRT arm
126038	126	Polymyalgia rheumatica	Polymyalgia Rheumatica	Y	68	M	HEPLISAV
131028	131	Viith nerve paralysis	Bells Palsy	Y	52	M	HEPLISAV
131109	131	Takayasu's arteritis	Takayasu's Arteritis	Y	49	M	HEPLISAV
132154†	132	Raynaud's phenomenon	Raynaud's Syndrome	Y	54	F	HEPLISAV
132154†	132	Sjogren's syndrome	Clinical Sjogren's Syndrome	Y	54	F	HEPLISAV
134044	134	Viith nerve paralysis	Bell's Palsy	Y	49	M	HEPLISAV
134064	134	Vith nerve paralysis	Partial left cranial 6th nerve palsy	Y	49	M	HEPLISAV
134123	134	Viith nerve paralysis	Bell's Palsy, right side	Y	29	M	Engerix-B
136149	136	Hypothyroidism	Hypothyroidism	Y	60	F	HEPLISAV
136200	136	Colitis ulcerative	Ulcerative Colitis	Y	46	F	HEPLISAV

† Subject had two events.

Source: Reviewer's Analysis. Applicant's Table 12-9 (CSR, Dv2-HBV-23) provides AE counts but not the details as above.

Thyroid AEs

A total of 23 subjects reported Thyroid AEs in the Heplisav arm, and 17 subjects reported such events in Engerix-B. Table 6.1.9 presents a list of these AEs. Overall, the data on these AEs did not show risk imbalance: RR=0.67 (95% CI: 0.36, 1.25) based on asymptotic method of calculation, including that for Hypothyroidism (RR=0.83, 95% CI: 0.31, 2.19; 90% CI: 0.36, 1.89).

Table 6.1.9: Thyroid AEs, Safety Population, DV2-HBV-23.

Preferred term**	HEPLISAV (N=5587)	Engerix-B (N=2781)
Subjects with at least 1 qualifying AE*	23 (0.4%)	17 (0.6%)
Autoimmune thyroiditis	2	2
Benign neoplasm of thyroid gland	1	1
Blood thyroid stimulating hormone abnormal	2	0
Blood thyroid stimulating hormone increased	2	2
Hyperparathyroidism	2	0
Hyperthyroidism	2	0
Hypothyroidism	10	6
Papillary thyroid cancer	0	1
Parathyroid tumour benign	1	0
Post procedural hypothyroidism	1	1
Primary hypothyroidism	0	1
Thyroid function test normal	1	0
Thyroid mass	0	2
Thyroid neoplasm	0	7

** variable name AEDECOD, * Applicant reported 19 such subjects for HEPLISAV and 12 subjects for Engerix-B (Table 12-12, CSR DV2-HBV-23, page 94).

Source: Reviewer's Analysis.

Reviewer's Summary and Safety Conclusions

An overall summary of analyses for major AEs is provided in Table 6.3.10, which is the basis for the following conclusions.

1. The study appeared to have an overall balance of risks when all reported AEs were considered together. Based on the reported occurrence of any AEs in each arm, the overall RR was 0.99 (95% CI: 0.95, 1.04) (Table 6.1.10).
2. However, there were several incidences of death in the HEPLISAV arm. The related point estimate of RR was 1.99. After exclusions of deaths that were considered by the clinical reviewer as probably unrelated to the vaccine, the RR point estimate (HEPLISAV vs Engerix-B) was 1.99, with 95% CI of (0.70, 5.67) and 90% CI (0.82, 4.85) when calculated with an asymptotic method, and (0.70, 7.62) and (0.81, 6.89), respectively, based on an exact method.

Table 6.1.10: Summary information about SAEs, Safety Population, DV2-HBV-23.

# Subjects reporting AEs	Heplisav (N=5587)	Engerix-B (N=2781)	Total (8368)	Relative risk (95% CI)	Relative risk (90% CI)
Any AEs	2596	1303	3899	0.99 (0.95, 1.04) (asympt)	0.99 (0.95, 1.03) (asympt)
Death	25*	7*	32*	1.99 (0.70, 5.67) (asympt) 1.99 (0.70, 7.62) (exact)	1.99 (0.82, 4.85) (asympt) 1.99 (0.81, 6.89) (exact)
Cardiac SAEs	52	15	67	1.73 (0.98, 3.04) (asympt)	1.73 (1.07, 2.78) (asympt)
AMI	14	1	15	6.97 (1.17, 41.44) (asympt) 6.97 (1.23, 184.9) (Exact)	6.97 (1.49, 32.65) (asympt) 6.97 (1.55, 91.31) (Exact)
AMI+MI	17	2	19	4.23 (1.09, 16.45) (asympt)	4.23 (1.32, 13.53) (asympt)
**New Onset of AI and AESI Diseases confirmed by SEAC	14	1	15	6.97 (1.17, 41.44) (asympt) 6.97 (1.23, 184.9) (Exact)	6.97 (1.49, 32.65) (asympt) 6.97 (1.55, 91.31) (Exact)

* 9 excluded from HEPLISAV and 3 excluded from Engerix-B, in RR calculations. ** New Onset of AI and AESI confirmed by SEAC.

3. Cardiac SAEs showed a tendency for increased risk in HELISAV over Engerix-B, since the CI marginally included or excluded the value 1, depending on the confidence level. The RR was 1.73, with 95% CI lower bound of 0.98 and 90% CI lower bound of 1.07.
4. The imbalance in risk for other SAEs, such as AMI and new onset of autoimmune diseases and adverse events of special interest confirmed by the SEAC, was less ambiguous. The RR point estimates were about 7.00. The associated confidence lower bounds far exceeded the risk-balance value of 1.00, with the upper confidence bounds skewed to as high as 32.0 and beyond, depending on the method of confidence interval computing.

5. I defer to the medical reviewers on whether any Guillain-Barre syndrome and Tolosa-Hunt syndrome were present in the data, or implied from the data documentations (AE preferred terms or codes, etc.) used in the study.

6.1.12.1 Methods

Please refer to section 6.1.2 for overview of design. The analytic calculations involved computing rates based on the number of subjects with 1 or more AEs and total number of subjects in each arm. The confidence intervals (asymptotic and exact) were also computed for the rates.

6.1.12.3 Deaths

Please refer to Table 6.1.5 and Table 6.1.10.

6.1.12.4 Nonfatal Serious Adverse Events

Please refer to Table 6.1.5 through Table 6.1.10 for all SAEs including deaths. Please also refer to medical officers' review for further clinical details.

6.1.12.5 Adverse Events of Special Interest (AESI)

Please refer to Table 6.1.8 and as well to medical officer's report.

6.1.12.6 Clinical Test Results

This section is deferred to the clinical reviewer.

6.1.12.7 Dropouts and/or Discontinuations

This section is deferred to clinical reviewer's report regarding clinical rationale for these events.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Endpoints

SPR. In the expanded safety data from study DV2-HBV-23, the SPRs measured at Week 24 for HELPISAV compared to Engerix-B at Week 28 showed non-inferiority. In the study, with SPR=95.4% (95% CI: 94.8%, 96.0%) in HEPLISAV and SPR=81.3% (95% CI: 79.6%, 82.8%) in Engerix-B, the observed difference, HELPISAV-Engerix-B, was 14.2% (95% CI: 12.5%, 15.9%). The SPR difference's lower bound far exceeded the margin of -10% and as such met the non-inferiority criterion (Table 6.1.2). Similar conclusion was reached in the original BLA.

GMC. The GMC was a secondary endpoint. Please refer to the statistical review of the original BLA, STN 125428/0. In study DV2-HBV-23, the GMCs in HERPLISAV and Engerix-B arms were respectively 401.0 (95% CI: 380.0, 423.2) at Week 24, and 324.0 (95% CI: 286.6, 366.2) at Week 28 (Table 6.1.2).

The DV2-HBV-23 protocol is a single trial expanded safety study with immunogenicity as the secondary endpoint. The subsections 7.1.1 through 7.1.10 that describe integration of multiple studies are not applicable in this review.

7.1.11 Efficacy Conclusions

Study DV2-HBV-23 demonstrated non-inferiority of SPR induced by HEPLISAV at Week 24, compared to that induced by Engerix-B at Week 28. The SPR difference between 95.4% in HEPLISAV and 81.3% in Engerix-B was 14.2% (95% CI: 12.5%, 15.9%), and the confidence lower bound far exceeded the margin of -10%, supporting HEPLISAV'S non-inferiority. The study also showed that the overall GMC in the HEPLISAV arm was higher than in the Engerix-B arm [GMC ratio=1.20 (95% CI: 1.1-1.4)].

8. INTEGRATED OVERVIEW OF SAFETY

Please refer to BLA STN 125428/0 for the original analysis, where the applicant's integrated safety was presented by combining data from the two pivotal studies, DV2-HBV-10 and DV2-HBV-16. The safety analysis based on the expanded safety database of more than 8368 subjects was already provided in section 6.1. Following the CR letter, DV2-HBV-23 was the phase 3 study used for safety evaluation.

Sections 8.1 through 8.5 where the descriptions include clinical test results, product-disease and product-product interactions, and human carcinogenicity etc. are not discussed in this review. Please refer to Clinical/Medical/product reviewer's reports.

8.6 Safety Conclusions

1. The study showed an overall balance of AEs between arms, based on the reported occurrence of any AEs (RR =0.99, 95% CI: 0.95, 1.04) in Table 6.1.10.
2. However, there were several incidences of death in the HEPLISAV arm. When deaths potentially unrelated to vaccine are excluded, the RR of death becomes 1.99 (95% CI: 0.70,7.62; 90% CI: 0.81, 6.89), based on an exact statistical method of calculation. Although a relative risk of 1 (indicating no difference) is not excluded, the RR point estimate of almost 2-fold along with its upper confidence bound exceeding 7-fold suggest potential excess risk for a hard endpoint like death among the HEPLISAV vaccinees.
3. The study showed evidence of excess risk of AMI and as well of new onset of autoimmune diseases and adverse events of special interest confirmed by the SEAC. The RR point estimate based on an exact statistical method was almost 7, with the 95% confidence lower bound exceeding 1.23.
4. Whether any Guillain-Barre syndrome and Tolosa-Hunt syndrome were present or implied from the data documentations (AE preferred terms or codes, etc.) as used in the study, is not in this reviewer's expertise to determine. Such decision is deferred to the medical reviewers.

9. ADDITIONAL STATISTICAL ISSUES

None.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Efficacy

Non-inferiority of SPR as primary endpoint was supported in study DV2-HBV-23 where SPR was measured at Week 24 for HEPLISAV and at Week 28 for Engerix-B.

The review and analyses of revised immunogenicity data (for DV2-HBV-10 and DV2-HBV-16) are postponed until the discrepancy issues noted by clinical reviewers are resolved in the next review cycle.

Safety

1. The study showed an overall balance of AEs between arms, per the reported occurrence of any AEs (RR =0.99, 95% CI: 0.95, 1.04) in Table 6.1.10.
2. There were several incidences of death in the HEPLISAV arm. After deaths potentially unrelated to vaccine were excluded, the RR was 1.99 (95% CI: 0.70, 7.62; 90% CI: 0.81, 6.89), based on an exact statistical method of calculation. Although a relative risk of 1 (indicating no difference) is not excluded, the RR point estimate of almost 2-fold along with its upper confidence bound exceeding 7-fold suggest potential excess risk for a hard endpoint like death among the HEPLISAV vaccinees.
3. The study data suggested excess risk of AMI and as well of new onset of autoimmune diseases and adverse events of special interest confirmed by the SEAC. The RR point estimate, according to an exact statistical method, was almost 7 with the 95% confidence lower bound of 1.23; the upper bound was as high as 185 for both AEs.
4. Whether any Guillain-Barre syndrome or Tolosa-Hunt syndrome were present or implied from the data documentations (AE preferred terms or codes etc.) as used in the study, is not in this reviewer's expertise to determine. Such assessment is deferred to the medical reviewers.

10.2 Conclusions and Recommendations

1. The study DV2-HBV-23 provided evidence supporting HEPLISAV's non-inferiority of SPR compared to the comparator vaccine.
2. For safety, however, the data suggest excess risk with regard to AMI and autoimmune diseases including AEs of special interest confirmed by the SEAC in HEPLISAV versus

the comparator vaccine. I defer to the medical reviewers regarding the implications of this finding.