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Priority Review	No
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Review Completion Date / Stamped Date	
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Applicant	Dynavax Technologies Corporation
Established Name	Hepatitis B Vaccine (Recombinant), Adjuvanted
(Proposed) Trade Name	Heplisav
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Each 0.5 mL dose contains 20 mcg of recombinant yeast cell-derived hepatitis B virus surface antigen (HBsAg) and 3000 mcg Dynavax's proprietary adjuvant, 1018
Dosage Form(s) and Route(s) of Administration	Solution for Intramuscular Injection
Dosing Regimen	Two 0.5 mL doses administered four weeks apart
Indication(s) and Intended Population(s)	Immunization against all subtypes of hepatitis B virus infection in adults 18-70 years of age

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1. EXECUTIVE SUMMARY

Dynavax submitted a Biologics License Application (BLA), STN 125428/0, to the Food and Drug Administration (FDA) on April 26, 2012 to support its application to license a recombinant hepatitis B virus vaccine with the proposed trade name Heplisav. The vaccine is intended for active immunization against all subtypes of hepatitis B virus infection in adults 18-70 years of age. On February 22, 2013, the Office of Vaccines Research and Review (OVRR) in the Center for Biologics Evaluation and Research (CBER) at the FDA issued a Complete Response Letter (CRL). In addition to a number of non-clinical concerns, three clinical items precluded approval of Heplisav at that time: 1) the inadequate size of the safety database; 2) the need for additional information regarding a number of specific adverse events; and 3) the need for information regarding a case of possible Tolosa-Hunt syndrome in a Heplisav recipient in Study DV2-HBV-16. Following the CR Letter, the applicant conducted an additional study to increase the size of the total safety database, Study DV2-HBV-23.

On March 15, 2016, the applicant submitted a Complete Response. In addition to the supporting documents from the required safety study, DV2-HBV-23, the submission included revised CSRs for Studies DV2-HBV-10 and DV2-HBV-16. The applicant determined that these revisions were necessary due to errors detected during audits performed after another regulatory agency's inspections had identified concerns with data quality in a study not submitted to the BLA. On April 18, 2016, the FDA notified the applicant that the datasets constituted a Major Amendment because they contained a substantial amount of new data not previously submitted to, or reviewed by the agency. The applicant did not submit a complete listing of subjects newly excluded from and newly included into the per protocol population for Studies DV2-HBV-10 and -16. Despite a number of communications with the applicant during that review cycle, including Information Requests (IRs) and teleconferences, persistent inconsistencies in the datasets submitted required significant re-evaluation and correction before any further review of these data could ensue. Furthermore, potentially clinically significant imbalances between the Heplisav and Engerix-B groups in Study DV2-HBV-23 were noted regarding deaths and Acute Myocardial Infarctions (AMI).

On September 9, 2016, the FDA issued an IR regarding additional information to support assessment of safety in Study DV2-HBV-23, as well as information needed to support evaluation of immunogenicity assessments and subject disposition for Studies DV2-HBV-10 and DV2-HBV-16. The clinical team considered that the information submitted with the Complete Response and subsequent IR responses prior to September 9, 2016, was not adequate to recommend approval of Heplisav by December 15, 2016, which was the action due date, and that review of information submitted after September 23, 2016 would proceed beyond the action due date in order to accurately assess the potential safety signals that had been identified and to verify immunogenicity results. Review of any information the applicant submitted following the September 9 IR was deferred until the next review cycle, which is ongoing.

In the 2nd CR Letter issued on November 10, 2016, items 23-25 were related to the Immunogenicity of Studies HBV -10 and HBV-16, which were a reiteration of the FDA's

IR dated September 9, 2016. The applicant submitted the response on October 8, 2016 to address the issues in items 17 and 23-25. This review focuses on the response to CR Letter items 23-25.

I verified the clarifications in the response to CR Letter items 23-25 and reviewed the dataset “adpp 16.xpt” submitted with the response on October 8, 2016, finding it consistent with the correct datasets submitted previously to Amendment 125428/0.42 on March 15, 2016. I also verified the immunogenicity analysis results in the revised CSR for Studies DV2-HBV-16 and DV2-HBV-10 dated March 15, 2016, using the correct dataset “adlb.xpt” (lab results included) submitted on March 15, 2016. Overall, the response submitted on October 8, 2016 addressed the issues in the CR Letter items 23-25.

The CR Letter item 2, issued on November 10, 2016, requested the applicant to submit additional analysis of the imbalance in SAEs with a System Organ Class (SOC) of Cardiac Disorders and the imbalance in acute myocardial infarction observed in Study HBV-23. The applicant submitted the response to CR Letter items 2, 3, 5, 6, 9, 10 on October 7, 2016. In the response to item 2, Dynavax performed an evaluation of the imbalances between the Heplisav and Engerix-B groups in AMI and Major Adverse Cardiovascular Events (MACE). This review also covers a partial review of the statistical results in this evaluation report produced by the applicant. The applicant stated that the observed numerical difference between treatment groups in the incidence of acute myocardial infarction in HBV-23 is not statistically significant. I investigated this statement and performed additional statistical analyses. Please refer to Section 8 for details of the analyses. Please also refer to Dr. Chowdhury’s review memo for a more complete statistical safety assessment.

On July 28, 2017, a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting was held for Heplisav. The committee voted 12 yes, 1 no, with 3 abstentions that the available data were adequate to support the safety of Heplisav when administered to adults 18 years and older. Committee members commented that the differences in frequency of AMI between treatment groups were probably due to chance. However, they strongly emphasized the need for a well-designed post-marketing prospective study that can provide early detection of an AMI signal to evaluate cardiovascular risk associated with Heplisav in a population that should include subjects at risk for cardiovascular disease.

CBER decided in 2016 that it would not review the immunogenicity data derived from the subpopulations in Study HBV-23 and submitted in response to the 2nd CR Letter, since CBER did not request that data as part of the CR Letter. However, this issue was further discussed within CBER after the July 2017 VRBPAC meeting. It was then determined that because the original application in 2012 included analysis of immunogenicity in the diabetic and other subgroups based on Studies HBV-10 and HBV-16, inclusion of diabetic and other subgroup immunogenicity data in Study HBV-23 should be reviewed under the current BLA. Consequently, I reviewed the subgroup analysis of immunogenicity in Study HBV-23. The immunogenicity analysis results for each subpopulation (diabetes, age, sex, obesity, smoking) in the CSR for Study HBV-

23 appear to be acceptable. However, the applicant has made an assertion of higher seroprotection rate for Heplisav vs. Engerix-B within race subgroups that is not supported by appropriate analysis of the data. Please refer to Section 6.3 for details of this review. Overall, the immunogenicity data in Studies HBV-10, HBV-16, and HBV-23 show Heplisav has a higher seroprotection rate than Engerix-B in the adult population.

2. CLINICAL AND REGULATORY BACKGROUND

Dynavax submitted STN 125428/0 to the FDA on April 26, 2012 to support its application to license a recombinant hepatitis B virus vaccine with the proposed trade name Heplisav, which contains recombinant Hepatitis B surface antigen (rHBsAg), subtype *adw*, produced in yeast cells and a novel cytosine phosphoguanine (CpG) enriched oligodeoxynucleotide (ODN) phosphorothioate immunostimulatory adjuvant. Each 0.5 mL dose contains 20 mcg rHBsAg and 3000 mcg 1018 immunostimulatory sequence adjuvant. The dosing regimen is two 0.5 mL doses administered four weeks apart. The proposed indication is for immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older.

2.1 Disease or Health-Related Condition(s) Studied

Hepatitis B

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

Two licensed vaccines, both made from yeast-derived recombinant antigen adsorbed to aluminum compounds are currently available for the prevention of Hepatitis B virus (HBV) in adults in the U.S.: Engerix-B (GlaxoSmithKline) and Recombivax HB (Merck). There is also one combination vaccine for adults, Twinrix (GlaxoSmithKline), which includes a hepatitis A vaccine component. Engerix-B and Recombivax HB are both approved for use in adults and adolescents as a three-dose series to be administered at months 0, 1 to 2, and 6 to 12. A two-dose Recombivax HB series, administered at 0, and 4 to 6 months, is also approved for adolescents 11 to 15 years of age. Additionally, an accelerated schedule is licensed for Twinrix—a series of four doses (1 mL each), given on Days 0, 7, and Days 21 to 30, followed by a booster dose at Month 12.

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

NA

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

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

November 15, 2012: VRBPAC stated concerns with the size of the safety database, as well as underrepresentation of Asian subjects enrolled in the trials. Committee voted 8:5,

with one abstention, that the safety data available on this vaccine with a new adjuvant was inadequate to recommend approval.

February 22, 2013: The FDA issued a Complete Response Letter for submission STN 125428/0.

March 15, 2016: The applicant submitted a Complete Response. In addition to the Clinical Study Report (CSR) and supporting documents from the required safety study, DV2-HBV-23, the submission included revised CSRs for Studies DV2-HBV-10 and DV2-HBV-16.

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

April 18, 2016: The FDA notified the applicant that the datasets constituted a Major Amendment because they contained a substantial amount of new data not previously submitted to, or reviewed by the agency.

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

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

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

October 7, 2016: The applicant responded to FDA IR items 2, 3, 5, 6, 9, 10 issued on September 9 regarding the safety assessment for Study DV2-HBV-23.

October 8, 2016: The applicant responded to FDA IR items 23-25 issued on September 9 regarding the immunogenicity assessments and subject disposition for Studies DV2-HBV-10 and DV2-HBV-16.

November 10, 2016: The FDA issued the 2nd CRL for submission STN 125428/0.

July 28, 2017: The VRBPAC members voted 12 yes, 1 no, with 3 abstentions that the available data were adequate to support the safety of HepB when administered to adults 18 years and older.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission provided in the March 15, 2016 Complete Response did not include datasets for Studies DV2-HBV-10 and DV2-HBV-16 to support the revised CSRs. This deficiency resulted in a Major Amendment. The applicant did not submit a complete listing of subjects newly excluded from and newly included into the per protocol population for Studies DBV-HBV-10 and -16. During the review process, the clinical reviewer noted additional subject accounting discrepancies. The clinical team considered that the information submitted with the Complete Response and subsequent IR responses prior to September 9, 2016 failed to clarify in each of the revised CSRs that a subset of subjects in Studies DV2-HBV-10 and -16 were newly included into the per protocol population as a result of the applicant's audit of these studies. Review of any information they had submitted following the September 9 IR was deferred until the next review cycle, which is ongoing.

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

NA

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

5.1 Review Strategy

I reviewed the applicant's response to the CR Letter items 2 and 23-25, issued on November 10, 2016, and the immunogenicity data discrepancies in a series of submissions between March 15, 2016 and July 12, 2016. I verified the immunogenicity analysis results in the revised CSR for Studies HBV-10 and HBV-16 submitted to 125428/0.42, using the correct datasets. In addition, I reviewed the statistical results of the applicant's evaluation of the imbalances between the Heplisav and Engerix-B groups regarding AMI and MACE. I also reviewed the immunogenicity subgroup analysis in the CSR for Study HBV-23 submitted to 125428/0.42.

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

The following documents were reviewed:

- 125428/0.42 Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertaining to the Claimed Indication
- 125428/0.42 Module 5.3.5.3 Reports of Analyses of Data from More than One Study
- 125428/0.45 Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

- 125428/0.49 Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
- 125428/0.54 Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
- 125428/0.68

5.3 Table of Studies/Clinical Trials

Table 1. Summary of studies for the immunogenicity analyses in this review

Study Name	Study Design	Hepelisav Dose/Schedule/N	Comparator Dose/Schedule/N	Key Endpoints
DV2-HBV-10 Pivotal NCT00435812	Phase 3, observer-blind, randomized, active-controlled, parallel group, multicenter study in healthy subjects 11-55 years of age conducted in Canada and Germany	Hepelisav: 20 mcg HBsAg/3000 mcg 1018 adjuvant Schedule: 0, 4 weeks IM (placebo at 24 weeks) N=1511	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks IM N=521	Primary Endpoint: SPR at Week 12 for Hepelisav and Week 28 for Engerix-B Major Safety Endpoints: Solicited reactions 7 days following each injection, AEs/SAEs Study Week 28
DV2-HBV-16 Pivotal NCT01005407	Phase 3, observer- blind, randomized, active-controlled, parallel group, multicenter study in healthy adult subjects 40-70 years of age conducted in Canada and Germany	Hepelisav: 20 mcg HBsAg/3000 mcg 1018 adjuvant Schedule: 0, 4 weeks IM (placebo at 24 weeks) N=1121	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks IM N=353	Primary Endpoint: SPR at Week 12 for Hepelisav and Week 32 for Engerix- B Lot consistency of Hepelisav measured by GMC at Week 8 Major Safety Endpoints: Solicited reactions 7 days following each injection, AEs Study Week 28, SAEs/AESIs Study Week 52
DV2-HBV-23 Pivotal NCT02117934	Phase 3, observer-blind, randomized, active-controlled, parallel group, multicenter study in adults 18-70 years of age conducted in US	Hepelisav: 20 mcg HBsAg/3000 mcg 1018 adjuvant Schedule: 0, 4 weeks IM (placebo at 24 weeks) N = 4537	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks IM N = 2289	Secondary Efficacy Endpoint: SPR at Week 24 for Hepelisav and Week 28 for Engerix-B Major Safety Endpoints: MAEs/SAEs/AESIs Study Week 56

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

Source: Adapted from Table 1 in Dr. Everett and Dr. Worobec’s clinical review memo for STN 125428 stamped on April 7, 2017.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

In the previous review cycle, the applicant submitted revised CSRs for Studies DBV-HBV-10 and -16 to Amendment 42. However, the applicant did not submit a complete listing of subjects newly excluded from and newly included into the per protocol population. The CRL item 24 requested that the applicant provide documentation of all differences between final databases, other databases the applicant has sent to the FDA and the original 2012 databases for these studies, and explanations and documentation for those differences, to include an accurate accounting of all newly excluded and newly included subjects, for the non-inferiority and lot consistency per protocol populations for Studies DV2-HBV 10 and DV2-HBV-16. On October 8, 2016, the applicant responded to FDA IR items 23-25 issued on September 9 regarding subject disposition for Studies DV2-HBV-10 and DV2-HBV-16, and clarified these exclusions and inclusions in the per protocol populations. I verified the revised data. The review of the immunogenicity data for studies -10 and -16 presented below are based on the revised data.

6.1 Trial #1

DV2-HBV-10: A Phase 3 safety and efficacy study to compare immune responses following injection with either two doses of Heplisav or three doses of Engerix-B.

A revised CSR for Study DV2-HBV-10 was submitted with the Complete Response on March 15, 2016. The applicant determined that a revision to Study DV2-HBV-10 was necessary to correct errors in the CSR for this study, which was submitted previously to the BLA in 2012. The applicant stated that errors were detected in an audit of this study, performed after another regulatory agency's inspections identified concerns with data quality in a study not submitted to the BLA.

The objectives, study design, immunogenicity endpoints, safety monitoring procedures, and safety analysis of Study DV2-HBV-10 were previously addressed in the statistical review of the original Heplisav BLA dated January 29, 2013 and thus are not reviewed here. I reviewed and verified the submitted revised immunogenicity data and the immunogenicity analysis results in the revised CSR for this study.

6.1.10 Study Population and Disposition

As requested by the CRL item 24, Dynavax submitted a master dataset for Study HBV-10 "adpp 10.xpt" on October 8, 2016. Below is a summary of Per-Protocol Populations Subject Counts for Study HBV-10.

Table 2. Per-Protocol Populations Subject Counts for Study HBV-10

Population (data submitted)	Original (16 July, 2012)	Amended (15 March, 2016)	Changed from Included to Excluded	Changed from Excluded to Included	Net Change
All Subjects	2101	2043	63	5	-58
Adult Subjects	2090	2032	63	5	-58

Source: Table 1 in the attachment 24c4 in the response to IR (4) dated September 9, 2016, submitted to STN 125428/0.68 on October 8, 2016.

Reviewer Comment:

I reviewed the dataset “dapp10.xpt” submitted with the response on October 8, 2016 and verified the counts in Table 2 using the dataset “adpp10.xpt”.

6.1.10.1 Populations Enrolled/Analyzed

Only the Per-Protocol Population was changed between the original and revised CSR. The Intent-To-Treat analysis population and Safety analysis population remain the same. Subject demographic and baseline characteristics are based on the safety analysis population, and thus also remain the same. Table 3 shows the subject disposition for adults in Study HBV-10.

Table 3. Subject Disposition: Adult Only

	Heplisav	Engerix-B	Total
PP Population	1511	521	2032
ITT Population	1789	603	2392
Safety Population	1809	606	2415

Source: Adapted from Table 10-1 in the revised CSR submitted to STN 125428/0.42.

6.1.11 Efficacy Analyses

The Per Protocol (PP) Population was used for the primary immunogenicity endpoint analysis. Results for adult subjects only (18 through 55 years) of the PP and Intent-to-Treat (ITT) populations are presented in this section.

6.1.11.1 Analyses of Primary Endpoint(s)

The primary immunogenicity endpoint was seroprotective immune response (anti-HBsAg ≥ 10 mIU/mL) at Week 12 following 2 injections of Heplisav or at Week 28 following 3 injections of Engerix-B. The primary statistic was seroprotection rate (SPR), defined as the percentage of subjects achieving a seroprotective immune response at Week 12 in Heplisav recipients compared with the SPR at Week 28 in those receiving Engerix-B.

The SPRs for the Heplisav group at Week 12 (8 weeks post the last dose) and the Engerix-B group at Week 28 (4 weeks post the last dose) and the statistical comparisons of those rates for all adult subjects aged 18 through 55 years are presented in Table 4.

Reviewer comment:

The applicant first tested non-inferiority of Heplisav SPR to Engerix-B SPR and, after non-inferiority was established, tested the null hypothesis of equal SPR, which they referred to as a superiority test. I will adopt this usage in this memo, but note that significantly higher SPR does not necessarily indicate a superior vaccine.

The estimated difference between the Engerix-B and Heplisav groups and the associated 95% confidence interval (CI) was -13.74% [-17.46%, -10.42%] in the PP Populations. The upper limit of the CI was -10.42%, which is below the pre-specified non-inferiority criterion of 10%. Therefore, the immune response as measured by the SPR at Week 12 following 2 injections of Heplisav is non-inferior to that at Week 28 following 3 injections

of Engerix-B. Furthermore, the upper limit of the CI is less than 0, providing statistical evidence that the immune response, as measured by the SPR at Week 12 following 2 injections of Hheplisav, is higher than that at Week 28 following 3 injections of Engerix-B. Immunogenicity results for the ITT populations were consistent with those for the PP populations.

Table 4. Statistical Comparison of Estimated Seroprotection Rates at Week 12 for Hheplisav and Week 28 for Engerix-B: Adults Only (18 through 55 Years)

Population	Hheplisav (WEEK 12) n/N	Hheplisav (WEEK 12) %	Engerix-B (WEEK 28) n/N	Engerix-B (WEEK 28) %	Mean difference in SPR (Engerix-B -Hheplisav) (95% CI)	Non-inferiority Criterion/ Superiority Criterion
PP	1436/1511	95.02	423/521	81.28	-13.74 (-17.46, -10.42)	met/ met
ITT	1756/1676	95.44	479/590	81.2	14.29 (-17.78, -11.16)	met/ met

N = number of subjects with non-missing results in the analysis population in the treatment group; n = number of subjects with post-injection anti-HBsAg \geq 10 mIU/mL.

Confidence intervals for the differences are calculated using the Miettinen and Nurminen method with adjustment for age groups.

Source: Section 14.1.2, Tables 26.1.2 and 26.2.2 in the revised CSR in STN 125428/0.42.

6.1.11.2 Analyses of Secondary Endpoints

The secondary immunogenicity endpoint was seroprotective response 4 weeks after the first injection (Week 4) in both Hheplisav and Engerix-B groups. The estimated difference in SPR between the groups and the associated 95% CI were -19.46% (-22.24%, -16.55%) in the PP Populations. The upper limit of the CI is less than 0, indicating that the immune response of Hheplisav as measured by the SPR was higher than that of Engerix-B after 1 injection. Immunogenicity results for the ITT populations were consistent with those for the PP populations.

The SPRs for Hheplisav and Engerix-B at Week 4 and the statistical comparisons of those rates for all adult subjects 18-55 years old are presented in Table 5.

Table 5. Statistical Comparison of Estimated Seroprotection Rates at Week 4: Adults Only (18 through 55 Years)

Population	Hheplisav (WEEK 4) n/N	Hheplisav (WEEK 4) %	Engerix-B (WEEK 4) n/N	Engerix-B (WEEK 4) %	Mean difference in SPR (Engerix-B -Hheplisav) (95% CI)	Non-inferiority Criterion/ Superiority Criterion
PP	354/1502	23.54	21/529	4.07	-19.46 (-22.24, -16.55)	met/ met
ITT	431/1779	24.23	24/601	3.99	-20.23 (-22.79, -17.55)	met/ met

N = number of subjects with non-missing results in the analysis population in the treatment group; n = number of subjects with post-injection anti-HBsAg \geq 10 mIU/mL.

Confidence intervals for the differences are calculated using the Miettinen and Nurminen method with adjustment for age groups.

Source: Section 14.1.2, Tables 27.1.2 and 27.2.2 in the revised CSR in STN 125428/0.42.

6.1.11.3 Subpopulation Analyses

Analyses for the primary, secondary, and exploratory endpoints were repeated by age stratum (18 through 39 years and 40 through 55 years). Table 6 summarizes the anti-HBsAg response by age stratum. Throughout this section, the use of “younger subjects” refers to 18-39 year-old subjects, and the use of “older subjects” refers to those aged 40-55 years old.

For the primary immunogenicity endpoint, the Heplisav group had higher SPRs at Week 12 than the Engerix-B group at Week 28 in both the younger subjects (98.78% vs 88.69%) and the older subjects (92.17% vs 75.67%); a larger difference between treatment groups was observed in the older subjects. For the secondary immunogenicity endpoint, the Heplisav group had higher SPRs than the Engerix-B group at Week 4 in both the younger subjects (30.82% vs 5.94%) and the older subjects (18.05% vs 2.67%).

GMC results by age stratum were generally consistent with overall GMC results for all age groups combined, as well as with SPR results by age stratum. Higher GMCs were reported in the Heplisav group compared with the Engerix-B group, for each age group at all time points from Week 4 through Week 24.

Table 6. SPR by Visit and Age Stratum: Per-Protocol Analysis Population; Adults Only (18 Through 55 years)

Visit Age Stratum	Engerix-B		Heplisav	
	n/N	SPR(95% CI)	n/N	SPR(95% CI)
Week 12 ^a / Week 28 ^b				
18 – 39 years	196/221	88.69 (84.51, 92.86)	647/655	98.78 (97.94, 99.62)
40 – 55 years	227/300	75.67 (70.81, 80.52)	789/856	92.17 (90.37, 93.97)
Week 4				
18 – 39 years	13/219	5.94 (2.81, 9.07)	200/649	30.82 (27.26, 34.37)
40 – 55 years	8/300	2.67 (0.84, 4.49)	154/853	18.05 (15.47, 20.64)
Week 8				
18 – 39 years	72/219	32.88 (26.66, 39.10)	621/653	95.10 (93.44, 96.76)
40 – 55 years	66/300	22.00 (17.31, 26.69)	709/851	83.31 (80.81, 85.82)
Week 12				
18 – 39 years	66/221	29.86 (23.83, 35.90)	647/655	98.78 (97.94, 99.62)
40 – 55 years	52/300	17.33 (13.05, 21.62)	789/856	92.17 (90.37, 93.97)
Week 24				
18 – 39 years	87/219	39.73 (33.25, 46.21)	650/653	99.54 (99.02, 100.00)
40 – 55 years	83/300	27.67 (22.60, 32.73)	826/850	97.18 (96.06, 98.29)
Week 28				
18 – 39 years	196/221	88.69 (84.51, 92.86)	650/655	99.24 (98.57, 99.90)
40 – 55 years	227/300	75.67 (70.81, 80.52)	829/856	96.85 (95.67, 98.02)
Week 8 ^a / Week 28 ^b				
18 – 39 years	196/221	88.69 (84.51, 92.86)	621/653	95.10 (93.44, 96.76)
40 – 55 years	227/300	75.67 (70.81, 80.52)	709/851	83.31 (80.81, 85.82)

a: Heplisav.

b: Engerix-B.

Source: Table 11-6 in the revised CSR in STN 125428/0.42.

6.1.11.5 Exploratory and Post Hoc Analyses

The exploratory immunogenicity endpoints were seroprotective response at Weeks 8, 12, 24, and 28 and Anti-HBs Geometric Mean Concentrations at Weeks 4, 8, 12, 24, and 28

in both groups. An additional exploratory endpoint was seroprotective response at 4 weeks after the final active injection (Week 8 for the Heplisav group and Week 28 for the Engerix-B group).

At all time points from Week 8 through Week 28, the difference in SPRs supported not only non-inferiority but also the ability of Heplisav to elicit higher levels of immune response, in comparison with Engerix-B. The GMC was notably higher in the Heplisav group than in the Engerix-B group at all visits from Week 8 through Week 24. At Week 28, 4 weeks after the Engerix-B group received the third active injection, the GMCs in the 2 groups were similar: Heplisav 316.99 mIU/mL (95% CI: 295.14, 340.45) versus Engerix-B 352.14 mIU/mL (95% CI: 267.95, 462.78).

6.2 Trial #2

DV2-HBV-16: An observer-blinded, randomized, parallel-group, multi-center phase 3 study comparing the safety and immunogenicity of Heplisav to licensed vaccine (Engerix-B) among healthy adults 40 to 70 years of age.

A revised CSR for Study DV2-HBV-16 was submitted with the applicant's Complete Response on March 15, 2016. Similar to Study DV2-HBV-10, the applicant determined that a revision to Study DV2-HBV-16 was necessary to correct errors in the CSR, which was submitted previously to the original BLA in 2012.

In the CRL issued on November 10, 2016, items 23-25 pointed out that inconsistencies remain between the new datasets, the old datasets, and the tabular summaries of the data that the applicant provided for Study HBV-16.

Dynavax's response regarding items 23-25 acknowledged that the following datasets contain errors:

- *Tabular presentation in May 27, 2016 response to FDA IR dated 4/27/2016*
- *Tabular presentation in July 12, 2016 response to FDA IR dated 6/28/2016*
- *The dataset "HBV 16-ex.xpt" submitted on 7/12/2016*

In addition, the response stated that the following datasets are correct and consistent:

- *"adsl.xpt" submitted on March 15, 2016*
- *"adsl.xpt" submitted on April 8, 2016 (consistent with the other datasets, but 3 subjects without treatment were excluded)*
- *"adsl.xpt" submitted on May 27, 2016*

Furthermore, Dynavax created a master dataset for HBV-16, "adpp 16.xpt", located in Module 5.3.5.1 in the submission dated October 8, 2016. This dataset contains several additional variables indicating the population change between the original and revised datasets.

The objectives, study design, immunogenicity endpoints, safety monitoring procedures, and safety analysis of Study DV2-HBV-16 were previously addressed in the statistical review of the original Heplisav BLA dated January 29, 2013, and thus are not covered here. The submitted revised immunogenicity data and the immunogenicity analysis results in the revised CSR for this study were reviewed and verified.

6.2.10 Study Population and Disposition

Below is a summary of Per-Protocol Populations Subject Counts for Study HBV-16.

Table 7. Summary of Per-Protocol Populations Subject Counts for Study HBV-16

Population (data submitted)	Original (31 October, 2012)	Amended (27 May, 2016)	Changed from Included to Excluded	Changed from Excluded to Included	Net Change
Non-inferiority PP	1482	1474	23	15	-8
Lot Consistency PP	1290	1264	39	13	-26
Lot consistency Randomized Parallel with Lot 6 PP	957	932	30	5	-25

Source: Table 1 in the attachment 24c1 in the response to IR (4) dated September 9, 2016, submitted to STN 125428/0.68 on October 8, 2016.

Reviewer Comment:

I reviewed the dataset “dapp16.xpt” submitted with the response on October 8, 2016 and found it consistent with the previous correct datasets. I also verified the counts in Table 7, using dataset “adpp16.xpt”.

6.2.10.1 Populations Enrolled/Analyzed

Table 8 presents the revised subject disposition for Study HBV-16. Subject demographics and characteristics are based on the randomized population and have not been changed significantly from the original CSR.

Table 8. Subject Disposition

	Lot TDG008	Lot TDG009	Lot TDG010	Lot TDG006	Engerix-B
Non-inferiority PP	366	375	380	NA	353
Lot Consistency PP	423	427	414	NA	NA
Lot consistency Randomized Parallel with Lot 6 PP	165	163	158	446	NA

Note that Heplisav Lot 6 was excluded from non-inferiority and lot consistency analyses because it is not a proposed commercial formulation.

Source: Adapted from Figure 10-1 in the revised CSR in STN 125428/0.42.

6.2.11 Efficacy Analyses

The primary objectives of Study HBV-16 are:

- 1.) to demonstrate non-inferiority of the immune response to Heplisav as measured by the SPR at 8 weeks after the last active dose (Week 12), compared to the SPR for Engerix-B vaccination at 8 weeks after the last active dose (Week 32), and
- 2.) to demonstrate lot consistency for immune response as measured by the GMC at 4 weeks after the last active dose (Week 8) among 3 consecutively manufactured lots of Heplisav from the manufacturing process after minor modification.

The non-inferiority PP population that combines the 3 Heplisav consistency lots (TDG008, TDG009, and TDG010, referred to as the Heplisav group) was used for the primary immunogenicity endpoint analysis. The lot consistency PP population was used for the co-primary objective of lot consistency in subjects who received 1 of the 3 Heplisav consistency lots. Some results for Modified Intent-to-Treat (MITT) populations are also presented in this section.

6.2.11.1 Analyses of Primary Endpoint(s)

The primary immunogenicity endpoint was seroprotective immune response (anti-HBsAg ≥ 10 mIU/mL) at Week 12 following 2 injections of Heplisav compared with the SPR at Week 32 following 3 injections of Engerix-B. The primary statistic was seroprotection rate (SPR), defined as the percentage of subjects achieving a seroprotective immune response at Week 12 in Heplisav recipients compared with the SPR at Week 32 in those receiving Engerix-B.

The SPR in the Heplisav group was 90.1% and the SPR in the Engerix-B group was 70.5%; the estimated difference between these rates (Heplisav - Engerix-B) was 19.6% with 95% CI (14.7%, 24.8%). The SPR for the Heplisav group at Week 12 was non-inferior to the SPR for the Engerix-B group at Week 32 because the lower limit of the 95% CI (14.7%) was greater than -10%. A secondary objective was to assess superiority if the non-inferiority criterion was met. Because the lower limit of the 95% CI was greater than 0%, the SPR in the Heplisav group was statistically significantly higher than the SPR in the Engerix-B group.

Table 9. Statistical Comparison of Estimated Seroprotection Rates at Week 12 for Heplisav and Week 28 for Engerix-B

Population	Heplisav ^a (WEEK 12) n/N	Heplisav (WEEK 12) %	Engerix-B ^b (WEEK 28) n/N	Engerix-B (WEEK 28) %	Mean difference in SPR (Heplisav - Engerix-B) (95% CI)	Non-inferiority Criterion/ Superiority Criterion
Per Protocol	1010 /1121	90.1	249/353	70.5	19.6% (14.7%, 24.8%)	met/ met
MITT	1250/1426	87.7	318/476	66.8	20.9% (16.4%, 25.5%)	met/ met

N = number of subjects in the analysis population in the treatment group; n = number of subjects with post-injection anti-HBsAg ≥ 10 mIU/mL. Confidence intervals for the differences are calculated using the Newcombe score method with continuity correction.

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

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

Source: Section 14.1.3, Tables 14.1.3-1 and 14.1.3-13 in the revised CSR in STN 125428/0.42.

To evaluate lot consistency of Heplisav, subjects were randomized to receive 1 of 3 consecutively manufactured lots (consistency lots): TDG008, TDG009, or TDG010. The trial was designed with Week 8 (4 weeks after the last active dose) as the time point for this objective, because an initial analysis of data from Trial DV2-HBV-10 suggested that the SD of the GMC induced by Heplisav at that time point was smaller than at later time points and would provide greater statistical power. However, after DV2-HBV-16 was unblinded and the data were analyzed, Dynavax discovered that the SD of the GMC at Week 8 was actually larger than at later weeks. Dynavax then reanalyzed the data from DV2-HBV-10 and found similar results to this study and different from the initial analysis of the SD in study DV2-HBV-10.

Because of the error in the analysis used for planning DV2-HBV-16, data from both Week 8 and Week 12 were analyzed and presented (Table 10). At the pre-specified time point, 4 weeks after the last active dose of Heplisav (Week 8), GMCs for the lots were 36.1 mIU/mL (TDG008), 32.1 mIU/mL (TDG009), and 39.8 mIU/mL (TDG010). The 95% CI of the ratio of the GMCs between lots TDG008 and TDG009 (ratio = 1.13; 95% CI, 0.83, 1.53), TDG010 and TDG008 (ratio = 1.10; 95% CI, 0.81, 1.50), and lots TDG010 and TDG009 (ratio = 1.24; 95% CI, 0.91, 1.69) were not embedded in the interval of 0.667 to 1.5 and thus did not meet the pre-specified criterion. At 8 weeks after the last active dose of study treatment (Week 12), the GMCs were 80.3 mIU/mL (TDG008), 81.2 mIU/mL (TDG009), and 89.0 mIU/mL (TDG010). The 95% CIs of the pair-wise ratios of the GMCs between the lots were entirely embedded within the interval between 0.667 and 1.5. Clinical consistency of the 3 consecutively manufactured lots of Heplisav as measured by GMC was established at Week 12.

Table 10. Anti-HBs Geometric Mean Concentrations (mIU/mL) Among Heplisav Consistency Lots at Week 8 and Week 12 (Lot Consistency PP Population)

Visit	GMC (mIU/mL) (95% CI)			Adjusted GMC Ratio (95% CI)		
	Lot TDG008	Lot TDG009	Lot TDG010	Lot TDG008/ Lot TDG009	Lot TDG010/ Lot TDG008	Lot TDG010/ Lot TDG009
Week 8 ^a	N = 423 36.1 (28.1, 46.4)	N = 427 32.1 (24.8, 41.5)	N = 414 39.8 (30.7, 51.5)	1.13 (0.83, 1.53)	1.10 (0.81, 1.50)	1.24 (0.91, 1.69)
Week 12 ^b	N = 420 80.3 (65.4, 98.5)	N = 424 81.2 (65.8, 100.2)	N = 412 89.0 (72.0, 109.9)	0.99 (0.77, 1.27)	1.11 (0.86, 1.43)	1.10 (0.85, 1.41)

^a 4 weeks after last active dose of Heplisav.

^b 8 weeks after last active dose of Heplisav.

Source: Section 14.1.3, Table 14.1.3-5 in the revised CSR in STN 125428/0.42.

Reviewer Comments:

Although lot consistency criteria were not met at the pre-specified time point of 4 weeks after the last dose, lot consistency criteria were met at 8 weeks after the last dose, as well as at several other later time points. Therefore, in a previous review of the CSR dated July 27, 2011, CBER agreed that clinical consistency of the consecutively manufactured lots of Heplisav has been demonstrated.

6.2.11.2 Analyses of Secondary Endpoints

As mentioned in Section 6.2.11.1, an error in the analysis used for planning protocol DV2-HBV-16 led to the inappropriate designation of 4 weeks after the last active dose as the primary time point for determination of lot consistency. In addition to the data at the pre-specified time point of 4 weeks after the last active dose, the SPR data at 8 weeks after the last active dose and at each study visit were analyzed.

At the pre-specified time point of 4 weeks after the last active dose of Heplisav (Week 8), SPRs were 76.6% (TDG008), 72.6% (TDG009), and 76.8% (TDG010). The 95% CI for the pair-wise comparisons of the differences of SPRs between lots TDG008 and TDG009 (95% CI, -1.9%, 9.8%), between lots TDG010 and TDG008 (95% CI, -5.5%, 5.9%), and between lots TDG010 and TDG009 (95% CI, -1.7%, 10.0%) were embedded in the interval between -10% and 10% and therefore met the pre-specified lot consistency criterion. At Week 12, the primary analysis time point (8 weeks after the last active dose of Heplisav), the SPRs were 89.5% (TDG008), 88.4% (TDG009), and 90.5% (TDG010), and the 95% CIs of the pair-wise differences of the SPRs between the lots were entirely embedded in the interval between -10% and 10%. Clinical consistency of the 3 consecutively manufactured lots of Heplisav as measured by the SPR was established at Week 12 (Table 11).

At every subsequent study visit (Weeks 18, 24, 28, 32, 36, 44, and 52), the 95% CIs of all the 3 pair-wise comparisons of the differences in SPRs were embedded in the interval between -10.0% and 10.0%.

Table 11. Comparisons of Seroprotection Rates Among Heplisav Consistency Lots at Week 8 and Week 12 (Lot Consistency PP Population)

Visit	Number (%) of Subjects With anti-HBs ≥ 10 mIU/mL (Seroprotection Rate) (95% CI) ^a			% Difference (95% CI) ^b		
	Lot TDG008	Lot TDG009	Lot TDG010	Lot TDG008 - Lot TDG009	Lot TDG010 - Lot TDG008	Lot TDG010 - Lot TDG009
Week 8 ^c	N = 423 324 (76.6%) (72.3%, 80.6%)	N = 427 310 (72.6%) (68.1%, 76.8%)	N = 414 318 (76.8%) (72.4%, 80.8%)	4.0% (-1.9%, 9.8%)	0.2% (-5.5%, 5.9%)	4.2% (-1.7%, 10.0%)
Week 12 ^d	N = 420 376 (89.5%) (86.2%, 92.3%)	N = 424 375 (88.4%) (85.0%, 91.3%)	N = 412 373 (90.5%) (87.3%, 93.2%)	1.1% (-3.2%, 5.3%)	1.0% (-3.1%, 5.1%)	2.1% (-2.1%, 6.3%)

^a Calculated using the Clopper-Pearson method.

^b Two-sided 95% CI of the % differences in seroprotection rates were calculated using the Newcombe score method with continuity correction.

^c 4 weeks after last active dose of Heplisav.

^d 8 weeks after last active dose of Heplisav.

Source: Section 14.1.3, Table 14.1.3-4 in the revised CSR in STN 125428/0.42.

Lot consistency was also established in the mITT population by the SPR at 4 weeks after the last active dose of Heplisav (Week 8), as well as at other subsequent time points.

Heplisav induced a higher immune response than Engerix-B in subjects with diabetes. At 8 weeks after the last active dose of study treatment in this small subpopulation of 131 subjects, the SPR at Week 12 in 101 subjects with type 2 diabetes mellitus who received Heplisav (74.3%) was higher than the SPR at Week 32 in 30 subjects with type 2 diabetes mellitus who received Engerix-B (63.3%), with a difference of 10.9% and 95% CI (-6.3%, 30.2%) (Table 12). At Weeks 8, 12, 18, 24, 32, 36, and 44, the SPR in subjects with diabetes who received Heplisav was statistically significantly higher than the SPR in subjects with diabetes who received Engerix-B, as shown by the lower limit of the 95% CI of the difference in SPRs being greater than 0.

Table 12. Seroprotection Rates in Subjects With Type 2 Diabetes Mellitus at 8 Weeks After the Last Active Dose of Study Treatment and by Visit (Non-inferiority PP Population)

	Heplisav		Engerix-B		% Difference (95% CI) Heplisav - Engerix-B ^c
	n/N	SPR (95% CI)	n/N	SPR (95% CI)	
Week 12 ^a / Week 32 ^b	75/101	74.3% (64.6%, 82.4%)	19/30	63.3% (43.9%, 80.1%)	10.9% (-6.3%, 30.2%)
Week 4	12/101	11.9% (6.3%, 19.8%)	2/30	6.7% (0.8%, 22.1%)	5.2% (-10.7%, 13.9%)
Week 8	56/101	55.4% (45.2%, 65.3%)	3/30	10.0% (2.1%, 26.5%)	45.4% (26.7 %, 56.4%)
Week 12	75/101	74.3% (64.6%, 82.4%)	3/30	10.0% (2.1%, 26.5%)	64.3% (45.7%, 73.7%)
Week 18	84/101	83.2% (74.4%, 89.9%)	2/30	6.7% (0.8%, 22.1%)	76.5% (59.1%, 83.6%)
Week 24	86/101	85.1% (76.7%, 91.4%)	4/30	13.3% (3.8%, 30.7%)	71.8% (53.2%, 81.0%)
Week 28	86/101	85.1% (76.7%, 91.4%)	23/29	79.3% (60.3%, 92.0%)	5.8% (-7.3%, 24.5%)
Week 32	85/101	84.2% (75.6%, 90.7%)	19/30	63.3% (43.9%, 80.1%)	20.8% (4.1%, 39.5%)
Week 36	83/100	83.0% (74.2%, 89.8%)	17/28	60.7% (40.6%, 78.5%)	22.3% (4.7%, 41.5%)
Week 44	77/96	80.2% (70.8%, 87.6%)	17/29	58.6% (38.9%, 76.5%)	21.6% (3.6%, 40.6%)
Week 52	76/98	77.6% (68.0%, 85.4%)	18/29	62.1% (42.3%, 79.3%)	15.5% (-2.1%, 34.8%)

^a Heplisav.

^b Engerix-B.

^c Two-sided 95% CI of the % differences in seroprotection rates between Heplisav at 12 weeks and Engerix-B at 32 weeks were calculated using the Newcombe score method with continuity correction.

Source: Section 14.1.3, Table 14.1.3-25 and Table 14.1.3-28 in the revised CSR in STN 125428/0.42.

Table 13 presents the comparison of the percentage of subjects with anti-HBs \geq 100 mIU/mL 8 weeks after the last active dose of study treatment, between those who

received Heplisav (Week 12) and those who received Engerix-B (Week 32). At 8 weeks after the last active dose, the percentage of subjects who received Heplisav and had anti-HBs ≥ 100 mIU/mL (53.5%) was similar to subjects who received Engerix-B (51.3%). The difference in the percentage of subjects with anti-HBs ≥ 100 mIU/mL was 2.2% with 95% CI (-3.7%, 8.2%).

Table 13. Subjects With Anti-HBs ≥ 100 mIU/mL at 8 Weeks After the Last Active Dose of Study Treatment (Non-inferiority PP Population)

Visit	Heplisav		Engerix-B		% Difference Heplisav - Engerix-B ^c
	n/N	% (95% CI)	n/N	% (95% CI)	
Week 12 ^a / Week 32 ^b	600/1121	53.5% (50.6%, 56.5%)	181/353	51.3% (45.9%, 56.6%)	2.2% (-3.7%, 8.2%)

^a Heplisav.

^b Engerix-B.

^c Two-sided 95% CI of the difference in proportions between Heplisav at 12 weeks and Engerix-B at 32 weeks were computed using the Newcombe score method with continuity correction.

Source: Section 14.1.3, Table 14.1.3-3 in the revised CSR in STN 125428/0.42.

6.2.11.3 Subpopulation Analyses

Table 14 presents a comparison of SPRs by age stratum (40 through 49, 50 through 59, and 60 through 70 years) and visit. The SPR in the Heplisav group was statistically significantly higher than that in the Engerix-B group at all visits for each age group; the lower limits of the 95% CIs of the differences in SPRs were greater than 0. In both treatment groups, after Week 4, the SPRs were higher in the youngest age group than in the older age groups at all time points. In the Heplisav group, the SPR increased more rapidly in the younger age group than in the oldest age group.

The SPR in the oldest age group who received Heplisav was higher than the SPR in the youngest age group who received Engerix-B at each visit. For example, at Week 28, the SPR in 60- to 70-year-old subjects who received Heplisav was 89.8%, while the SPR in 40- to 49-year-old subjects who received Engerix-B was 77.9%.

In the oldest age group, the SPR in the Heplisav group (90.4%) peaked 20 weeks after the last active dose of Heplisav and decreased 4.3% to 86.5% at Week 52. The peak SPR in the oldest group who received Engerix-B (68.9%) was at Week 28, 4 weeks after the last dose of active vaccine, and decreased 23.9% to 52.4% at Week 52.

Table 14. Seroprotection Rates by Age Strata and Visit (Non-inferiority PP Population)

Visit Age Stratum	Hepelisav		Engerix-B		% Difference Hepelisav - Engerix-B ^a
	n/N	SPR (95% CI)	n/N	SPR (95% CI)	
Week 4					
40 - 49 years	86/364	23.6% (19.4%, 28.3%)	3/113	2.7% (0.6%, 7.6%)	21.0% (14.5%, 25.8%)
50 - 59 years	99/454	21.8% (18.1%, 25.9%)	8/136	5.9% (2.6%, 11.3%)	15.9% (9.5%, 20.8%)
60 - 70 years	35/303	11.6% (8.2%, 15.7%)	4/104	3.8% (1.1%, 9.6%)	7.7% (1.1%, 12.3%)
Week 8					
40 - 49 years	307/364	84.3% (80.2%, 87.9%)	26/113	23.0% (15.6%, 31.9%)	61.3% (51.8%, 68.9%)
50 - 59 years	347/453	76.6% (72.4%, 80.4%)	30/136	22.1% (15.4%, 30.0%)	54.5% (45.8%, 61.7%)
60 - 70 years	203/303	67.0% (61.4%, 72.3%)	16/104	15.4% (9.1%, 23.8%)	51.6% (41.7%, 59.1%)
Week 12					
40 - 49 years	344/364	94.5% (91.6%, 96.6%)	23/113	20.4% (13.4%, 29.0%)	74.2% (65.3%, 80.7%)
50 - 59 years	416/454	91.6% (88.7%, 94.0%)	22/136	16.2% (10.4%, 23.5%)	75.5% (67.8%, 81.1%)
60 - 70 years	250/303	82.5% (77.8%, 86.6%)	15/104	14.4% (8.3%, 22.7%)	68.1% (58.7%, 74.7%)
Week 18					
40 - 49 years	355/364	97.5% (95.4%, 98.9%)	27/113	23.9% (16.4%, 32.8%)	73.6% (64.7%, 80.6%)
50 - 59 years	437/454	96.3% (94.1%, 97.8%)	27/136	19.9% (13.5%, 27.6%)	76.4% (68.6%, 82.3%)
60 - 70 years	268/303	88.4% (84.3%, 91.8%)	15/104	14.4% (8.3%, 22.7%)	74.0% (65.0%, 80.2%)
Week 24					
40 - 49 years	356/364	97.8% (95.7%, 99.0%)	25/113	22.1% (14.9%, 30.9%)	75.7% (66.9%, 82.4%)
50 - 59 years	436/454	96.0% (93.8%, 97.6%)	30/136	22.1% (15.4%, 30.0%)	74.0% (65.9%, 80.2%)
60 - 70 years	274/303	90.4% (86.5%, 93.5%)	21/104	20.2% (13.0%, 29.2%)	70.2% (60.7%, 77.3%)
Week 28					
40 - 49 years	354/363	97.5% (95.3%, 98.9%)	88/113	77.9% (69.1%, 85.1%)	19.6% (12.7%, 28.3%)
50 - 59 years	436/454	96.0% (93.8%, 97.6%)	97/135	71.9% (63.5%, 79.2%)	24.2% (17.0%, 32.4%)
60 - 70 years	272/303	89.8% (85.8%, 92.9%)	71/103	68.9% (59.1%, 77.7%)	20.8% (11.9%, 30.8%)
Week 32					
40 - 49 years	357/364	98.1% (96.1%, 99.2%)	89/113	78.8% (70.1%, 85.9%)	19.3% (12.5%, 27.8%)
50 - 59 years	435/454	95.8% (93.5%, 97.5%)	94/136	69.1% (60.6%, 76.8%)	26.7% (19.2%, 35.0%)
60 - 70 years	271/303	89.4% (85.4%, 92.7%)	66/104	63.5% (53.4%, 72.7%)	26.0% (16.5%, 36.0%)

Visit Age Stratum	Heplisav		Engerix-B		% Difference Heplisav - Engerix-B ^a
	n/N	SPR (95% CI)	n/N	SPR (95% CI)	
Week 36					
40 - 49 years	350/359	97.5% (95.3%, 98.8%)	84/110	76.4% (67.3%, 83.9%)	21.1% (13.9%, 30.0%)
50 - 59 years	429/450	95.3% (93.0%, 97.1%)	87/136	64.0% (55.3%, 72.0%)	31.4% (23.4%, 39.9%)
60 - 70 years	269/301	89.4% (85.3%, 92.6%)	58/103	56.3% (46.2%, 66.1%)	33.1% (23.1%, 43.1%)
Week 44					
40 - 49 years	345/357	96.6% (94.2%, 98.3%)	73/108	67.6% (57.9%, 76.3%)	29.0% (20.6%, 38.5%)
50 - 59 years	420/449	93.5% (90.9%, 95.6%)	81/136	59.6% (50.8%, 67.9%)	34.0% (25.7%, 42.6%)
60 - 70 years	263/295	89.2% (85.0%, 92.5%)	53/103	51.5% (41.4%, 61.4%)	37.7% (27.4%, 47.7%)
Week 52					
40 - 49 years	342/357	95.8% (93.2%, 97.6%)	71/109	65.1% (55.4%, 74.0%)	30.7% (22.0%, 40.1%)
50 - 59 years	414/447	92.6% (89.8%, 94.9%)	80/136	58.8% (50.1%, 67.2%)	33.8% (25.4%, 42.4%)
60 - 70 years	257/297	86.5% (82.1%, 90.2%)	54/103	52.4% (42.4%, 62.4%)	34.1% (23.8%, 44.2%)

^a Two-sided 95% CIs of the difference in SPRs between Heplisav and Engerix-B were computed using the Newcombe score method with continuity correction.

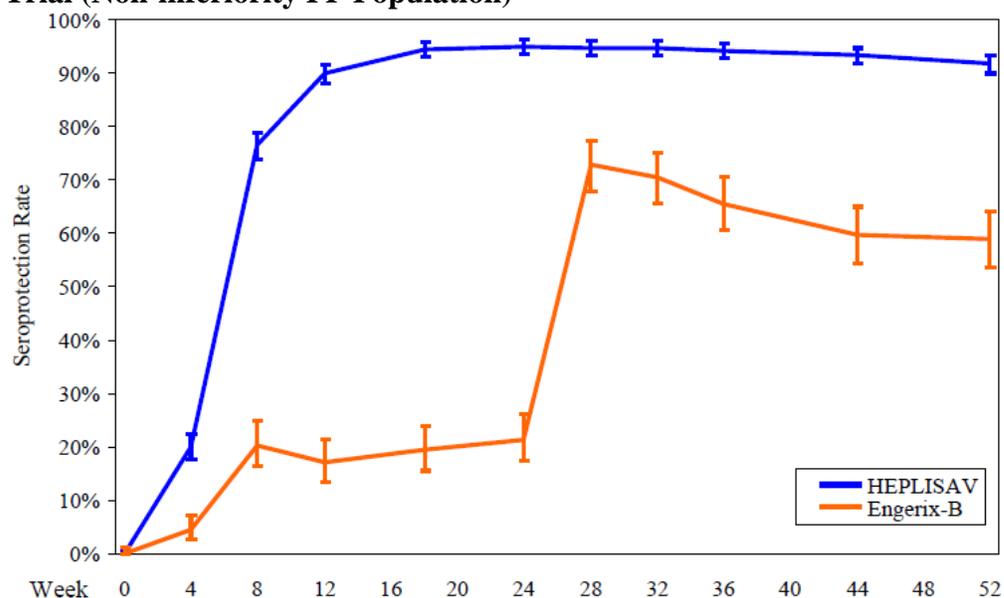
Source: Section 14.1.3, Table 14.1.3-31 in the revised CSR in STN 125428/0.42.

In terms of GMC, results by age strata were generally consistent with those reported for the SPR. In all 3 age groups (40 through 49, 50 through 59, and 60 through 70 years), subjects who received Heplisav had a demonstrably higher GMC than subjects who received Engerix-B at every visit from Week 4 through Week 52.

6.2.11.5 Exploratory and Post Hoc Analyses

Figure 1 graphically presents SPRs over the course of the study. The SPR in the Heplisav group increased rapidly from Week 4 to Week 8 (4 weeks following the last active dose), then increased gradually until Week 24, and then decreased slightly to Week 52. In contrast, in the Engerix-B group, the SPR increased moderately until Week 8, then remained low until a sharp increase between Weeks 24 and 28 (4 weeks following the third and last active dose), and decreased steadily over the remainder of the study. The SPR in the Heplisav group decreased 3.3% from peak at Week 24 to Week 52 while the SPR in the Engerix-B group decreased 19.2% from peak at Week 28 to Week 52.

Figure 1. Seroprotection Rate and 95% Confidence Interval over the Course of the Trial (Non-inferiority PP Population)



Source: Figure 11-1 in the revised CSR in STN 125428/0.42.

Table 15 presents the approximate distribution of anti-HBs responses at Week 28 by treatment group. At Week 28, when the GMC induced by Engerix-B peaks, a much higher proportion of subjects who received Heplisav had antibody levels between 10 and 1000 mIU/mL than subjects who received Engerix-B. Subjects who received Engerix-B had a nearly equal probability of having levels < 10 mIU/mL as \geq 1000 mIU/mL.

Table 15. Distribution of Anti-HBs Responses at Week 28 by Treatment Group

	Anti-HBs Concentration		
	< 10 mIU/mL	10 - <1000 mIU/mL	\geq 1000 mIU/mL
Heplisav (n = 1120)	58 (5.2%)	897 (80.1%)	165 (14.7%)
Engerix-B (n = 351)	95 (27.1%)	150 (42.7%)	106 (30.2%)

Source: Section 14.1.3, Table 14.1.3-39 in the revised CSR in STN 125428/0.42.

6.3 Trial #3

DV2-HBV-23: A randomized, observer-blind, active-controlled, multicenter, phase 3 trial. Eligible subjects were randomized in a 2:1 ratio to receive Heplisav or Engerix-B (approximately 5500 Heplisav subjects and 2750 Engerix-B subjects). At least 413 subjects with type 2 diabetes mellitus were to be enrolled. Enrollment was stratified by site, age group (18 to 39, 40 to 70 years), and type 2 diabetes mellitus status. The Heplisav group received a 2-dose series of Heplisav at 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.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

Table 16 presents a summary of subjects included in all the analysis populations as well as a summary of subjects with protocol-defined type 2 diabetes mellitus included in all the analysis populations.

Table 16. Analysis Populations

Population	Heplisav n (%)	Engerix-B n (%)	Total n (%)
Randomized	5592	2782	8374
mITT ^a	5278 (94.4)	2635 (94.7)	7913 (94.5)
Per-Protocol ^a	4537 (81.1)	2289 (82.3)	6826 (81.5)
Safety ^a	5587 (>99.9)	2781 (>99.9)	8368 (> 99.9)
Laboratory Safety Substudy ^b	207 (3.7)	102 (3.7)	309 (3.7)
Subjects with Type 2 Diabetes Mellitus	763	381	1144
mITT ^c	737 (96.6)	367 (96.3)	1104 (96.5)
Per-Protocol ^c	640 (83.9)	321 (84.3)	961 (84.0)
Safety ^c	762 (99.9)	381 (100.0)	1143 (> 99.9)

mITT = modified intent-to-treat.

^a Denominator is Randomized Population.

^b Denominator is Safety Population.

^c Denominator is subjects with type 2 diabetes mellitus.

Source: Tables 14.1.1.2 and 14.1.1.3 in the Study HBV-23 CSR in STN 125428/0.42.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

The primary immunogenicity objective of this study is to demonstrate noninferiority of the SPR induced by Heplisav compared with the SPR induced by Engerix-B at Week 28 in subjects with type 2 diabetes mellitus. Table 17 compares SPRs at Week 28 between Heplisav and Engerix-B in subjects with type 2 diabetes mellitus. The SPR in the Heplisav group at Week 28 was significantly higher than in the Engerix-B group at Week 28. The difference between SPRs (Heplisav minus Engerix-B) was 24.9% (95% CI: 19.3%, 30.7%), which met the prospectively-defined criterion for the primary assessment of noninferiority (lower limit of the 95% CI greater than -10%) as well as the secondary objective of statistical significance (lower limit of the 95% CI greater than 0%). Results were similar for the mITT Population.

A sensitivity analysis for the primary endpoint examined duration of diabetes (< 5 years vs ≥ 5 years), baseline hemoglobin A1c category (< 6.5%, 6.5% - 9.0%, and > 9.0%), number of diabetes complications, metformin use, immunosuppressive medication use, as well as treatment group, age, sex, race, BMI, and smoking history. A stepwise logistic regression found that treatment group, age, and BMI significantly affected the level of SPR at the 0.05 level of significance. None of the diabetes variables affected the SPR. The odds ratio for seroprotection between Heplisav and Engerix-B was 4.946 (95% CI: 3.462, 7.065). Older subjects were less likely than younger subjects to be seroprotected

following hepatitis B vaccination, and non-obese subjects were more likely to be seroprotected than the obese subjects (Table 19 and Table 21).

Table 17. Comparison of Seroprotection Rates Between Heplisav and Engerix-B at Week 28 for Subjects With Type 2 Diabetes Mellitus (Per-Protocol Population)

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

Heplisav ^a			Engerix-B ^b			Difference	Non-inferior/ Superior
N	n	SPR (%) (95% CI) ^c	N	n	SPR (%) (95% CI) ^c	(Heplisav - Engerix-B) (95% CI) ^d	
640	576	90.0 (87.4 - 92.2)	321	209	65.1 (59.6 - 70.3)	24.9 (19.3 - 30.7)	Yes/ Yes

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

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

^d 95% CI was calculated using the Miettinen and Nurminen method without stratification.

Source: Table 14.1.3.1.1 in the Study HBV-23 CSR in STN 125428/0.42.

6.3.11.2 Analyses of Secondary Endpoints

The secondary immunogenicity objectives of this study were:

- To demonstrate that the SPR at Week 28 induced by Heplisav is statistically significantly higher than the SPR induced by Engerix-B in subjects with type 2 diabetes mellitus, ONLY if it is established that Heplisav is noninferior to Engerix-B with regard to SPR at Week 28.
- To demonstrate that the SPR at Week 24 induced by Heplisav is noninferior to the SPR at Week 28 induced by Engerix-B in all subjects and in the following subgroups: by age, sex, body mass index (BMI), and smoking status.
- To demonstrate that the SPR at Week 24 induced by Heplisav is statistically significantly higher than the SPR at Week 28 induced by Engerix-B in all subjects and in the following subgroups: by age, sex, BMI, and smoking status, ONLY if it is established that Heplisav is noninferior to Engerix-B with regard to SPR.

Table 18-22 compares the SPRs between Heplisav at Week 24 and Engerix-B at Week 28 in all subjects and in the following subgroups: by age, sex, body mass index (BMI), and smoking status. In all subjects and each subpopulation (age group, sex, obesity, smoking), the SPR at Week 24 in the Heplisav group was statistically significantly higher than in the Engerix-B group at Week 28.

Table 18. Comparison of Peak Seroprotection Rates Between Heplisav at Week 24 and Engerix-B at Week 28

Heplisav		Engerix-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)

Source: Table 14.1.3.3 in the Study HBV-23 CSR in STN 125428/0.42.

Table 19. Comparison of Seroprotection Rates Between Heplisav at Week 24 and Engerix-B at Week 28 by Age Group

Age Group	Heplisav			Engerix-B			Difference
	N	n	SPR (%) (95% CI)	N	n	SPR (%) (95% CI)	(Heplisav-Engerix-B) (95% CI)
18 - 29	174	174	100.0 (97.9 - 100.0)	99	93	93.9 (87.3 - 97.7)	6.1 (2.8 - 12.6)
30 - 39	632	625	98.9 (97.7 - 99.6)	326	300	92.0 (88.5 - 94.7)	6.9 (4.2 - 10.4)
40 - 49	974	947	97.2 (96.0 - 98.2)	518	436	84.2 (80.7 - 87.2)	13.1 (9.9 - 16.6)
50 - 59	1439	1370	95.2 (94.0 - 96.3)	758	604	79.7 (76.6 - 82.5)	15.5 (12.6 - 18.7)
60 +	1157	1060	91.6 (89.9 - 93.1)	588	427	72.6 (68.8 - 76.2)	19.0 (15.2 - 23.0)

Source: Table 14.1.3.9 in the Study HBV-23 CSR in STN 125428/0.42.

Table 20. Comparison of Seroprotection Rates Between Heplisav at Week 24 and Engerix-B at Week 28 by Sex

Sex	Heplisav			Engerix-B			Difference
	N	n	SPR (%) (95% CI)	N	n	SPR (%) (95% CI)	(Heplisav-Engerix-B) (95% CI)
Male	2203	2082	94.5 (93.5 - 95.4)	1150	906	78.8 (76.3 - 81.1)	15.7 (13.2 - 18.3)
Female	2173	2094	96.4 (95.5 - 97.1)	1139	954	83.8 (81.5 - 85.9)	12.6 (10.4 - 15.0)

Source: Table 14.1.3.7 in the Study HBV-23 CSR in STN 125428/0.42.

Table 21. Comparison of Seroprotection Rates Between Heplisav at Week 24 and Engerix-B at Week 28 by BMI Category

BMI Category	Heplisav			Engerix-B			Difference
	N	n	SPR (%) (95% CI)	N	n	SPR (%) (95% CI)	(Heplisav-Engerix-B) (95% CI)
Obese	2165	2051	94.7 (93.7 - 95.6)	1076	811	75.4 (72.7 - 77.9)	19.4 (16.7 - 22.2)
Non-obese	2208	2122	96.1 (95.2 - 96.9)	1212	1049	86.6 (84.5 - 88.4)	9.6 (7.6 - 11.7)

Source: Table 14.1.3.11 in the Study HBV-23 CSR in STN 125428/0.42.

Table 22. Comparison of Seroprotection Rates Between Heplisav at Week 24 and Engerix-B at Week 28 by Smoking Status

Smoking Status	Heplisav			Engerix-B			Difference
	N	n	SPR (%) (95% CI) ^c	N	n	SPR (%) (95% CI)	(Heplisav-Engerix-B) (95% CI)
Smokers	1371	1315	95.9 (94.7 - 96.9)	711	559	78.6 (75.4 - 81.6)	17.3 (14.2 - 20.6)
Nonsmokers	3005	2861	95.2 (94.4 - 95.9)	1578	1301	82.4 (80.5 - 84.3)	12.8 (10.8 - 14.8)

Source: Table 14.1.3.13 in the Study HBV-23 CSR in STN 125428/0.42.

Table 23 compares SPRs by race between Heplisav at Week 24 and Engerix-B at Week 28.

Table 23. Comparison of Seroprotection Rates Between Heplisav at Week 24 and Engerix-B at Week 28 by Race

Race	Heplisav			Engerix-B			Difference
	N	n	SPR (%) (95% CI)	N	n	SPR (%) (95% CI)	(Heplisav-Engerix-B) (95% CI)
White	3084	2910	94.4 (93.5 - 95.1)	1675	1350	80.6 (78.6 - 82.5)	13.8 (11.7 - 15.9)
Black or African American	1169	1147	98.1 (97.2 - 98.8)	554	456	82.3 (78.9 - 85.4)	15.8 (12.7 - 19.3)
Asian	45	43	95.6 (84.9 - 99.5)	29	27	93.1 (77.2 - 99.2)	2.5 (-9.3 - 18.2)
Other	76	74	97.4 (90.8 - 99.7)	31	27	87.1 (70.2 - 96.4)	10.3 (0.6 - 26.6)

Source: Table 14.1.3.10 in the Study HBV-23 CSR in STN 125428/0.42.

Reviewer comments:

1. I consider the applicant’s assertions of greater immunogenicity for age, sex, obesity, and smoking subgroups to be statistically acceptable, because one of the objectives in the HBV-23 Statistical Analysis Plan (SAP) is to test statistical significance after noninferiority of Heplisav compared to Engerix-B is established and all the null hypotheses of no difference for age, sex, obesity, and smoking subgroups are rejected -- even if a Bonferroni adjustment is applied. However, the applicant stated in the CSR that “The Heplisav SPR was also significantly higher than Engerix-B SPR in all races except Asians in whom the number of subjects was small.” Note that there are four race subgroups in Table 23; each of the four significance tests are conducted at level 0.05. As more race subgroups are considered, it becomes more likely that Heplisav will appear to be superior in any one of the four race subgroups. If the null hypothesis of no difference in any one of the race subgroups is not rejected and one claims the remaining subgroups to be significant, this procedure will result in inflated family-wise Type I error probability. In fact, only the differences in White and Black or African American subgroups are significant after a Bonferroni adjustment is made. Thus, I do not agree with the applicant’s assertions regarding immunogenicity by race.

2. A few counts in Tables 19-23 above differ by one or two from my own analysis, which is based on the dataset submitted on 3/15/2016. However, this discrepancy does not have an appreciable effect on the CIs for the differences. Therefore, I consider the CIs acceptable.

7. INTEGRATED OVERVIEW OF EFFICACY

Overall, the primary and secondary endpoints of non-inferiority of the immune response to Heplisav compared to Engerix-B were demonstrated in both Studies HBV-16 and HBV-10.

Lot consistency criteria were met at 8 weeks after the last active dose of Heplisav (Week 12), which was the time point corresponding to the primary immunogenicity endpoint, as well as at multiple other time points. All Heplisav consistency lots induced a higher

immune response at all time points compared with Engerix-B. In addition, the immune response to the consistency lots was similar to that of a previously manufactured lot.

In subjects with type 2 diabetes mellitus, the SPR in the Heplisav group at Week 28 was statistically significantly higher than in the Engerix-B group at Week 28 in Study HBV-23. In the total trial population and each subpopulation (age, sex, obesity, smoking), the SPR at Week 24 in the Heplisav group was statistically significantly higher than in the Engerix-B group at Week 28.

8. INTEGRATED OVERVIEW OF SAFETY

As a response to the CR Letter item 2, issued on November 10, 2016, Dynavax submitted a report “Evaluation of acute myocardial infarction and major adverse cardiovascular events in the phase 3 Heplisav clinical trials” on October 7, 2016. This review only constitutes a partial review of the response. Specifically, this statistical review was performed on the applicant’s data presented in Table 24 below (Table 3-3 in the report.)

8.1 Safety Assessment Methods

In order to assess the numerical imbalance in events coded according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term acute myocardial infarction reported in HBV-23, Dynavax applied several analytic approaches to data collected in HBV-10, HBV-16, HBV-23, and the primary safety population (PSP), which is the combined population of Studies HBV-10, HBV-16, and HBV-23:

- Ascertainment of the number of treatment-emergent events coded to the preferred term acute myocardial infarction and a broader evaluation using a search strategy applying the MedDRA myocardial infarction Standardized Medical Query (MI SMQ).
- Ascertainment of preferred terms selected to identify treatment-emergent serious composite 3-point MACE outcomes comprising death due to cardiovascular cause, first non-fatal myocardial infarction, and first non-fatal stroke.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Studies DV2-HBV-10, DV2-HBV-16, and DV2-HBV-23.

8.4 Safety Results

Table 24 presents the applicant’s analysis of confirmed 3-point events by trial and in the PSP.

Table 24. Adjudicated and Confirmed Treatment-Emergent, Serious 3-point Major Adverse Cardiovascular Events by Treatment Group (Primary Safety Population)

	HBV-16			HBV-23			PSP		
	Heplisav (N=1968) % (n)	Engerix-B (N=481) % (n)	Relative Risk (95% CI)	Heplisav (N=5587) % (n)	Engerix-B (N=2781) % (n)	Relative Risk (95% CI)	Heplisav (N=9365) % (n)	Engerix-B (N=3867) % (n)	Relative Risk (95% CI)
Composite 3-point MACE events	0.15% (3)	0.42% (2)	0.37 (0.06, 2.19)	0.50% (28)	0.22% (6)	2.32 (0.96, 5.60)	0.33% (31)	0.21% (8)	1.60 (0.74, 3.48)
Death from cardiovascular cause ^a	0.05% (1)	0.21% (1)	0.24 (0.02, 3.9)	0.05% (3)	0.04% (1)	1.49 (0.16, 14.35)	0.04% (4)	0.05% (2)	0.83 (0.15, 4.51)
Acute Myocardial infarction ^b	0.10% (2)	0.21% (1)	0.49 (0.04, 5.38)	0.25% (14)	0.04% (1)	6.97 (0.92, 52.97)	0.17% (16)	0.05% (2)	3.30 (0.76, 14.36)
Stroke ^c	0	0	N/A	0.20% (11)	0.14% (4)	1.37 (0.44, 4.30)	0.12% (11)	0.10% (4)	1.14 (0.36, 3.56)

^a Cardiovascular cause of death comprises the following preferred terms: Death from cardiovascular cause includes death due to Acute Coronary Syndrome, Acute Myocardial Infarction, Acute Respiratory Failure, Cardiac Arrest, Cardiac Failure, Cardio-respiratory Arrest, Death, Hypertensive Heart Disease, Myocardial Infarction, or Pulmonary Embolism.

^b Myocardial infarction includes deaths due to myocardial infarction and comprises the following preferred terms: Myocardial infarction includes Acute Coronary Syndrome, Acute Myocardial Infarction, Coronary Artery Embolism, Coronary Artery Thrombosis, Coronary Bypass Thrombosis, Myocardial infarction, Post Procedural Myocardial Infarction, or Silent Myocardial Infarction.

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

NOTE: There were no deaths adjudicated as caused by myocardial infarction or stroke. There were no MACE events in HBV-10.

Source: Table 3-3 in the response (2) to September 9, 2016 information request in STN 125428/0.65

Table 24 shows imbalances for several events. One notable imbalance is in the event of acute myocardial infarction (Heplisav: n = 14 [0.25%]; Engerix-B: n = 1 [0.04%]; relative risk [RR] = 6.97; 95% confidence interval [CI]: 0.92, 52.97). Since the lower bound of the relative risk is 0.92, which is less than 1, the applicant stated that the observed numerical difference between treatment groups in the incidence of acute myocardial infarction in HBV-23 is not statistically significant.

Reviewer comment:

It is well known that a confidence interval can include the value 1 (for RR) simply due to inadequate sample size. Thus, such finding cannot be used as evidence of no imbalance in risk; it could just mean that the sample size was not large enough to detect a true imbalance. Moreover, whether or not a CI includes the value 1 is not the optimal way to use a CI for safety assessment. Instead, focus on the upper CI limit is more relevant, since it indicates the level of RR that can be ruled out at a specified confidence level, for

the given sample size. In the above CI, the upper limit suggests that a RR as high as 52.97 cannot be ruled out with the given sample size.

The CI computed by the applicant is the Wald asymptotic CI. Based on my analysis, the Wald asymptotic CI for rare events in this dataset is overly conservative and tends to give a wider and less accurate interval. Table 25 shows my analysis of the coverage probability and power comparison between the Wald CI and two other approaches: Bayesian credible interval using uniform(0, 1) priors and Koopman score asymptotic CI, assuming that true risks are the estimates from the data (i.e., $p_1=1/2781$, $p_2=14/5587$). It can be seen that the coverage probability for the Wald asymptotic CI is 0.965, which implies that this method is conservative and will produce a wider CI than less conservative methods. The Bayesian credible interval has the closest coverage probability to the nominal level 0.95. The Koopman score CI has the highest power 0.669, whereas the Wald CI has much lower power, 0.237, to detect an imbalance.

Table 25. Comparison between applicant’s method and reviewer’s methods

	Coverage probability (nominal level=0.95)	Power(based on 1000 simulations)
Wald asymptotic	0.965	0.237
Koopman score	0.957	0.669
Bayes Uniform	0.947	0.652

Analysis results are presented in Table 26, based on the Bayesian method with uniform(0, 1) priors and the Koopman score asymptotic method.

Table 26. Comparison between applicant’s and reviewer’s analysis results

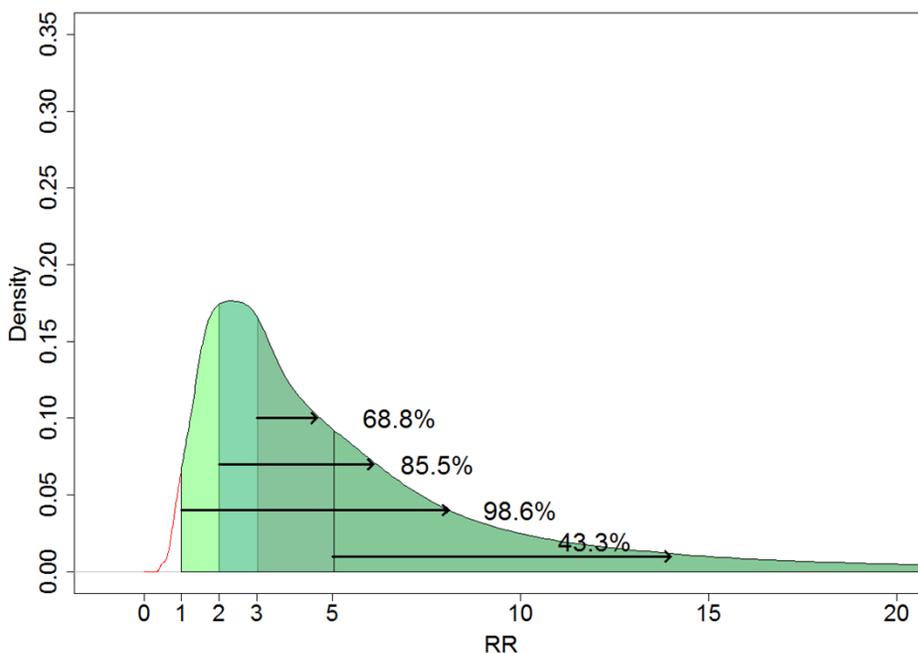
	HBV-16			HBV-23			PSP		
	Heplisav (N=1968) % (n)	Engerix-B (N=481) % (n)	Relative Risk (95% CI) ^a	Heplisav (N=5587) % (n)	Engerix-B (N=2781) % (n)	Relative Risk (95% CI) ^a (95% CI) ^b (95% CI) ^s	Heplisav (N=9365) % (n)	Engerix-B (N=3867) % (n)	Relative Risk (95% CI) ^a (95% CI) ^b (95% CI) ^s
Composite 3-point MACE events	0.15% (3)	0.42% (2)	0.37 (0.06, 2.19)	0.50% (28)	0.22% (6)	2.32 (0.96, 5.60) (0.99, 5.37) (0.99, 5.46)	0.33% (31)	0.21% (8)	1.60 (0.74, 3.48) (0.75, 3.39) (0.75, 3.42)
Death from cardiovascular cause	0.05% (1)	0.21% (1)	0.24 (0.02, 3.9)	0.05% (3)	0.04% (1)	1.49 (0.16, 14.35) (0.20, 8.94) (0.21, 10.42)	0.04% (4)	0.05% (2)	0.83 (0.15, 4.51) (0.17, 3.76) (0.18, 3.85)
Acute Myocardial infarction	0.10% (2)	0.21% (1)	0.49 (0.04, 5.38)	0.25% (14)	0.04% (1)	6.97 (0.92, 52.97) (1.15, 31.58) (1.17, 41.44)	0.17% (16)	0.05% (2)	3.30 (0.76, 14.36) (0.83, 11.79) (0.85, 12.90)
Stroke	0	0	N/A	0.20% (11)	0.14% (4)	1.37 (0.44, 4.30) (0.45, 4.02) (0.46, 4.07)	0.12% (11)	0.10% (4)	1.14 (0.36, 3.56) (0.38, 3.33) (0.38, 3.38)

^a. Wald asymptotic CI, applicant's method
^b. Bayesian credible interval using uniform(0, 1) prior, by reviewer's analysis
^s. Koopman score asymptotic CI, by reviewer's analysis

It is worth noting from Table 26 that 1) the Bayesian method with uniform priors and Koopman score method produce similar CIs, and they are both narrower than the applicant's Wald CI; 2) the lower bound of the 95% CI for relative risk of AMI in Study HBV-23 is 1.15 using the Bayesian method, which disagrees with the applicant's conclusion. The lower bound of the 95% CI for relative risk of Composite 3-point MACE events using the Bayesian or Koopman score method is 0.99, which is only slightly below 1.0. It should be emphasized, however, that for safety evaluation, attention should be placed on estimation rather than hypothesis testing, thus the upper limits of the CIs for relative risk also provide important information on the potential magnitude of the relative risk, given the sample size.

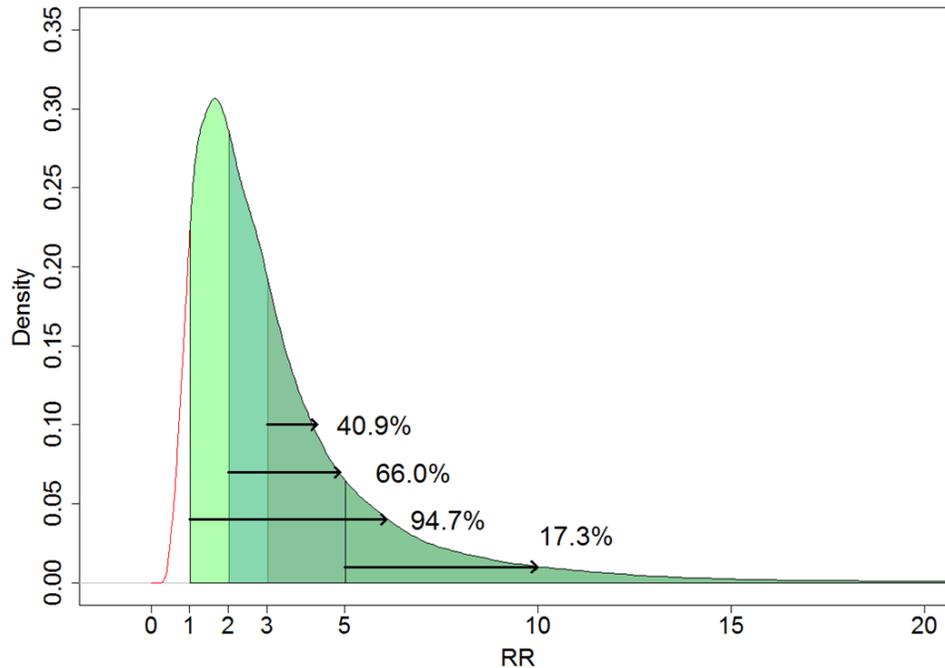
I also produced the posterior density plot of relative risk using a Uniform(0, 1) prior and computed the posterior probabilities of RR being greater than 1, 2, 3, and 5, which is more directly interpretable than CIs. Figure 2 is the posterior distribution of RR for AMI in Study HBV-23. Figure 3 is the posterior distribution of RR for AMI in Studies HBV-10, HBV-16, and HBV-23.

Figure 2. Posterior density of RR based on 14:1 cases in Study HBV-23



The posterior probabilities of RR of Heplisav vs. Engerix-B being greater than 1, 2, 3, and 5 are 98.6%, 85.5%, 68.8%, and 43.3%, respectively.

Figure 3. Posterior density of RR based on 16:2 cases in Studies HBV-10, HBV-16, and HBV-23



The posterior probabilities of RR of Heplisav vs. Engerix-B being greater than 1, 2, 3, and 5 are 94.7%, 66.0%, 40.9%, and 17.3%, respectively.

9. ADDITIONAL STATISTICAL ISSUES

NA

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

I verified the applicant's clarifications regarding the immunogenicity data discrepancies in the response to CR Letter items 23-25. I also reviewed the dataset "adpp 16.xpt" submitted with the response on October 8, 2016 and found that it is consistent with the previous correct datasets. I also verified the immunogenicity analysis results in the revised CSRs for Studies DV2-HBV-16 and DV2-HBV-10 dated March 15, 2016, using the correct dataset "adlb.xpt" (lab results included) submitted on March 15, 2016. Overall, the response submitted on October 8, 2016 addressed the issues in the CR Letter items 23-25.

I also verified the immunogenicity analysis results for all subjects and each subpopulation (diabetes, age, sex, obesity, smoking) in the CSR for Study HBV-23. For the race

subgroup, I disagree with the applicant's assertion that "The Heplisav SPR was also significantly higher than Engerix-B SPR in all races except Asians in whom the number of subjects was small." In fact, only the differences in White and Black or African American race subgroups are statistically significant after a Bonferroni adjustment is made.

In response to CR Letter item 2, Dynavax performed an evaluation of the imbalances between the Heplisav and Engerix-B groups in AMI and MACE. The applicant stated that the observed numerical difference between treatment groups in the incidence rates of acute myocardial infarction in HBV-23 is not statistically significant. I investigated this statement by performing some additional statistical analyses presented in Section 8. The analyses show evidence of elevated risk of AMI associated with Heplisav in Study HBV-23.

10.2 Conclusions and Recommendations

I find the applicant's clarifications regarding the immunogenicity data discrepancies in the response to CR Letter items 23-25 dated October 8, 2016 and the immunogenicity analysis results in the revised CSRs for Studies DV2-HBV-16 and DV2-HBV-10 to be acceptable. The immunogenicity analysis results for each subpopulation (diabetes, age, sex, obesity, smoking) in the CSR for Study HBV-23 appear to be acceptable. However, the assertion of statistical significance within racial subpopulations is not supported by appropriate analyses of the data. Overall, the immunogenicity data in Studies HBV-10, HBV-16, and HBV-23 show Heplisav has statistically significantly greater immunogenicity than Engerix-B in the adult population.

However, the statistical analyses presented in Section 8 provide evidence of elevated risk of AMI associated with Heplisav. Therefore, this suggestion of elevated risk warrants further investigation, preferably prior to licensure of Heplisav.