

STN	125428/0/74
CBER Received Date	8 February 2017
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Division / Office	DVRPA /OVR
Committee Chair	Marian E. Major, Ph.D.
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Priority Review	No
Reviewer Name(s)	Mridul K. Chowdhury, Ph.D.
Review Completion Date / Stamped Date	24 October 2017
Supervisory Concurrence	Tsai-Lien, Ph.D., Team Leader, VEB
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	John Scott, Acting Director, Division of Biostatistics
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.

Statistical Review of Clinical Safety
Addendum to Statistical Review of STN 125428/0/42
(Heplisav Vaccine, EDR Review Memo 15 Nov 2016)

1. Executive Summary

This review is an addendum to the earlier Statistical Review of BLA STN 125428/0/42, completed on 15 November 2016. This addendum reviews additional safety information the applicant submitted in February 2017 in response to the November 2016 complete response (CR) letter the FDA issued. The CR letter pointed out imbalances in cardiovascular and autoimmune adverse events (AEs) between trial arms, and the applicant's response included post hoc analyses of major adverse cardiovascular events (MACE). From the MACE analyses, the relative risk (RR) imbalance in this composite 3-point MACE event between arms (Heplisav-B vs Engerix-B) was more than two-fold (RR=2.32, 95% CI: 0.96, 5.60, applicant's analysis; 95% CI: 0.99, 5.46, reviewer's results¹ from the asymptotic method in StatXact) in study DV2-HBV-23. Since this is a safety evaluation, consideration of the upper confidence limit is appropriate to see what level of RR can be ruled out with the given sample size. In this regard, a RR of MACE of 5.60 associated with Heplisav compared to Engerix-B cannot be ruled out at the 95% confidence level and without consideration of multiplicity. Please refer to the medical officer's report for further details about MACE. With regard to acute myocardial infarction (AMI), where the applicant reports for Heplisav vs Engerix-B a RR=6.97 (95% CI: 0.92, 52.97), a RR of almost 53 cannot be ruled out with the given sample size. Overall, concerns regarding imbalance of serious adverse events (SAEs) remain after review of the additional information included in the current submission. Please refer to Table 1 and Table 2 for further details.

2. Sources of Clinical Data and Other Information Considered in the Review

2.1 Review Strategy

For this BLA resubmission, I provided statistical review of safety data. Dr. Ruoxuan Xiang performed additional safety review based on Bayesian methodology, as well as statistical review of the immunogenicity data.

2.2 BLA Documents That Serve as the Basis for the Statistical Review

This statistical review was based on the following documents:

STN 125428/0/42 submitted 16 March 2016.

Module 1: Administrative information and labeling.

¹ Numerical values were same as obtained from the Koopman's score method.

Module 2: Overviews of clinical safety.

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 datasets and SAS programs.

STN 125428/0/45 IR response submitted 11 April 2016.

STN 125428/0/54 IR response submitted 13 July 2016.

STN 125428/0/65 IR response submitted 3 October 2016.

Modules 1.11.3: IR response and MACE report.

Module 5: Clinical study reports.

STN 125428/0/74 IR response submitted 8 February 2017.

Modules 1.2, 1.11.3: Administrative information and clinical information amendment.

Module 2: Technical document summaries.

Module 5: Clinical study reports.

2.3 Vaccine and Related Biologic Products Advisory Committee (VRBPAC) Discussions on Safety.

This BLA has been the subject of two VRBPAC meetings. The first of these was held on 15 November 2012. The Committee voted 8:5 (with one abstention) that the available safety data were inadequate to recommend Heplisav-B's approval. The BLA showed occurrence of autoimmune adverse events, including one case each of Guillain-Barre syndrome and Wegener's Granulomatosis (study DV-HBV-10) and Tolosa-Hunt syndrome (study DV-HBV-16) in the investigational arm. The Committee recommended that another study be performed to obtain a larger pre-market safety database.

Study DV2-HBV-23 was conducted largely to obtain additional safety data. The second VRBPAC convened on 28 July 2017, and discussion centered around the safety of Heplisav-B, specifically autoimmune AEs and the apparent elevated risk of AMI compared to Engerix-B.. The Committee voted 12:1 (with 3 abstentions) that the safety data were adequate to support Heplisav-B's safety. The committee members considered that the observed differences in AMI could be due to chance, and considered as well that a sound post marketing surveillance study could provide early detection of an AMI signal in adult recipients of the Heplisav-B vaccine.

3. Safety Analyses

Results. The summary information about SAEs in study DV2-HVB-23, as presented in the previous BLA review, is provided again here in Table 1. Overall, the table reveals imbalance in SAE incidences in the Heplisav arm compared to the Engerix-B arm, as reported for deaths, AMI, and autoimmune events discovered in the previous BLA review. Since the lower confidence limits can include RR of 1 merely due to insufficient sample size, I looked also at the upper CI limit to see what level of RR can be ruled out with the given sample size. This latter approach is similar to testing non-inferiority (Fleming 2008a, 2008b). For these SAEs, the 95%

confidence upper limits of RR (Heplisav vs Engerix-B) suggest that the possibility of several fold excess risk cannot be ruled out with the given sample size.

Table 1: Summary information about SAEs, Safety Population, DV2-HBV-23.

# Subjects reporting AEs	Heplisav (N=5587)	Engerix-B (N=2781)	Total (8368)	Relative risk ^c (95% CI)	Relative risk ^c (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 AIAEs and AESIs adjudicated 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)

Source: Statistical Review (BLA 125428/0/42) Memo in EDR, 15 November 2016.

*9 excluded from Heplisav-B and 3 excluded from Engerix-B, in RR calculations. The excluded deaths were due to illicit drug overdose or injury, based upon narratives submitted and were not considered by the medical officer to be potentially related to vaccine. **Source: CSR DV2-HBV-23, Table 12-9, page 88 of 138 (BLA 125428/seq no. 0040). ^cHeplisav vs Engerix-B.

Based on MACE information submitted as IR response (BLA 125428/0.65, module 1.11.3, Response to IR (2) 9 September 2016, Appendix E, p. 50/55), Table 2 presents MACE events and their relative risks (RR). Please refer to the medical officer's report for details about MACE.

Table 2: Additional summary information of SAEs, Safety Population, DV2-HBV-23

# Subjects reporting AEs	Heplisav (N=5587)	Engerix-B (N=2781)	Total (N=8368)	Relative risk ^c (95% CI) ^e
Death ^a from cardiovascular cause ^a	11	3	14	1.83 (0.55, 6.07)
SMQ narrow MI ^{**}	19	3	22	3.15 (1.00, 9.98)
Composite 3-point MACE ^{**} event	28	6	34	2.32 (0.99, 5.46)

Source: Adapted from BLA 125428/0.65, module 1.11.3, Response to IR (2) 09 September 2016, ^aTable 6-1, p. 36/55, ^{**}Appendix E, p. 50/55.

^aPlease refer to medical officer's report for details on preferred terms regarding these deaths.

^cHeplisav vs Engerix-B. ^eAsymptotic calculations.

The 95% upper confidence limits were 6.07, 9.98, and 5.46 for death, SMQ narrow MI, and MACE, respectively, suggesting that risks associated with Heplisav of several fold higher compared to Engerix-B cannot be ruled out, with the given sample size.

As an additional exploratory safety analysis, I calculated 90% confidence intervals to consider the findings, allowing a lower nominal level of confidence. Based on these intervals, which are (1.18, 8.41) for standard medical query (SMQ) narrow MI and (1.13, 4.79) for MACE, the 90% confidence upper limits suggest that RR of up to 8 fold cannot be ruled out for the former and up to almost 4.8 fold for the latter, with the given sample size and without considering multiplicity. Please refer to the medical officer's report for details about the term SMQ narrow MI.

Since age is a known risk factor, I further explored the AMI and cardiac SAEs by defining post-hoc strata age <50 years and age ≥ 50 years, with results presented in Table 3. The risks for AMI and cardiac SAEs appear to be prominent in the ≥ 50 year age group, with upper confidence limits for RR ranging from about 3 to almost 36, indicating that risks up to such high level

Table 3: AE Relative Risk (RR) for Heplisav vs Engerix-B, by age categories, DV2-HBV-23

AE	Age (yrs) category	Heplisav-B n/N	Engerix-B n/N	Relative Risk (RR) ^a	95% CI ^c
AMI	Age 50+	12/3186	1/1588	5.98	(1.00, 35.85)
AMI	Age <50	2/2401	0 ^b /1193	^b ∞	(0.26, ∞)
Cardiac AE	Age 50+	47/3186	13/1588	1.80	(0.99, 3.29)
Cardiac AE	Age <50	5/2401	2/1193	1.24	(0.28, 5.54)

Source: Reviewer's analysis, Safety Population, based on data submitted to BLA 125428/0/42.

^aHeplisav vs Engerix-B. ^bBecause of observed zero in cell, the RR point estimate was not computed.

^cAsymptotic calculations.

cannot be ruled out with the given sample size. For individuals < age 50, there were 2 AMIs in the Heplisav group versus none in the Engerix-B group (with point estimate and upper CI limit not calculated due to 0 denominator). For cardiac AE, relative risk in the 50+ age group was higher than in the younger group (1.80 vs 1.24). Both CIs included the value 1, but based on the sample size, the possibility for RR being as high as almost 5.5 cannot be ruled out in view of the upper confidence limit in the <50 age group. However, these results should be interpreted with caution, since post hoc subgroup analyses can be subject to both spurious negative associations as well as spurious positive findings, depending on how the CIs are interpreted.

Please refer to Dr. Ruoxuan Xiang's review for additional statistical safety analysis based on the Bayesian approach.

Integrated safety. The applicant pooled safety information from pivotal studies DV2-HBV-10 and DV2-HBV-16 of the initial BLA and from pivotal study DV2-HBV-23 conducted in response to the CR. The pooling of cardiac safety information from these studies had limitations, a main one being that the study populations had different age ranges and age is a known risk factor for cardiac events. In these three studies, respectively, the age ranges were 11-55, 40-70, and 18-70 years. Thus, the pooled data are not discussed in this review.

Applicant's general approach. The resubmission included a number of post-hoc approaches regarding the observed AMI AEs. The main ones are the following:

(1) Partition of AMIs by AE start date, before Day 196 and after Day 196. Day 196 is equivalent to 24 weeks after the last vaccination with Heplisav or 4 weeks after the last vaccination with Engerix-B. In the time period of < Day 196, the AMIs were 6 in the Heplisav group vs 0 in the Engerix-B group, which did not allow computing the RR point estimate because of zero in the denominator, but led to RR 95% CI LB of 0.78 and RR 90% CI LB of 1.10 (asymptotic method), with N=5587 receiving Heplisav and N=2781 Engerix-B. In the time period >Day 196, the AMIs were 8 and 1 in Heplisav and Engerix-B groups, respectively, and the RR was

3.98 (95% CI: 0.65, 24.53; 90% CI: 0.82, 19.27), with CI including the value 1 but also indicating a RR as high as 24 cannot be ruled out at a 95% confidence level. Similar conclusion holds for RR values as high as 19 with 90% confidence. These post-hoc results, individually with smaller numbers of events in each time period, did not yield the same conclusion with the comparison of 14 (Heplisav) vs 1 (Engerix-B) AMIs reported in the entire trial (RR=6.97, 95% CI: 1.17, 41.44).

(2) The resubmission compared AMIs observed vs expected for study DV2-HBV-23 using MACE and risk-prediction models. The comparisons were 14 vs 13 in the Heplisav group and 1 vs 6 in the Engerix-B group (Table 3-4, BLA 125428/0.65, module 1.11.3, Response to IR 2 dated 9 September 2016, p. 19/55). To explain the imbalance in AMIs, the applicant claims that fewer than expected AMIs were observed in the comparator Engerix-B group. Given that the trial was randomized and observer-blinded, this argument does not seem compelling.

Conclusion: Overall, the data suggest elevated risk for acute myocardial infarction in the Heplisav recipients compared to the Engerix-B recipients. Therefore, I conclude that these data do not support safety of the Heplisav vaccine.

References:

Thomas R. Fleming. Current issues in non-inferiority trials. *Statistics in Medicine* 2008a; 27:317-332.

Thomas R. Fleming. Identifying and addressing safety signals in clinical trials. *New England Journal of Medicine* 2008b; 359: 1400-1402.