Dear Elaine,

We have the following requests for information:

Regarding Safety for Study HBV-23:

We acknowledge your complete study report (CSR), datasets, narratives and case report forms (CRFs) for selected subjects and events, and other supporting documents submitted for Study HBV-23. We also acknowledge your Summary of Clinical Safety integrating safety from all studies and have the following requests:

1. For study HBV-23, please provide narratives and CRFs for all subjects who reported a serious adverse event (SAE) with a System Organ Class (SOC) of Cardiac Disorders. Please ensure there is a full narrative that describes each cardiac SAE that was reported. For example, a narrative for subject 140-099 was submitted for the SAEs of cardiac failure, atrial fibrillation, cardiac ventricular thrombosis, pneumonia, pleural effusion, pulmonary embolism, sepsis, and ischemic hepatitis. However, you did not provide a narrative for the SAE of acute myocardial infarction for subject 140-099, which was reported at a different time than the events listed above. The narratives should include at a minimum the cardiac diagnosis, basis for diagnosis, temporal relationship to vaccination, all co-morbid conditions, the treatment and outcome.

2. We acknowledge your analysis of the imbalance in SAEs with an SOC of Cardiac Disorders and the imbalance in acute myocardial infarction observed in HBV-23 in the CSR on page 104 and your analysis of these events in the Summary of Clinical Safety on page 82. Please submit any other analyses you have performed or are performing in order to assess these imbalances.

3. For subject 140-099, who reported the SAEs of acute coronary syndrome, acute myocardial infarction, and later cardiac ventricular thrombosis, among others, please clarify how many events of cardiac ventricular thrombosis occurred during the study. One SAE of cardiac ventricular thrombosis is noted in the datasets. The narrative provided for this subject for the SAEs of cardiac failure, atrial fibrillation, cardiac ventricular thrombosis, pneumonia, pleural effusion, pulmonary embolism, sepsis, and ischemic hepatitis notes that he had a “prior history of left ventricular thrombosis”. Please clarify when this subject acquired a history of left ventricular thrombosis – prior to study enrollment, coincident with the ST elevation MI as seems to be implied from the description of events on page 82 of the CSR, or another time. If another event of cardiac ventricular thrombosis occurred while the subject was enrolled in the study, please clarify why this was not reported as an AE. Please also provide the narrative for the SAE of acute myocardial infarction, as requested in #1 above.

4. Please provide a brief narrative and the CRFs for the following subjects reporting non-serious cardiac MAEs:

a. Subject 122-631, who received Engerix-B and reported the non-serious MAE with an investigator term of "cocaine induced coronary vaso spasm", which was coded as the preferred term "drug abuse." Please also state your rationale for selecting the preferred term of "drug abuse" instead of "arteriospasm coronary."

b. Subject 125-359, who received Engerix-B and reported the non-serious MAEs of chest pain and "catheterisation cardiac".

c. Please also provide the total number from each arm of the study all cardiac MAE's not considered to be SAE's.

5. We note an imbalance in new-onset adverse events of special interest (AESIs), including autoimmune events, between study groups in study HBV-23. We acknowledge the Safety Evaluation and Adjudication Committee's assessment of these events and your analyses of this imbalance presented in the CSR and the Clincal Summary of Safety. Please submit any other analyses you have performed or are performing in order to assess this imbalance.

6. Subject 131-035 reported the treatment-emergent AE of granulomatous dermatitis, for which sarcoidosis was a primary diagnosis in the differential and for which the dermatopathologist makes the following recommendation "Sarcoidosis should be excluded clinically". The narrative states that the subject did not receive a pulmonary consult and chest computed tomography to evaluate for sarcoidosis because the subject's insurance denied the request, leading the subject to decline the studies. Given the events of granulomatous disease that were identified in previous studies, the primary objective of HBV-23 was to evaluate the safety of HEPLISAV, and a secondary objective was to describe the frequency of specific new-onset granulomatous diseases, please provide your rationale for not pursuing a complete evaluation to rule out a systemic granulomatous disease in subject 131-035.

7. For subject 115-124, who reported the AE of "dry mouth", we note that the event start date is listed as study Day 267, but the action taken with regard to treatment (Engerix-B) is drug withdrawn. Day 267 is well after the subject should have received the third study injection. Please clarify. In addition, as per the narrative, this subject was reporting symptoms of dry mouth prior to Day 267, yet the rheumatologist assessed her as having xerostomia on Day 267. Please explain why Day 267 was chosen as the AE start date.

8. In reviewing subject narratives for AESIs, which may have a prolonged period between symptom onset and diagnosis, we note inconsistencies in the reported AE start dates. For example:

a. Subject 129-084: Systemic lupus erythematosus is reported with a start date of August 17, 2014, which is when the subject's hand pain worsened. She was evaluated by a rheumatologist and received the diagnosis in January and February

2015. This start date is based upon symptom starting or worsening when an evaluation and diagnosis occurred later.

b. Subject 115-124: Xerostomia is reported with a start date of April 28, 2015, which is when the subject was evaluated by a rheumatologist who diagnosed xerostomia. She was referred to an otolaryngologist for dry mouth on November 12, 2014 and presumably symptoms preceded this date. This start date is based upon diagnosis when symptoms clearly preceded evaluation and diagnosis.

c. Subject 130-115: Autoimmune thyroiditis is reported with a start date of June 16, 2014, which is the day the subject received her pre-vaccination blood draw and was first dosed with study vaccine. An abnormal TSH is first reported in the narrative on July 16, 2014. Analysis of a banked serum sample, presumably by Dynavax, collected prior to study vaccine, demonstrated abnormal TSH and "…the investigator changed the event onset date..." This start date is based upon analysis of banked sera.

d. Subject 125-133: Autoimmune thyroiditis is reported with a start date of July 23, 2014, which is the day that an abnormal TSH is first reported in the narrative. Subsequently, an analysis of a banked serum sample, presumably by Dynavax, collected prior to study vaccine on June 11, 2014, demonstrated an abnormal TSH. This start date is based upon first clinically recognized thyroid abnormality.

e. Was there a systematic way for reporting AE start dates? Please explain how you instructed investigators to assign the AE start date.

9. Subject 134-228 reported the potential autoimmune event of "myalgias". Please provide any available additional information on this subject's "intermittent headaches with diminishing vision in his left eye," which was associated with floaters, confusion, and hallucinations, and for which he underwent temporal artery biopsy (negative) and received two courses of steroids. Specifically include the following:

a. Were the headache and visual changes further evaluated by a neurologist or ophthalmologist?

b. Was any imaging obtained to evaluate these symptoms?

c. Did the subject's diminished vision and headaches resolve following steroids?

d. To what etiology were the headaches and visual changes attributed?

e. Please provide a narrative, admission note, discharge summary, pathology report from the temporal artery biopsy, and the reports of any head imaging performed from his hospital admission for pneumonia, during which the evaluation for temporal arteritis occurred, in September 2014.

10. We acknowlwedge your analysis of the imbalance in deaths observed between the study groups in HBV-23 presented in your CSR and your Clinical Summary of Safety. Please submit any other analyses you have performed or are performing in order to assess these imbalances.

11. Please provide the narratives and CRFs for the following subjects who reported the following SAEs:

    a. Subject 119-279, who reported the SAE of chest pain on Day 7 following Dose 2 of HEPLISAV.

    b. Subject 130-219, a 34 year-old woman who reported the SAE with investigator term "end stage renal failure" on Day 10 following Dose 2 of HEPLISAV of 7 days duration.

    c. Subject 131-103, who reported the SAE of cerebrovascular accident the day of Dose 1 of HEPLISAV.

    d. Subject 129-038, who reported the SAE of transient ischemic attack on Day 24 following Dose 1 of HEPLISAV.

    e. Subject 132-078, who reported the SAE of cerebrovascular accident on Day 11 following Dose 1 of HEPLISAV.

    f. Subject 105-314, who reported the SAE of chronic obstructive pulmonary disease on Day 6 following Dose 1 of HEPLISAV.

12. On page 55 and 56 of the CSR for study HBV-23, you note that 469 subjects (5.6%) were lost to follow-up. You also note that you utilized a vendor to research the status of 271 subjects considered lost to follow-up. Please explain why only 271 of the 469 subjects lost to follow-up were referred to the vendor and how you determined which subjects were referred. Please comment on whether these subjects were selected at random or on what basis subjects were selected to be referred to the vendor.

13. On page 57 of the CSR for study HBV-23, you note that 48 subjects had a major protocol deviation of "MAE/SAE." Please explain what a major protocol deviation of this category means and how it impacted the disposition of these 48 subjects.

14. For subject 125-113, who reported the event of "lung cancer metastatic", please identify the histological type of lung cancer.

15. Please provide a brief narrative of subject 124-171 who reported the MAE of urticaria two days following the first injection with HEPLISAV, which resulted in discontinuation

from study treatment, but was assessed as unrelated. Additionally, please identify the alternative cause to which the urticaria was attributed.

16. Please clarify how Table 12-18, "Study Drug-Related Treatment-Emergent Medically-attended Adverse Events That Were Primary Reason for Early Study Treatment Discontinuation by System Organ Class and Preferred Term (Safety Population)" on page 107 of the CSR was constructed. There appear to be five events that were assessed by the investigator as at least possibly related and have an action taken of "drug withdrawn" that do not appear in the table (deep vein thrombosis in two subjects, one in each of the HEPLISAV and Engerix-B arms, urticaria in the HEPLISAV arm, and rash in two subjects in the Engerix-B arm).

17. There are several entries in the dataset ADAE that appear to be the same event listed multiple times when an event progressed from non-serious to serious (for example, subject 118-229 chest pain and angina pectoris). Event terms are the same or similar and the stop date for one event is the same as the start date for the other event. Please clarify if this dataset intended to capture the evolution of AEs. If so, which, if any, dataset captures the single event with the greatest severity? This information is critical to be able to reconcile the number of events per subject. Please provide a list of adverse events that appear in the datasets as two separate events but that describe the same actual event. This list should include, at a minimum, subject number, reported term, preferred term, toxicity grade, seriousness, start date, end date, study onset day, and duration of the events. The above information should be provided for each event entry as it is currently listed in the ADAE dataset. If the number of events that are currently listed as more than one entry in the ADAE dataset, but that actually describe the same event, exceeds 15, please provide a revised ADAE dataset with one entry for each adverse event. The severity and seriousness of each event should reflect the greatest values of these variables and the duration and start and stop variables should reflect the total duration of the event.

18. For subject 126-079, it appears that all eight of the subject's adverse events are listed with an action taken of "drug withdrawn," including the MAE of dysphonia that starts on study day 346 (after all injections should have been administered). For other subjects, additional adverse events reported as occurring after the event(s) that leads to withdrawal are assessed as "dose not changed." Withdrawal of treatment should be attributed to one event or one group of events and not to every event that is reported subsequent to the decision to withdraw study treatment. Please describe the event(s) subject 126-079 reported that led to the decision to withdraw study treatment.

Regarding the Summary of Clinical Safety:

19. Page 91 of the Summary of Clinical Safety (BLA 125428 Sequence 0040 Module 2.7.4) states that "The overall rate of myocardial infarction per person-year of follow up in the combined dataset of the large US studies in the TSP, HBV-16 and HBV-23, is consistent with National Heart, Lung, and Blood Institute (NHLBI) population estimates adjusted for age, sex, and race (SCS Table 2.2.1.1)" (Mozaffarian, Benjamin et al. 2015). Please

provide a clear comparison of the specific rate used from the paper by Mozaffarian, et al., as well as the specific rate determined from studies HBV-23 and HBV-16 in order to support this statement.

20. Page 91 of the Summary of Clinical Safety notes that "While the NHLBI dataset describes events rather than subjects and is limited to events of myocardial infarction, the number of subjects in the pooled safety populations of HBV-16 and HBV-23 reporting events identified by the Myocardial infarction SMQ (22 in the HEPLISAV treatment group and 5 in the Engerix-B group) is similar to the expected number of events based on the NHLBI data." Please provide a comparison of the number of events in the pooled safety population of HBV-16 and HBV-23 to the expected number of events based on the NHLBI data. Also, please describe how the expected number of events was calculated.

21. Please provide the same comparisons, as described above in Questions #19 and #20 between those population estimates described in Mozaffarian, et al., and the specific rate and number of events determined from study HBV-23 alone.

22. Please provide the specific rate determined from a combination of studies HBV-10, HBV-16, and HBV-23.

Regarding the Immunogenicity of Studies HBV -10 and HBV-16 :

In your Complete Response dated March 15, 2016 (CR dated February 22, 2013), you submitted revised Complete Study Reports (CSRs) for studies DV2-HBV-10 and DV2-HBV-16. You state that you determined the revisions were necessary following audits you performed after another regulatory agency identified concerns with a study not included in your U.S. licensing application. Following review of your revised data and responses to our information requests seeking further clarification, we have identified the following issues:

23. There remain inconsistencies between the new datasets, the old datasets, and the tabular summaries of the data that you have provided. In order to perform a complete review of the data from studies DV2-HBV-016 and DV2-HBV-010, CBER requires submission of accurate datasets and summaries, along with clear explanations for inconsistencies and differences among versions of these files that have already been submitted. Specifically, we have noted the following inconsistencies that need to be addressed:

    a. In study DV2-HBV-016 subject 35020 is identified in the original 2012 ADSL16 dataset (submitted with the original BLA, amendment 0 4/28/12) as included in the lot consistency per protocol population (LCPPFLG = 1). Revised April and May ADSL datasets (submitted in amendments 45 and 49) and the May tabular response to the FDA April 27, 2016 IR (amendment 49) indicate that the subject is newly excluded (LCPPFLG=0). However, in the response to the FDA June 28, 2016 IR (amendment 54), the July ADSL dataset and the July tabular presentation of data indicate that the subject is ***not*** newly excluded (ELCPP = N). Please explain how the original 2012 ADSL16 dataset, the April and May ADSL datasets and the May tabular presentation and the July HBV-16-EX dataset and tabular presentation were

generated such that the fields LCPPFLG and ELCPP were populated with the current results, how generating those data resulted in conflicting results and which results are accurate.

b. In the original DV2-HBV-16 2012 ADSL16 dataset the NIPPFLG for all subjects = ".". Please explain by what flag and in what dataset the non-inferiority per protocol population was identified.

c. In DV2-HBV-16 the following subjects are identified as newly excluded (identified as NIPPFLG = 0) from the non-inferiority per protocol population in the revised ADSL datasets submitted April 8, 2016 and May 27, 2016 (amendments 45 and 49) and in the hbv-16-ex dataset submitted July 7, 2016 (identified as ELCPP = Y, amendment 54) : subjects 37002, 37003, 37004, 37005, 37006, 37007, 37009, 37011, 37013, 37014, 37015, 37016, 37020, 37021, 37024, 37025, 37301, 37302, 37304, 37305, 37308, 37310, 37312, 37313, 37314, 37317, 37320, 37601, 37602, 37603, 37604, 37605, 37606, 37607, 37611, 37612. However in your May 27, 2016 response to FDA's April 27, 2016 IR, a tabular presentation of original data from 2012 and revised data from 2016 indicate that the subjects were originally ***included*** in the NIPPFLG and remain ***included*** in the NIPPFLG in the revised 2016 datasets. Please explain in which 2012 dataset subjects were designated as being included or excluded from the non-inferiority population (NIPPFLG = 0 or 1; see question #2). Please explain how the tables presented in the response to the April 27, 2016 IR were generated, i.e., what dataset(s) were used. Please explain the apparent discrepancy between the April, May and July datasets and the May tabular presentation of the data.

24. In your response, we request that you clearly describe which database contains accurate final study information for studies DV2-HBV-10 and DV2-HBV-16. We also request that you provide documentation of all differences between your final databases, other databases you have sent us and the original 2012 databases for these studies, and explanations and documentation for those differences, to include an accurate accounting of all <u>newly</u> excluded and <u>newly</u> included subjects, for the non-inferiority and lot consistency per protocol populations for Studies DV2-HBV-10 and DV2-HBV-16. We also request accurate summaries based on the final datasets. Provision of the following information would satisfy this request for documentation of these changes:

a. One new master ADSL dataset each for study DV2-HBV-10 and study DV2-HBV-16 in which the master ADSL dataset merges the original ADSL dataset used to generate the CSRs for DV2-HBV-10 and -16 in 2012 with the respective revised ADSL dataset used to generate the revised CSRs for DV2-HBV-10 and -16 in 2016. Each subject would have two rows in this master dataset: one representing 2012 data and one representing 2016 data. Each row must clearly designate which is the 2012 data row and which is the 2016 data row.Each dataset would have the following additional columns: a column indicating if the LCPPFLG changed from 2012 to 2016 (y or n), a column indicating if the NIPPFLG changed from 2012 to 2016 (y or n). Please make sure that

all columns in submitted datasets include the definition for each variable within the column info description box.

b. A separate excel file that replicates each dataset and provides additional information to describe changes between 2012 and 2016, including highlighting of all fields that changed from 2012 to 2016 and inclusion of a 2016 outcome column in the excel file containing a comment that explains why the change took place. The comment in this column should link to the source data that identifies the protocol violation/deviation or correction that warrants the change in population assignment. Please see the attached sample excel file.

BookL.xls

c. A document for each dataset that lists the changes between 2012 and 2016 and why the change was made. Please include in the document a summary of the total number of subjects with changes from 2012 to 2016 (i.e. In DV2-HBV-16 a total of X subjects were newly excluded from the NIPP, a total of X subjects were newly included in the NIPP, a total of X subjects were newly excluded from the LCPP, a total of X subjects were newly included in the LCPP.)

25. Please confirm that the revised CSRs for study DV2-HBV-10 and DV2-HBV-16 are accurate and that no other datasets were affected by the inconsistencies observed in the DV2-HBV-16 ADSL datasets.