

From: Agnihothram, Sudhakar
Sent: Monday, October 16, 2017 7:37 PM
To: Elaine Alambra <EAlambra@dynavax.com>
Cc: Berkhousen, Katherine <Katherine.Berkhousen@fda.hhs.gov>; Daemer, Richard J. <Richard.Daemer@fda.hhs.gov>
Subject: ** STN 125428/0 : Summary of Post Marketing Studies**

Dear Elaine,

Below is a summary of the post marketing studies that you proposed in your HEPLISAV-B application, STN 125428/0. The text provides description of the studies, and includes the Requirement/Commitment dates we will be requesting of you.

Based on appropriate scientific data, we have determined that you are required to conduct the following study:

1. "Post-Marketing Observational Study to Evaluate the Occurrence of Acute Myocardial Infarction in Adults 18 Years of Age and Older Who Receive HEPLISAV-B Compared with Another Hepatitis B Vaccine." As outlined in your submission of October 8, 2017, using a non-randomized clustered design, the study conducted in Kaiser Permanente Southern California will evaluate approximately 25,000 patients who receive HEPLISAV-B and approximately 25,000 patients who receive another hepatitis B vaccine. Two interim and one final comparison between vaccine groups of unconfirmed acute myocardial infarctions will be conducted and reviewed by an independent data monitoring committee. The final primary analysis will be performed on confirmed acute myocardial infarctions. In the final analysis, the study will have approximately 87% statistical power to exclude an upper bound of a hazard ratio of ≥ 2.0 .

We acknowledge the timetable you submitted on October 8, 2017, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: December 31, 2017

First Interim Analysis Report Submission: August 31, 2019.

Second Interim Analysis Report Submission: February 29, 2019.

Study Completion Date: May 31, 2020

Final Analysis of Unconfirmed Events Report Submission: September 30, 2020.

Final Report Submission: June 30, 2021.

We acknowledge your written commitment(s) as described in your letter(s) of October 8, 2017, as outlined below:

2. Post-Marketing Observational Surveillance of the Safety of HEPLISAV-B in Adults 18 years of Age and Older to Evaluate the Incidence of New Onset Immune-mediated Diseases, Herpes Zoster, and Anaphylaxis. As outlined in your submission of October 8, 2017, using a cohort design, the study conducted in Kaiser Permanente Southern California and Kaiser Permanente Northern California will evaluate approximately 30,000 patients who receive HEPLISAV-B and approximately 30,000 patients who receive another hepatitis B vaccine.

Final protocol submission: December xx, 2017

Study/Clinical trial completion: August xx, 2020

Final Report Submission: February xx, 2022

3. To establish a pregnancy registry for providing information on outcomes following pregnancy exposure to HEPLISAV-B. Data in this registry will be used to assess risks relevant to pregnancy, including pregnancy outcomes of major congenital malformations, pre-term births, spontaneous abortions, still births, pre-eclampsia and thromboembolic events. The registry will prospectively collect information on 250-300 pregnant women.

Final protocol submission: Feb 9, 2018

Study/Clinical trial completion: August 9, 2023

Final Report Submission: December 31, 2023

Please provide the dates where we have marked 'xx' and edit the proposed dates, as needed. Please provide the new date(s) in track changes. We request a response of 48 hrs.

Thanks,
Sudhakar

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