

From: Agnihothram, Sudhakar
Sent: Wednesday, June 07, 2017 11:27 AM
To: 'Elaine Alambra'
Cc: Berkhausen, Katherine; Daemer, Richard J.
Subject: Information Request Regarding Risk Management Plan Version 2.0

Hi Elaine,

We need the following clarification on your response to the Information Request (dated May 18 2017), regarding Risk Management Plan Version 2.0.

Amendment Referred

Risk Management Plan Version 2.0. BLA 125428/ SEQ No. 0072

Response to Information Request 18 May 2017. BLA 125428/ SEQ No. 0088

(1) On page 2 of your response to the IR, your reply to the question 1,a,i "*Most recent estimate of KPNC members ages 18 years or older eligible for Hepatitis B vaccination*", states that based on the best estimates at the time of concept development, KPNC accrues approximately (b) (4) hepatitis B vaccinees per year among people 18 to 79 years of age, therefore, assuming a 50:50 allocation ratio between HEPLISAV and other hepatitis B vaccines, accrual of 8,000 HEPLISAV recipients per year is meant to be a conservative estimate.

However, the Risk Management Plan version 2.0 (RMP) states that in KPNC, approximately (b) (4) adults are immunized with a hepatitis B vaccine annually and assuming a subject accrual rate of 8,000 subjects per year, it would take 5 years to achieve the goal of 40,000 subjects immunized 1:1 with either HEPLISAV or comparator vaccine.

Please, clarify the discrepancy and confirm the estimates for subject accrual rate per year, and total number of patients per arm.

(2) On page 3 of your response to the IR, your reply to the question 1,a,iv "Potential plans for introduction of HEPLISAV in KPNC" states that "Dynavax would provide HEPLISAV to the KPNC regional pharmacy where it would then distribute it to providing sites"

Would Dynavax provide HEPLISAV to KPNC free of cost or with any kind of incentives? Please provide further details.

(3) In regard to the assessment of a potential association between HEPLISAV and myocardial infarction and other Major Adverse Cardiovascular Events (MACE), we consider that self-controlled risk interval approach is not appropriate to assess this potential signal. Therefore, we ask you to:

(a) Provide additional details on the head-to-head comparison of HEPLISAV vs. other hepatitis B vaccine recipients you propose (on page 11) to investigate this potential association, including details on the "multivariable modeling which may include techniques to adjust for potential differences among cohorts", follow-up period, study period and sample size calculation.

(b) Have you considered using matching techniques?

(4) You state on page 11 of your response to the IR that *“HEPLISAV may be administered preferentially to patients with diabetes, obesity, the elderly, and those with other comorbidities associated with cardiovascular disease risk”*.

(a) What proportion of hepatitis B vaccine recipients at KPNC has these comorbidities? Based on that estimate, what sample size do you anticipate for the HEPLISAV and other hepatitis B vaccine arms?

(b) Would you match the subjects by these characteristics including severity of the condition?

(5) On page 12, your response to the question *“In regard to the study objective: “Comparison of the rates of medical events other than immune-mediated diseases or MACE during risk intervals with control intervals in HEPLISAV recipients” (page 56). Please specify to which medical events you are referring?”* does not specify the conditions that you plan to study. Given that the proposed post-marketing study would observe the study outcomes retrospectively, the events of interest should be defined in advance.

Please specify to which medical events other than MACE and immune-mediated diseases you are referring

(6) According to the data received, an imbalance in herpes zoster occurrence between HEPLISAV and Engerix-B recipients has been observed in the HBV-23 safety population. There were 38 cases among 5,587 HEPLISAV recipients (mostly following second dose administration) vs. 9 cases among 2,781 Engerix-B recipients.

Please justify why this potential signal is not mentioned in the Pharmacovigilance Plan and provide an appropriate approach to address this potential concern.

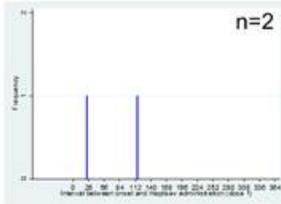
DV2-HB23: Herpes zoster

HEPLISAV: two-dose series at Weeks 1 and 4; placebo given at week 24

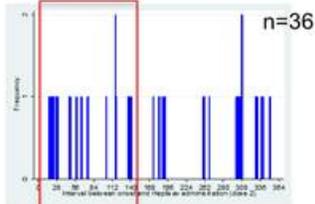
Engerix-B: three-dose series at Week 1, 4, and 24

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Dose 1



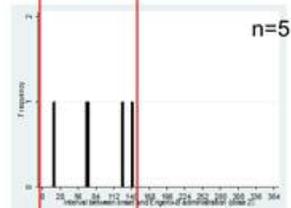
Dose 2



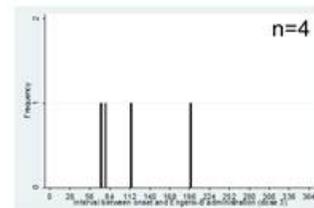
Heplisav population=5,587
Engerix-B population=2,781

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No cases



Dose 3



(7) Given the potential need for a rapid post-marketing assessment, including, but not limited to cardiac events, have you considered using, from the start, additional databases to be able to rule out a relative risk of 2.0 with 90% power within two years after study start? Would you be able to provide interim overall and per dose analyses at one and one and a half year after study start accounting for the alpha-spending limits?

Please send your response by **COB 06/19/2017**.

Thanks, Sudhakar

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