

RECORD OF TELEPHONE CONVERSATION

Submission Information

Application Type	BLA
STN	125428/0.0
Review Office	OVRR
Applicant	Dynavax Technologies Corporation / Lic. # 1883
Product	Hepatitis B Vaccine (Recombinant), Adjuvanted
Trans-BLA Group:	No

Telecon Details

Telecon Date/Time	15-SEP-2017 01:15 PM
Author	AGNIHOTHAM, SUDHAKAR
EDR	No
Post to Web	Yes
Outside Phone Number	18777464263
FDA Originated?	Yes
Communication Categories	AD - Advice
Related STNs	None
Related PMCs	None
Telecon Summary	CBER Dynavax Telecon to discuss issues related to Pharmacovigilance plan
FDA Participants	CBER - Sudhakar Agnihothram, Silvia Perez-Vilar, Ruoxuan Xang, Amelia Horne, Philip Krause, Steven Anderson, , Marian Major, Richard Daemer, Katherine Berkousen, Mridul Chowdhury.
Applicant Participants	Elaine Alambra, Graeme Curie, Rob Janssen, Randy Hyer, Biao Xing.

Telecon Body:

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CBER reviewed the synopses of the pharmacovigilance plan, submitted in STN125428/0/100 by Dynavax on 09/11/2011. Based on VRBPAC's recommendation that the post marketing studies to evaluate the risk of Acute Myocardial Infarctions should yield timely results, CBER provided advice to Dynavax on the following issues.

CBER provided the following advice, as summarized below, to the following points in terms of obtaining final study results faster.

A. Timeliness of the Study Results

i) The ability to obtain the final study results of the study will depend upon will depend on Dynavax's capability to recruit (vaccinate) individuals in a timely manner. Dynavax's current proposal states that "it should take no more than 1 year to achieve the goal of at least 20,000 patients vaccinated with HEPLISAV and approximately 40,000 patients vaccinated with another hepatitis B vaccine". Based on these estimates, the final report would not be submitted to CBER until November 2021 (3.5 years after study initiation), but only if the proposed accrual is completed within one year (final report submission will occur within 16 months after completion of follow-up of the last HEPLISAV recipient).

Hence, CBER advised Dynavax to consider the following:

- a. Completing recruitment within six months
- b. Inclusion of additional healthcare organizations.
- c. The older age groups of Hepatitis B vaccinees be over represented in the study population.
- d. The feasibility of shortening the time of final data analysis from sixteen months to six months, so that the overall time of the study can be shortened to twenty-five months and the final report can be submitted by July 2020.
- e. To provide specific timelines for start of data collection, recruitment completion, end of data collection, DMC meeting/s, case confirmation activities, and FDA availability of interim and final reports.

Dynavax acknowledged CBER's suggestions and indicated that they will consider them. Dynavax indicated that they will also consider including more subjects in the Engerix group, and they could enrich the comparator group by 1:3. CBER cautioned Dynavax that adding more Engerix patients will provide the same power to the analyses, and that they can maintain a 1:2 ratio instead. Dynavax indicated that they will discuss this issue with Kaiser Permanente and will get back to CBER.

ii) CBER further indicated that the post-marketing observational study will be conducted only by Kaiser Permanente Southern California (KPSC) which serves approximately 4.4 million members. However, all previous versions of the proposed study included Kaiser Permanente Northern California (KPNC). Both HMOs together serve a total of 8.5

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million members. CBER asked Dynavax to provide reasons why KPNC will not participate in the current proposal.

Dynavax indicated that the KPNC vaccinates only (b) (4) individuals (not an appreciable sample size as they have had a (b) (4) decrease from 2015 to 2016), the pooling of data from KPNC and KPSC will delay the timing of submission of the interim analyses and final analyses to the FDA, and that KPNC cannot implement the study design proposed by Dynavax.

iii) CBER acknowledged that enrichment of the study population with particular age groups or at-risk groups for cardiovascular disease is challenging given that the observational study will be conducted in medical center organization/s providing routine clinical care. CBER insisted that Dynavax provide the number of expected HEPLISAV vaccinees by age groups (based on differences on cardiovascular risk), overall and stratified by medical center. CBER further suggested that Dynavax looks into the possibility of including additional medical care organizations in which older age groups of hepatitis B vaccinees could be overrepresented.

Dynavax acknowledged CBER's comments and indicated that they will consider the request and get back to CBER.

B. Outcome Misclassification

CBER questioned Dynavax on the potential for outcome for misclassification, as Dynavax had stated that across both Cohorts as Dynavax had stated that "Across both cohorts, approximately 45% of persons with AMI were identified through claims submitted for care delivered outside of KPSC facilities". Dynavax indicated that they will use the information obtained from claims originating outside of KPSC. CBER requested Dynavax to indicate if the quality and completeness of the information obtained from claims originating outside of KPSC is similar to that from AIM episodes attended in KPSC facilities. Dynavax acknowledged CBER's advice.

C. Interim Analyses

CBER suggested Dynavax that they should include addition of one interim analysis that included final number of unconfirmed cases 30 days after end of follow-up for the last Heplisav-B recipient. Dynavax acknowledged CBER's suggestion, and indicated that in an effort to save time, they plan to perform interim analyses roughly at a 1 year mark, or in the event if 42 cases of AMIs have accrued at an earlier time point, they will perform the interim analyses more earlier. CBER emphasized that Dynavax perform the interim analyses as soon as they accrue 42 events, and addition of more events will provide more statistical power to the analyses.

D. Study Analysis/Results

i) CBER indicated that based on the submitted synopsis, Dynavax plans to use a standard covariate adjusted Cox proportional hazards model in their primary analysis, with a propensity score adjusted Cox model and inverse probability of treatment weighted (IPTW) Cox model included for sensitivity analyses. Since the trial is not randomized,

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Heplisav-B and control group may still be different due to potential selection bias. Hence, CBER recommends the IPTW Cox model for the primary analysis, although CBER would still consider results from the other models as well, as additional analyses. Dynavax acknowledged CBER's suggestions, and indicated that they will discuss these specifics with Kaiser Permanente and address them further. CBER further pointed out that despite the proposed study design, physicians still may avoid Heplisav-B vaccination based on the patient risk profile, and patients may choose medical centers offering specific hepatitis B vaccinations.

- ii) CBER suggested that propensity score matching is preferable to adjustment using propensity score as a covariate.
- iii) CBER indicated that the sample size (power) calculation does not appear to account for the cluster design. In a cluster design in which analysis and inference will be at the individual level, the sample size should be calculated accounting for the clustering, specifically the potential similarities among subjects within a cluster (intracluster correlation). Not accounting for the intracluster correlation can lead to loss of power (inflation of Type 2 error probability) due to insufficient effective sample size. Especially when the number of clusters is small and the cluster sizes are large, the standard sample size calculation should be adjusted even if the intracluster correlation is small. This impact applies as well to the statistical analysis, where failure to account for intracluster correlation can inflate the Type 1 error probability, thereby constituting an invalid analysis. Hence, CBER strongly encourages Dynavax to consider the intracluster correlation in the sample size calculation, as well as in the statistical analysis. Dynavax acknowledged CBER's suggestions.
- iv) CBER further suggested that Dynavax include an additional control group comprised a recent historical cohort of hepatitis B vaccinees. Dynavax acknowledged that they will discuss this issue with Kaiser Permanente and, will update CBER.