

From: Hoffman, Kelsy
Sent: Friday, February 12, 2016 9:33 AM
To: Kevin Smyth
Cc: Houck, Christina M; Sen, Goutam
Subject: BLA 125597/0 Information Request

Mr. Smyth,

Please submit the following information as an amendment to your BLA, 125597/0:

1. Please provide a summary of available published data and list of supporting references that address use of Orochol and/or Mutachol Berna in pregnant and/or lactating women.
2. Please provide the following additional information regarding the financial disclosure forms submitted in module 1.3.4:
 - a. Please specify the total number of investigators that are listed in the document attached to your Financial Certification and Disclosure form (Form FDA 3454).
 - b. Please specify the number of investigators who are sponsor employees (including both full-time and part-time employees).
3. Please submit draft labeling for the product package insert in XML format. If this was already submitted, please refer to its location within the BLA.
4. Please submit the coding dictionary (as a SAS transport file, if possible) used for mapping investigator verbatim terms to preferred terms. It should include a list of all investigator verbatim terms and the preferred terms to which they were mapped. If it is only available as a PDF document, it should be submitted in both directions (verbatim → preferred and preferred → verbatim). If a coding dictionary has already been submitted, please refer to its location within the BLA.
5. For all clinical studies submitted to the BLA (i.e., PXVX-VC-200-002, -003, -004 and -005), please submit revised tables for solicited safety data which include an additional row presenting the number and proportion of subjects who reported each solicited adverse event regardless of severity grading (e.g., the number and proportion of subjects who reported any diarrhea).
6. For studies PXVX-VC-200-003, -004 and -005, please submit a separate table for each study describing the rates of comorbidities of all vaccinated subjects (vaccine vs placebo recipients) and all challenged subjects (vaccine vs placebo recipients).
7. The following comments pertain to study PXVX-VC-200-003:
 - a. Please clarify whether the following endpoint was pre-specified as a secondary endpoint: number of days with grade 3 or higher stools.
 - b. We note that the solicited adverse reactions listed in tables 14.5.3.1 and 14.5.3.2 occurred during the in-patient stay following challenge. Please resubmit this table with the following additional information specified:
 - i. Mean (and corresponding standard deviation) and median (and corresponding range) number of days that subjects in the vaccine and placebo groups remained on the inpatient unit following the 10-day and 3-month challenges.
 - ii. For comparisons of each solicited adverse reaction in the 10-day and 3-month challenge groups, p-values for each comparison by severity grading.
 - c. We note that a demographics table was not provided for the immunogenicity evaluable, ITT and memory B-cell analysis populations. Please submit these demographic tables for each of these analysis populations. The tables should include the proportion of subjects in each study group by age, sex, race, ethnicity and ABO blood type.
 - d. Please comment on the extent to which the study population's demographics (including baseline medical history) are comparable to U.S. demographics.
 - e. Please submit a version of Table 16 from the clinical study report which includes geometric mean volumes of grade 3+ stools (with corresponding confidence intervals) by day through 10 days post-challenge.
 - f. Please submit a version of Table 19 from the clinical study report which includes geometric mean peak *V. cholerae* O1 concentration (with corresponding confidence intervals) in the stool.

- g. We note that the lower limit of the 95% CI was provided for efficacy estimates in the clinical study report. Please submit the entire 95% CI for each efficacy estimate, including for the subgroup analyses.
8. Please specify the estimated date that the deferred pediatric study in children 2 through 17 years of age will be completed.
9. Please submit a copy of the following reference: "Orochol Product Monograph, CSL Vaccines Ltd., Australia, 2000. In National Library of Australia."

Thank you,

Kelsy F. Hoffman, Ph.D.

LCDR, USPHS

Primary Reviewer/Regulatory Project Manager

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