

# Information Request Email, July 23, 2014 - BEXSERO

## RECORD OF TELEPHONE CONVERSATION

Submission Type: BLA    Submission ID: 125546/0    Office: OVRR

Product:  
Meningococcal Group B Vaccine

Applicant:  
Novartis Vaccines and Diagnostics, Inc.

Telecon Date/Time: 23-Jul-2014 10:37 AM    Initiated by FDA? Yes

Telephone Number:

Communication Category(ies):  
1. Information Request

Author: KIRK PRUTZMAN

Telecon Summary:  
CBER Comments/IR on iPSP and V72\_57

FDA Participants: KIRK PRUTZMAN, ED WOLFGANG, RAMACHANDRA NAIK

Non-FDA Participants: PATRICIA STOEHR

Trans-BLA Group: No

Related STNs: None

Related PMCs: None

Telecon Body:

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From: Prutzman, Kirk C  
Sent: Wednesday, July 23, 2014 10:37 AM  
To: Stoehr, Patricia (patricia.stoehr@novartis.com)

Cc: Wolfgang, Edward; Naik, Ramachandra  
Subject: STN 125546 - CBER Comment on iPSP and V72\_57

Dr. Stoehr,

Please find attached CBER's comments on your draft iPSP that was emailed to CBER on July 2, 2014, and on your study V72\_57. If you have any questions, please contact Ed Wolfgang, Ramachandra Naik, or me at the information below.

Regards,

Kirk Prutzman, PhD  
Primary Reviewer/Regulatory Project Manager  
CBER/OVRR/DVRPA/CMC3  
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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH  
OFFICE OF VACCINES RESEARCH AND REVIEW  
DIVISION OF VACCINES AND RELATED PRODUCT APPLICATIONS

Date: July 23, 2014

Pages: 4

To: Patricia Stoehr, Ph.D.  
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Subject: Meningococcal Group B Vaccine (Bexsero): CBER's comments concerning Novartis' proposed iPSP and study design for study V72\_57.

We have the following comments in response to your June 12, 2014, email containing your plans to address PREA requirements, the synopsis for study V72\_57 and your proposed iPSP that was emailed to CBER on July 2, 2014.

***CBER Comments regarding the proposed iPSP dated July 2, 2014:***

1. We view Study V72\_57, which evaluates the use of Bexsero in infants/toddlers and includes a US cohort of subjects to be an essential component of a supplemental BLA (sBLA) for use of your vaccine in infants and children 2 months through 9 years of age. Therefore this sBLA should not be submitted until the final report from this study is available for review.
2. Currently, we cannot determine whether your pediatric development program for children 2 months through 9 years of age will be adequate to support traditional approval or whether the accelerated approval pathway, with a required confirmatory study in this age group, will be more appropriate. We will need to consider the results of your confirmatory effectiveness study in adolescents and adults in order to make this determination.
3. In determining the lower age for approved use, we will consider the age of infants vaccinated in the study. Thus, if you intend to seek approval in infants as young as 6 weeks of age, please plan your study so that infants are vaccinated beginning at 6 weeks of age. We recommend the following statutory reason for a partial waiver in infants < 2 months (or < 6 weeks depending on the protocol) as specified under the Pediatric Research Equity Act (PREA) of 2007 (Section 505B) as follows:

*Section 505B(a)(4)(B)(iii): The drug or biological product—(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and (II) is not likely to be used by a substantial number of pediatric patients in that age group.*

4. We recommend that the following statutory reason be cited for deferral of pediatric assessment in individuals 2 months through 9 years of age:

*Section 505B(a)(3)(A)(i): The drug or biological product is ready for use in adults before pediatric studies are complete.*

5. The following additional clarifications are provided pertaining to what studies should be included as deferred pediatric studies in your PSP document:
  - a. Please include those pediatric (planned, ongoing, completed) studies which include an evaluation of the vaccine's final formulation in children 2 months through 9 years of age.
  - b. While the observational safety data from vaccination campaigns, currently underway in Quebec and planned for in the United Kingdom, may provide

supportive data for use in children 2 months to 10 years of age, these data do not need to be listed as a study captured in the pediatric study plan.

6. In Table 5.2 of the iPSP you have designated completed studies to be submitted in a sBLA as “N” (deferral not requested). However, you plan to request a deferral of submission of pediatric assessments to support approval for use in infants and children 2 months through 9 years of age (i.e., the data from these studies will be included in a sBLA). Therefore, please modify the table to designate these studies as “Y” (deferral of submission requested).
7. As noted above we view Study V72\_57 to be an essential component of a sBLA for use of Bexsero in infants and children 2 months through 9 years of age. Section 5 of your draft iPSP lists this study as a deferred study; however Section 9.2 does not provide an outline of the study. Please modify Section 9.2 of the iPSP to provide a *brief* outline of the study to include the study design, objective, age groups, dosing regimen, relevant endpoints and statistical approach. Details of the study are more appropriately described in the protocol and should not be included in the iPSP. In section 10 of the iPSP please include estimated dates for the following: V72\_57 protocol submission; V72\_57 study initiation date; V72\_57 final report submission; and the submission of the sBLA.

***CBER Comments to ‘IR Response’ dated June 12, 2014:***

8. We have the following specific advice pertaining to the study design for Study V72\_57:
  - a. The study power estimates shown appear adequate for the US / North American cohort based on the endpoints you proposed. However, we request that the sample sizes be estimated using the following endpoints: the proportion of subjects with a titer  $\geq 1:16$  to each strain and the proportion of subjects with a titer  $\geq 1:16$  to all strains.
  - b. We note that the immunogenicity assessment assumes a 24% loss of subjects from the per protocol population. While this assumption appears reasonable to assure adequate size sample estimates, we recommend that efforts be undertaken to minimize loss of subjects during the trial. A high drop-out rate reflects adversely on the quality of the clinical trial.
  - c. While exploratory evaluation of a composite safety endpoint is generally acceptable, CBER will evaluate the entirety of safety data. Specific comment on your proposed safety endpoints will be given at the time of the review of a submitted protocol.

In your responses to this information request, please restate each item and follow it with your explanation or clarification. Use of this format helps organize the relevant information and provides a self-contained document that facilitates future reference. In addition, we recommend that you incorporate the CBER recommendations above in a full PSP and submit it as an Amendment to your BLA (STN 125546) as soon as possible, within 30 days of the final rolling submission of the BLA. If you have any questions about this communication, please contact Kirk Prutzman, Ramachandra Naik, or Ed Wolfgang at (301) 796-2640.