

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: 05-Sep-2014 04:58 PM Initiated by FDA? Yes

Telephone Number:

Communication Category(ies):
1. Information Request

Author: KIRK PRUTZMAN

Telecon Summary:
IR regarding immunology data

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:

From: Prutzman, Kirk C
Sent: Friday, September 05, 2014 4:58 PM
To: Stoehr, Patricia (patricia.stoehr@novartis.com)
Cc: Wolfgang, Edward; Naik, Ramachandra
Subject: STN 125546 - Information Request

Dr. Stoehr,

Please find attached a request for additional information regarding STN 125546 (Meningococcal Group B Vaccine). If you have any questions about this communication, please contact Kirk Prutzman, Ramachandra Naik, or Ed Wolfgang at (301) 796-2640.

Regards,

Kirk Prutzman, PhD

Primary Reviewer/Regulatory Project Manager

CBER/OVRR/DVRPA/CMC3

Food and Drug Administration

10903 New Hampshire Avenue

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**DEPARTMENT OF HEALTH AND HUMAN
SERVICES**

**Food and Drug
Administration Silver
Spring MD 20993**

**CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
OFFICE OF VACCINES RESEARCH AND REVIEW
DIVISION OF VACCINES AND RELATED PRODUCTS APPLICATIONS**

DATE: SEPTEMBER 5, 2014 PAGES: 4

TO: NOVARTIS VACCINES AND DIAGNOSTICS, INC

**ATTENTION: PATRICIA STOEHR, PH.D.
Senior Group Manager Regulatory Affairs
Novartis Vaccines & Diagnostics**

**350 Massachusetts Avenue
Cambridge, MA 02139
USA**

FAX: (617) 871-8060

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**FROM: KIRK PRUTZMAN, PH.D.
Regulatory Project Manager**

FAX: (301) 595-1244

TEL: (301) 796-2640

SUBJECT: STN: BL 125546/0 – Request For Information

MESSAGE:

Dear Dr. Stoehr:

We have the following request for additional information regarding STN 125546
(Meningococcal Group B Vaccine):

1. We have reviewed the validation reports for the hSBA conducted at ---(b)(4)--- and ---(b)(4)--- in the context of their intended use. Please be advised that due to the limitations of data submitted to support the lower limit of quantitation (LLOQ) for either dilutional linearity or precision, we consider the hSBA assays to be adequately validated for a LLOQ of either 8 or 16 depending on the laboratory that performed the assay and/or the indicator strain assessed:
 - a. ---(b)(4)--- lab: 8 for the NZ98/254 strain, and 16 for the H44/76, 5/99, and (b)(4)--- strains;
 - b. ----(b)(4)---- lab: 8 for the 5/99 strain and 16 for the H44/76 and NZ98/254 strains.

Please acknowledge.

2. We reviewed the Integrated Summary of Efficacy (Section 5.3.5.3 submitted 23 July 2014). We do not agree with the definition of 4-fold rise used for creation of tables found in Section 3.2.3 Percentage of Subjects with 4-fold rise. Please reanalyze the data for Studies V72_P41, V72_P29, V72P10, and V102_03 for all strains for which data are available, using the LLOQs specified Item 1 and the following definitions of 4-fold rise:

A \geq 4-fold rise in hSBA titer against each strain was observed if:

 - a. For a negative (< 4) pre-immunization titer, the post-immunization titer was at least 16;
 - b. For a positive (≥ 4 but $< \text{LLOQ}$) pre-immunization titer, the post immunization titer was at least 4-fold the LLOQ;
 - c. For a positive ($\geq \text{LLOQ}$) pre-immunization titer, the post immunization titer was at least 4-fold the pre-immunization titer.
3. Using definitions of the LLOQs and \geq 4-fold rise specified above, please provide the following for studies V72_41, V72_29, V72P10, and V102_03:
 - a. A table presenting percentage of subjects achieving a composite response defined as hSBA titer $\geq \text{LLOQ}$ against all indicator strains at one month after the second dose. In addition, please provide a similar table for study V72P10 with post dose 1 data;
 - b. A table similar to Table 3.2.1-1 (ISE, page 51) presenting immunogenicity responses measured by the percentages of subjects with hSBA titers \geq

LLOQ. In addition, for study V72P10, a similar table with post dose 1 data;

- c. A table similar to Table 3.2.3-1 (ISE, page 61) presenting immunogenicity responses measured by percentages of subjects with ≥ 4 -fold rise in hSBA titer;
- d. A table similar to Table 3.3.2-1 (ISE, page 74) presenting, stratified by gender, immunogenicity responses measured by the percentage of subjects with hSBA titer \geq LLOQ. For study V72P10, please include in the table only groups with schedules (0,1) and (0,2). In addition, please provide a similar table for study V72P10 with post dose 1 data.

4. Using the criteria indicated in Item 1, please complete the following Tables A and B for Study V72_41 and V72_29:

Table A: Percentage of Subjects with ≥ 4 -Fold Rise in hSBA Titer by Meningococcal B Indicator Strain

Study (schedule) / Strain (antigen)	Study V72_41 ^{a,b,c} (0,1) N= % (95% CI)	Study V72_29 ^{d,e} (0,1) N= % (95% CI)
H44/76 (fHbp)		
5/99 (NadA)		
NZ98/254 (PorA P1.4)		

a: data for combined lots of rMenB+OMV (Rosia OMV and (b)(4) OMV lots)
b: Study V72_41: please specify evaluable immunogenicity population
c: LLOQ __
d: Study V72_29: please specify evaluable immunogenicity population
e: LLOQ __

Table B: Percentage of Subjects with hSBA Titer \geq LLOQ against all tested Meningococcal B Indicator Strain

Study (schedule) # Indicator Strains Assessed *	Study V72_41 ^{a,b,c} (0,1) N= % (95% CI)	Study V72_29 ^{d,e} (0,1) N= % (95% CI)
3 out of 3 strains		
2 out of 3 strains		
1 out of 3 strains		

a: data for combined lots of rMenB+OMV (Rosia OMV and (b)(4) OMV lots)
b: Study V72_41: please specify evaluable immunogenicity population
c: LLOQ __
d: Study V72_29: please specify evaluable immunogenicity population
e: LLOQ __
*3Indicator Strains: H44/76, 5/99, and NZ98/254

5. Please reanalyze the data for Study V72P13 comparing the geometric mean titers (GMTs) among the lots after setting all values less than the LLOQ to $\frac{1}{2}$ the LLOQ. Please provide the data as presented in Table 11.4.1-1 in the current clinical study report.
6. Please reanalyze the data for Study V72_41 comparing the GMTs among the lots after setting all values less than the LLOQ to $\frac{1}{2}$ the LLOQ. Please provide the data as presented in Table 11.4.1.1-1a in the current clinical study report.
7. For studies V72_41 and V72_29, please describe how the operators were blinded as to subject, group, and time point when assaying the samples in the hSBA.
8. For the purpose of the GMT estimation, titers below the LLOQ are generally set in the analysis to $\frac{1}{2}$ the LLOQ. For study V72_41 and all indicator strains, please perform a sensitivity analysis of hSBA GMTs using maximum likelihood estimation based on a left-censored method (see for example: Nauta J., *Statistics in Clinical Vaccine Trials*. 2010. Heidelberg: Springer).
9. For study V79_29, please supply detailed information on the method used for creation of the immunogenicity subset.

Please provide your responses to this information request in an Amendment to STN 125546. We recommend that you 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. If you have any questions about this communication, please contact Kirk Prutzman, Ramachandra Naik, or Ed Wolfgang at (301) 796-2640.