



DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA/CBER/OVRR/DBPAP

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From: Freyja Lynn, BS
Clinical Serology and Bioassay Reviewer
Division of Bacterial, Parasitic and Allergenic Products
Office of Vaccine Research and Review
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

To: Biologics License Application Submission Tracking Number 125546/0
Meningococcal Group B Vaccine (adsorbed)
Bexsero®

Through: Jay Slater, MD
Director
Division of Bacterial, Parasitic and Allergenic Products
Office of Vaccine Research and Review
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

Subject: Clinical Serology and Bioassay Review of Biological License Application for
Meningococcal Serogroup B Vaccine

Applicant: Novartis Vaccines and Diagnostics, Inc.

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1. Review Identifiers and Dates

1.1. Biologics License Application (BLA) Submission Tracking Number (STN)

125546/0

1.2. Submission received by CBER

23 July 2014

1.3. Review Completed

3 December 2014

1.4. Material Reviewed

The following general module sections of the BLA were reviewed:

m1	Regional
m2	Common Technical Document Summaries
m3	Quality
m5	Clinical Study Reports

A more detailed list of information in the BLA reviewed is provided below by amendment number:

Original submissions dated 16 June 2014, 9 July 2014, 23 July 2014

m1.11	Information Not Covered Under Modules 2 to 5
m1.14	Labelling
m2.5	Clinical Overview
m2.7.3	Summary of Clinical Efficacy
m3.2.P.5	Control of Drug Product (---(b)(4)potency)
m3.2.P.6	Reference Standards or Materials (---(b)(4)potency)
m3.2.P.8	Stability (---(b)(4)potency)
m5.3.1.4	Reports of Bioanalytical and Analytical Methods for Human Studies (meningococcal bactericidal assays)
m5.3.5.1	Study Reports of Controlled Clinical Pertinant to the Claimed Indication, v102_03, v72_29, v72_41
m5.3.5.4	Other Study Reports, V72P13

Amendment 4: Date Submitted: 29 July 2014

m1.11.1	Quality Information Amendment
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Amendment 7: Date Submitted: 19 August 2014

m1.11.1	Quality Information Amendment
m3.2.P.5	Control of Drug Product

Amendment 11: Date submitted 12 September 2014

m1.11.1	Quality Information Amendment
m3.2.P.5	Control of Drug Product

Amendment 12: Date submitted 16 September 2014

m1.11.1	Quality Information Amendment
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Amendment 16: Date submitted 2 October 2014

m1.11.1	Quality Information Amendment
m3.2.P.5	Control of Drug Product

Amendment 17: Date submitted 3 October, 2014

m1.11.3	Efficacy information
m5.3.5.3	Integrated summary of efficacy

Amendment 20: Date submitted 17 October 2014

m1.11.1	Quality Information Amendment
m3.2.P.5	Control of Drug Product

Amendment 30, Date submitted 1 December 2014

m1.11.1	Quality Information Amendment
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1.5. Related Master File, INDs and BLAs

IND --(b)(4), 14605

2. Executive Summary

I reviewed the -(b)(4) potency test for final drug product, also called the immunogenicity test. I also reviewed the clinical serologic assays, including the validation information, the data included in each of the clinical studies and the application of the data to endpoints to support clinical benefit of the vaccine.

2.1. Final Drug Product -(b)(4) potency test

An --(b)(4) potency test is used to assess the potency of the final drug product. The sponsor calls the test the immunogenicity test. The test uses -----
------(b)(4)-----, and determines the potency of the test vaccine relative to a reference vaccine.

The test has undergone changes over time and the current methods were initially validated in the context of earlier versions of the test. The validation to show the precision of the potency estimates combined all (b)(4) data from (b)(4)- tests to generate the relative potency. However, the data were generated during an earlier version of the potency test. The earlier method ------(b)(4)------. The current method uses a ------(b)(4)----- the immunizations in an independent test. The reanalysis of the data using the existing data used all possible combinations of -----(b)(4)----- assays. The analysis may underestimate the variability of the assay. A revalidation using data generated using the current methodology will be performed post licensure.

The validations for the -(b)(4)- used to generate the antibody titers for each -(b)(4)- are relevant for the current methods. However the (b)(4) validations had insufficient data to fully support the adequate performance of the assays. Additional optimizations and validation studies will be performed after licensure.

Additional data were requested during review of the BLA, including lot release data for over (b)(4) lots of final drug product, due to the limitations of the (b)(4) validation and test precision data. Based on the overall consistency of the lot release data and the lack of any trend indicating changes in the assay or product over time, the data do not indicate any major losses in DP potency that would indicate problems with the consistency of manufacturing. In addition, the data indicate that the test is likely to detect substantive changes in product potency and can be used as an interim test until Novartis can implement improvements and revalidate the test.

2.2. Clinical Effectiveness

The Novartis vaccine for protection against serogroup B disease combines three recombinant proteins (936-741, fHbp; 287-953, NHBA; 961c, NadA) with outer membrane vesicles (OMV). The proteins from which the recombinant antigens are derived vary in sequence and expression levels across strains, and the ability of the proteins as included in the vaccine to protect against strains expressing heterologous sequences is unclear. OMV based vaccines have been generally shown to be protective only against the strains from which the OMVs were derived. In addition, the additive effect of responses to the combinations of these proteins is unclear. While the benefit of the vaccine can be inferred from the vaccine induced serum bactericidal activity, the selection of appropriate strains to test in the assays is challenging. Attempts to correlate expression levels and sequences of the antigens expressed by the bacteria with individual responses to vaccination have not been successful. After discussions between Novartis and CBER, Novartis agreed to assess the immunogenicity of the vaccine components based on serum bactericidal responses to vaccination using strains that represent each component of the vaccine. These data will provide support regarding the immunogenicity of each component. Sufficient immunogenicity is evidence of likely benefit of the vaccine. However, the effectiveness of the vaccine to protect against meningococcal disease caused by highly diverse strains will be evaluated in Phase 3 clinical studies using endogenous complement to ensure breadth of coverage.

The performance of the hSBAs was supported with validation reports and additional assay performance data that were submitted to the IND and the BLA. The performance of the assays was found to be adequate for their intended use.

In order to evaluate the likely benefit of vaccination with the Novartis vaccine, CBER recommended clinical endpoint of four fold responses to each strain and the percent above the LLOQ. While Novartis submitted several studies with immunogenicity data, differences in background rates of prevaccination seropositivity and differences among assay methods limited the interpretation of much of the clinical data with regard to the relevance to the U.S. population. Data from Study V72_41 was deemed the most likely to predict benefit in the U.S. as it was performed in Canada and Australia where prevaccination titers were similar to those in the U.S. and the serum bactericidal assays (SBAs) were those using appropriate methods. Other studies were considered supportive.

Based on the immunogenicity of the vaccine as demonstrated in Study V72_41, vaccination with Bexsero is likely to confer clinical benefit when administered in two doses, at least one month apart to individuals 10 to 25 years of age.

3. Review

3.1. Final Drug Product --(b)(4) potency test

3.1.1. Assay Description

While Novartis has used the -----(b)(4)----- assay as the potency test for final drug product since before EU approval, the methods have been modified over time in an attempt to

3. Please provide the (b)(4) titer data for each -(b)(4)-, used to generate the summary in Table 3.2.P.5.3.3-1 estimating the number of OOS, OOL and invalid assays based on the calculation methods tested. Please verify the system suitability criteria used to invalidate assays for each calculation method. Please provide the data in a readable file format and fully annotated.

4. Please verify that the geometric mean titer (GMT) of all animals in the group was used to generate the dose response curves used for relative potency. Please describe how non responders are handled in the estimation of the GMTs.

The following comments pertain to -----(b)(4)-----
Relative Potency Assay (4CMenB – Suspension for Injection in Pre-filled Syringes), submitted in Section 3.2.P.5.3., and -----(b)(4)----- Relative Potency Assay (4CMenB – Suspension for Injection in Pre-filled Syringes), submitted in Section 3.2.P.5.3.

5. The reports include a range for the assay but no data are provided to support the range. Please describe how the range was determined.

6. No data were provided to support the lower limit of quantitation for the assays. Please describe on what basis the determination of responder versus non responder is made.

7. Please provide exemplar raw (b)(4) data from a typical assay including the reference sera, and samples spanning the titer range of the assay for each of the four (b)(4). Please provide the data in a readable file format and fully annotated.

The following comments pertain to the stability data in section 3.2.P.8.3.

8. Please provide the raw (b)(4) titers from the --(b)(4) potency testing for all time points for batches -----(b)(4)----- . Please include all data from all (b)(4) assays and potency tests that failed to meet the system suitability criteria.

9. Please provide the raw (b)(4) titers from all --(b)(4) potency testing for the lots used in study V72_41 A Phase 3, Randomized, Comparative, Multicenter Observer-Blind Study Evaluating the Safety and Immunogenicity of Novartis rMenB+OMV NZ Vaccine Formulated with OMV Manufactured at Two Different Sites, in Healthy Adolescents Aged 11-17 Years. Please include all data from all (b)(4) assays and potency tests that failed to meet the system suitability criteria.

IR dated 14 August 2014

In response to your question for Item 3 in the Information Request from CBER dated July 15, 2014, regarding the term “fully annotated”, we have the following clarification:

CBER expects your response to Item 3 in the July 15, 2014, Information Request to include the “raw” (b)(4) O.D. values from assays run in --- (b)(4) ----. We expect the data format will likely be presented in a --- (b)(4) --- array. We will need to know the locations of the references, controls, and samples along with the dilutions of each sample, reference and control run. Please include these annotations as necessary and any other annotations that may be relevant in your response to Item 3 in an Amendment to your BLA (STN 125546).

IR dated 18 September 2014

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

1. Please provide the --(b)(4) potency testing results (potency estimate and confidence intervals) and dates of manufacture for all final drug product lots tested since implementation of the -(b)(4) method. Please include all results that were out of specification.

IR dated 12 November 2014

Please respond to the following comments by either providing the data requested or providing reasonable timelines for conduct of the work requested and submission of the data.

1. The tests for the potency of the 936-741 antigens appear to be more variable than those for the other antigens. We believe this may be due in part to the -(b)(4)- conditions being used to assess the antibodies in the --- (b)(4) ----. Please further optimize the assay used to quantitate the antibodies to 936-741.
2. Please re-examine the dose response data in the immunogenicity test and provide additional data that verify that the optimum doses are being used to generate the dose response curve. Please provide data that verify that the dose levels and number of doses used are adequate to minimize the overall variability of the assay.
3. Please re-evaluate the system suitability criteria for both the (b)(4) and potency estimation to further verify that the criteria are rejecting assays that are performing outside expected performance criteria.
 - a. For the (b)(4), please indicate the statistical basis for the system suitability criteria and the likelihood of rejecting assays due to chance alone.
 - b. The system suitability criteria for the --(b)(4) potency test were based on simulated data. Please update the criteria using data from the assays run to date. Please indicate the likelihood of rejecting assay due to chance alone.
4. Please revalidate the -(b)(4)-- in the laboratory in which the assays are performed for product release. Validation studies should mimic routine use. Accuracy and precision should be demonstrated using incurred and mock samples across the

working range of the assay. The lower limit of quantitation (LLOQ) should be based on sample accuracy and precision at the reported LLOQ.

5. We find the specification for the Upper Confidence Limit to be inadequate as it does not provide relevant information regarding the potency of the product. As communicated to you previously, Upper Confidence Limit is not a proper way of ensuring non-inferiority of a test lot, especially given the large variability of your potency assay. Although you showed in your responses submitted to Amendment 4 that with the additional criterion of the point estimate of RP being (b)(4), the chance of passing a subpotent lot is extremely low when the relative potencies of all four components are only (b)(4), the probability of falsely accepting a lot with RP slightly below (b)(4) or with low RP for only one or two of the four components can be high. Please discuss the use of a criterion based on the confidence limits to eliminate assay data from tests that are not precise enough to provide confidence in the point estimate of potency.

6. Please propose drug product specifications based on the historical performance of the (b)(4) lots released since the introduction of the latest potency test. Please provide a comparison of the proposed specifications to the potency of lots shown to be immunogenic in clinical studies to demonstrate that the product as currently tested is similar to those clinical lots.

7. The ability of the potency test to detect degraded vaccine was determined by -----
--(b)(4)-- final drug product at -----(b)(4)-----.
If the current potency specifications are applied to the results, the data are inconsistent with regard to the ability of the assay to detect changes in the component antigens. The only antigen consistently affected by (b)(4) treatment was 287-953. Please provide additional data to demonstrate that the immunogenicity test can detect changes in product quality or concentration.

3.1.2. Review of Immunogenicity Test (--(b)(4)potency test)

3.2.P.5.1 and 3.2.P.5.6, Specifications and Justification of Specifications, Immunogenicity

The specification for the Immunogenicity test is that point estimate of the relative potency (RP) for each antigen must be at least (b)(4) and the 95% upper confidence level must be at least (b)(4). The justification of the specification is based on the sponsor's desire to show non-inferiority of the test vaccine to a full dose of clinically qualified reference vaccine that is assumed to have a relative potency of (b)(4). The link between the potency assay and clinical efficacy is based on the use of a clinical lot (101601 tested in Study V72_41) as the reference vaccine, assigned a potency of (b)(4). However the utility of the upper confidence interval to demonstrate noninferiority is unclear. Novartis justifies the specification of (b)(4) by stating that clinical studies using a half dose of vaccine induced "acceptable immune responses." In general specifications should be designed to ensure consistent manufacture compared to lots that have been shown to be safe and effective. The relationship between the specifications and

what is considered consistent is unclear. The sponsor should reevaluate the specifications to demonstrate that they are capable of detecting meaningful changes in potency in the product over time. However, the current specification of (b)(4) is likely sufficient to ensure that substantially subpotent lots are not released.

3.2.P.5.2 and 3.2.P.5.3, Analytical Procedures and Validation of Analytical Procedures.

----- (b)(4) ----- Relative Potency Assay [4CMenB – Suspension for Injection in Pre-filled Syringe]

The system suitability criteria for the (b)(4) are limits on the slope and intercept of the reference standard curve and limits on the reported value for the control sample. The SOP states that “The (b)(4) test must be ----- (b)(4) ----- contained in the acceptability requirements.” This statement implies that two of the three criteria may be outside the limits and the assay data would be accepted. In addition, no criteria on the fit of the reference standard curve data to the model used to generate reportable results are included. The system suitability criteria may not be appropriate to adequately control the assays.

A preliminary study was performed to determine the minimum dilution of test sera by checking a ----- (b)(4) ----- . The results of this preliminary study are presented in Table 3.2.P.5.3- 1 below and indicate that the non-specific OD value at the (b)(4) dilution was too high for all proteins and was therefore, not applicable for the (b)(4) test. At the (b)(4)--- dilution all the tested sera from the negative control group had OD values in an acceptable range (b)(4)---. All sera tested at the (b)(4)--- dilution had less than 4 consecutive points on the linear part of the titration curve and so are considered as non-responder mice.

For the assays for each antigen, precision was assessed using just the reference serum and the positive control. The criterion for repeatability was a %CV (b)(4), for reproducibility it was (b)(4). While all criteria were met, the precision data are not adequate to demonstrate precision across the working range of the assay due to the lack of data from samples that span the range of the assay. The data do not show any substantive differences between the research and quality control laboratory but a full validation in the quality control laboratory should be completed.

Accuracy was verified by the titration of four replicates of the reference standard at concentrations of ----- (b)(4) ----- . For the test to be satisfactory, the percent recovery of the sample titers had to fall between (b)(4)---. For the accuracy test, the titer assigned to the standard was --- (b)(4) ----- . No data were generated to assess the relative accuracy of incurred samples. While all assays met the accuracy criterion, the data are not sufficient to demonstrate relative accuracy of the assays.

Linearity was assessed using the reference curves generated during precision testing. The criterion was that the correlation coefficient of the regression curve had to be (b)(4)---. While

the assays passed the criterion, no data were provided to show the linearity of samples. The data are not sufficient to demonstrated linearity of the assays.

Robustness studies included -----(b)(4)-----
----- . Also tested was stability of the reference and control sera after multiple ---(b)(4)--- cycles. All robustness testing indicated consistent performance of the reference and controls across the assay conditions. However, multiple ---(b)(4)--- cycles increased the reported values for both the reference and control sera. Based on the data provided, samples should not be subjected to more than one or two ---(b)(4)--- cycles (depending on the antigen) before testing.

The limits of quantitation were not assessed. The lowest reported value for each assay is determined using the interpolation of the third degree polynomial function of the reference standard on each (b)(4) (see response to FDA comment 8 in STN145546/0.4). The precision and accuracy of the assay at that point in the range has not been demonstrated.

----- (b)(4) ----- Relative Potency [4CMenB – Suspension for Injection in Pre-filled Syringe]

The system suitability criteria for the (b)(4) are limits on the slope, OD of the third reference point, coefficient of determination, and titer of the reference standard curve, and limits on the reported values for the control samples. The SOP states that “The (b)(4)-- test must be repeated for all the plates that are not in accordance with at least one of the points listed in the requirements of acceptability.” In addition the SOP states that at least one of the two control sera inserted in the test must be within the limits of acceptability. The criteria imply that three out of the four criteria for the reference standard curve may be outside the limits and the assay data would be accepted. The system suitability criteria may not be appropriate to adequately control the assays.

Precision was assessed using just the reference serum and three positive sera (one high, one medium and one low). The criterion for repeatability was a %CV (b)(4), for reproducibility it was (b)(4). While all criteria were met, the precision data are only adequate to demonstrate precision across the range of the assay covered by the samples.

Accuracy was verified by the titration of four replicates of the reference standard at concentrations of -----(b)(4)----- . For the test to be satisfactory, the percent recovery of the sample titers had to fall between (b)(4)--. For the accuracy test, the titer assigned to the standard was ---(b)(4)----- . No data were generated to assess the relative accuracy of incurred samples. While all assays met the criterion, the data are not sufficient to demonstrate relative accuracy of the assays.

Linearity was assessed using the reference curves generated during precision testing. The criterion was that the correlation coefficient of the regression curve had to be (b)(4). While the assays passed the criterion, no data were provided to show the linearity of samples. The data are not sufficient to demonstrated linearity of the assays.

Robustness studies included -----(b)(4)----- . Also tested was stability of the ----(b)(4)----- after multiple ---(b)(4)---- cycles. All robustness testing indicated consistent performance of the reference and controls across the assay conditions. The samples appear to be stable over ----(b)(4)----- cycles.

The limits of quantitation were not assessed during validation. The lowest reported value for each assay is determined using (b)(4) dilution of the reference standard curve (see response to FDA comment 8 in STN145546/0.4). The precision and accuracy of the assay at that point in the range have not been demonstrated.

Additional comments pertaining to all (b)(4)

The data provided in STN125546/0.4 regarding the controls used in the (b)(4)- indicate that the system suitability limits for the control sera may not have been set properly. In addition, the performance of the controls could not be fully assessed as only the data from controls within the limits were presented. Also the y axis in the figures are plotted on the arithmetic rather than logarithmic scales which may indicate that the limits were not set based on the correct distribution of the data. The data also indicate that the mean and limits were not correctly set for the (b)(4) for 936-741 and 961c which could bias the reported data by skewing the rejection of assays.

----- (b)(4) ----- Relative Potency Assay [4CMenB – Suspension for Injection in Pre-filled Syringe]

The system suitability criteria appear to have been derived from statistical simulations. The performance of the assay and the verification of appropriate system suitability criteria should be reassessed as data from assay runs releasing final drug product are generated.

The dataset used for this validation was generated during the validation activities of the previously applied ----(b)(4)----- method. Since the modifications introduced with the application of the (b)(4) model are only related to the application of a new mathematical methodology and no change was introduced in the immunization and (b)(4) procedures, the complete dataset generated during the previous validation study was used for calculation of the validation parameters.

The immunization procedure used during the previous validation used -----(b)(4)----- per dose level. In the current validation study, the previously obtained antibody titers for each antigen and for each of the two independent immunization sessions (expressed as EU/mL), are used to calculate the Relative Potency of the test vaccine against the reference vaccine by applying the (b)(4) mathematical model

Precision was estimated by using all possible combinations of -----(b)(4)----- (within the same operator and lot). A nested design with (b)(4) assays (for each antigen) was obtained. The use of the same data to generate multiple iterations of testing is not appropriate in that it may underestimate the variability of the assay. In the original validation analysis, the precision criteria were only set for intermediate precision and were %CV (b)(4) for all

antigens. The previous validation failed for three of the four antigens and thus the precision criteria for the validation were set based on the precision achieved using the previous calculation method: 287-953: (b)(4), 936-741 (b)(4), 961c (b)(4) and OMV (b)(4). No information was provided to indicate how the increase in variability would affect the ability of the assay to detect subpotent lots. The criteria were met by the precision estimates for the potency against all antigens but the use of all possible combinations of a limited set of data does not provide sufficient information about the precision of the relative potency estimates. Additional analysis of precision should be provided using independent assays and estimates of precision as dictated by the current SOP.

The data for precision were presented as (b)(4) iterations. The relationship between these (b)(4) iterations and the (b)(4) iterations discussed above was unclear. In addition, several of the (b)(4) iterations were invalidated: six for the potency against 287-953, two for the potency against 936-741, five for potency against 961c, and five for the potency against OMV. The high number of invalid tests may be indicative of suboptimal (b)(4) used for quantitation of antibody levels in the ---(b)(4)----- causing higher than expected variability of the (b)(4) data.

Linearity was reported to be part of the system suitability criteria. Linearity as it relates to relative accuracy is not usually tested for immunopotency assays. However, for immunopotency assays using relative potency, samples of known relative concentration should be tested to support the ability of the assay to detect subpotent lots. The sponsor should be encouraged to perform additional studies to verify the ability of the assay to detect a two or four fold reduction in vaccine concentration.

3.1.3. 3.2.P.6 Reference Standards or Materials, additional information in amendment 0.4

The information provided regarding the reference standards for the (b)(4) and the (b)(4) potency estimation appears adequate. New references are calibrated against the existing reference. However insufficient detail was provided to determine if the qualification of new reagents will prevent assay drift. -----
----- (b)(5);(b)(7)(E) ----- should be included in the next biennial inspection.

3.1.4. Additional data request, IRs dated 15 July 2014 and 14 August 2014, 18 September 2014

Due to the uncertainties around the validations of the (b)(4) and the estimates of potency in the immunogenicity test, additional data were requested to enable assessment of routine assay performance and data submitted to support the ability of the assay to detect subpotent lots. The raw data from (b)(4) were limited to the exemplar data from one or two assays per antigen due to the inability of the sponsor to submit electronic data. The raw data from the potency estimates (the estimated titers for each animal) were submitted as requested. Review of all data submitted did not reveal any exceedingly unusual results; the data were consistent with that expected from an immunopotency assay in (b)(4). However, the estimate of relative

potency appeared to be highly dependent on the estimated slope of the reference and test vaccines.

The best indicator of consistent performance of the assay over time is likely to be found in the data from routine testing. All testing data from lots released using the new (b)(4)- method were requested (IR dated 18 September 2014). The following assumptions were made based on the request and the data submitted:

- All OOS and passing results are included. The specification for relative potency (RP) is that it must be (b)(4). The specification for the upper confidence level (UCL) is that it must be (b)(4).
- All data submitted are from assays that met the system suitability criteria for both the (b)(4) and the relative potency estimate.

Data from a total of (b)(4) lots were submitted. OOS results are noted for Lot 132501 for 936-741 however the comments indicate that retesting was not performed. The release status of this lot is unknown. OOS results are also noted for lots 131801 and 139501 for 287-953, both lots were retested and passed the specification on the second test. The figures below show the data for over the (b)(4) lots tested with the (b)(4) method for both the RP and UCL. The lot numbers are not listed but are in what appear to be chronological order.

Figure 1. Relative potency and upper confidence interval by consecutive lot for OMV

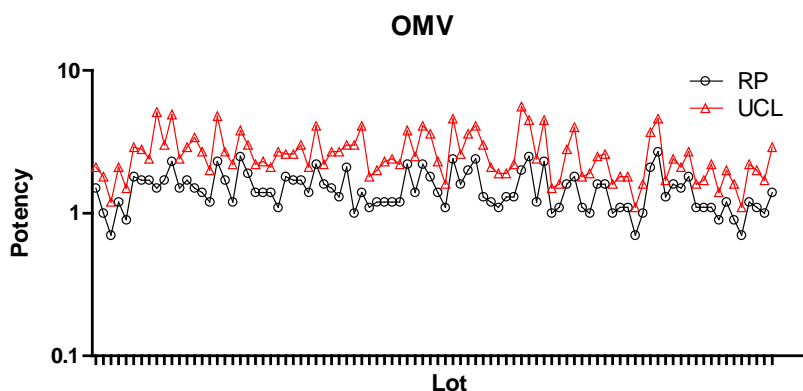


Figure 2. Relative potency and upper confidence interval by consecutive lot for 961c

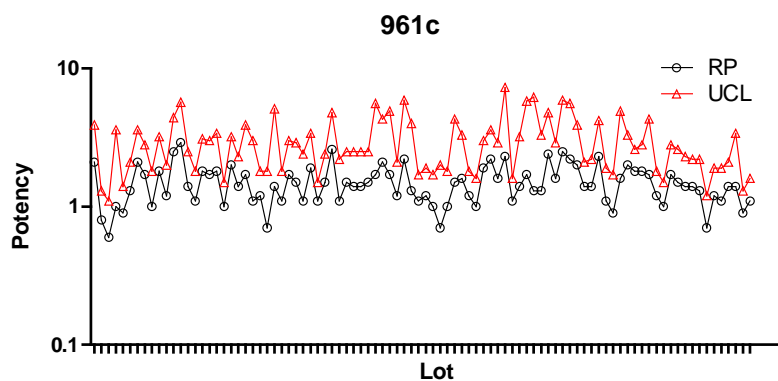
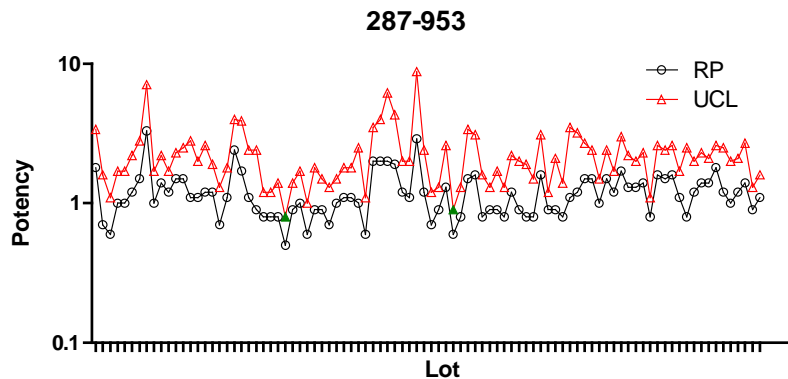
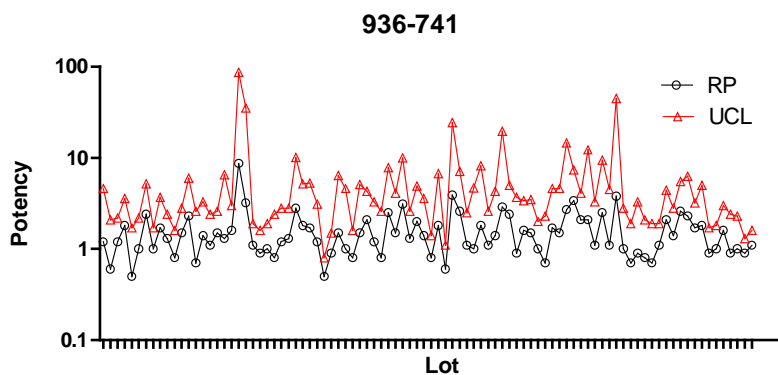


Figure 3. Relative potency and upper confidence interval by consecutive lot for 287-953



The green RP points indicate the OOS results.

Figure 4. Relative potency and upper confidence interval by consecutive lot for 936-741



Note that the extreme values of the UCL required a wider scale for the graph of 936-741. The figure below removes the extreme values to help visualize the differences in variability among

the tests for the different antigens. The purple data points indicate where the UCL was removed. The green RP point indicates the OOS result.

Figure 5. Relative potency and upper confidence interval by consecutive lot for 936-741 with lots with relative potency values greater than 10 removed

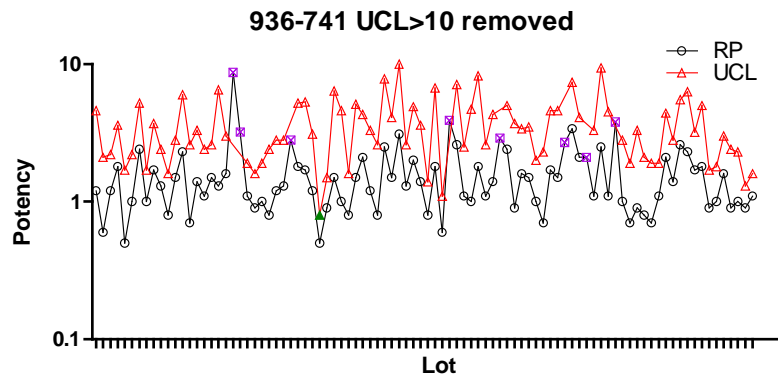


Table 1. Geometric means and the +/- 2 vs 3 standard deviation (SD) limits for the relative potency based on the (b)(4) lots for each antigen.

	287-953	936-741	961c	OMV
Mean	1.13	1.39	1.43	1.41
Upper 2 SD	2.28	3.84	2.71	2.59
Lower 2 SD	0.56	0.50	0.75	0.77
Upper 3 SD	3.24	6.37	3.74	3.51
Lower 3 SD	0.39	0.30	0.54	0.57

The upper and lower SD limits reflect the increased variability seen for the potency estimates for 287-953 and 936-741. Note that the -----(b)(4)----- are greater than (b)(4) indicating that the current specification may be too wide for those antigens.

Based on the data provided, I have the following summary comments.

Based on the overall consistency of the data and the lack of any trend indicating changes in the assay or product over time, the assay data do not indicate any major losses in DP potency that would indicate problems with the consistency of manufacturing. The test is likely to detect substantive changes in product potency and can be used as an interim test until Novartis can implement improvements.

The tests for the potency of the 936-741 antigens appear to be more variable than those for the other antigens. As discussed in my memo to IND (b)(4) dated 17 April 2014, Novartis can likely improve (b)(4) performance for both 287-953 and 936-741 by reoptimizing the assays.

The system suitability criteria for both the (b)(4) and potency estimation should be reexamined to verify that the criteria are rejecting assays that are performing outside expected performance parameters. Of note, the system suitability criteria for the--- (b)(4)- potency test were based on simulated data. The criteria should be updated using data from the assays run to date.

The (b)(4) should be revalidated in the laboratory in which the assays are performed for product release. Validation studies should mimic routine use. The LLOQ for each assay should be determined using incurred and mock samples and data demonstrating accuracy and precision provided. The validation data should demonstrate the accuracy and precision of the assay across the working range.

The dose response data should be reexamined to verify that the optimum number of doses are being used to generate the dose response curve. The use of only three points to generate a dose response curve may be increasing the overall variability of the assay.

The criterion for the Upper Confidence Limit does not provide relevant information regarding the potency of the product. However, the sponsor should consider a criterion based on the confidence limits to eliminate assay data from tests that are not precise enough to provide confidence in the point estimate of potency.

The criterion for RP should be based on the historical performance of the (b)(4) lots released since the introduction of the latest potency test. The current reference vaccine should be linked to the immunogenicity of lots shown to be immunogenic in the clinic.

The ability of the potency test to detect degraded vaccine was determined by (b)(4) treating final drug product at -----(b)(4)-----
If the potency specifications are applied to the results, the data are inconsistent with regard to the ability of the assay to detect changes in the component antigens. The only antigen consistently affected by (b)(4) treatment was 287-953. The ability of the assay to detect changes in product quality or concentration should be further evaluated.

The response to the IR sent 12 November 2014 commits Novartis to provide plans to improve the (b)(4) to quantitate 936-741 by January 2015. The plans will include additional information on the optimal dose response curves. Plans to evaluate the system suitability criteria for both the (b)(4) and the potency assay as well as a protocol for revalidation of the (b)(4) will be provided 1st quarter 2015. Analyses regarding the specifications will also be provided 1st quarter 2015. Additional studies demonstrating the ability of the potency assay to detect subpotent lots will be initiated after improvements to the existing potency assay are complete.

The following areas should be subject to review at the next biennial inspection.

- -----(b)(5);(b)(7)(E)-----
-----.
- -----(b)(5);(b)(7)(E)-----
-----.
- -----(b)(5);(b)(7)(E)-----

-----.

3.1.5. 3.2.P.8, Stability

Only the data submitted for the Immunogenicity Test to support stability of the Final Drug Product are reviewed here. The data submitted for lots tested using the previous immunogenicity method are difficult to interpret due to the unreliability of the test. The results of the previous test are highly variable, with up to 4 fold variability in the estimates of immunogenicity for the same lot over time, multiple invalid tests, and OOS results. However, no trend in loss of potency over time was seen with the previous test.

The real time stability data using the current immunogenicity test includes data for lots 101601 (used in Study V72_41) but only at (b)(4) months; lots 112201, 112301, 112121 at only 18, 24 and (b)(4) months; 124801, 124901, 125101, 125201, 125001A at only 6, 9 and 12 months; and 125401, 125501, 125601 at 3, 6, 9, and 12 months. OOS results are noted for lot 125101 at 6 and 9 months but not at 12 months, 125201 at 6 months but not at 9 or 12 months. Overall the data support stability of the potency of the product up to 12 months.

3.2. Clinical Serology Assays

3.2.1. Human Complement Serum Bactericidal Assays (Manual)

The manual serum bactericidal assay using human complement (hSBA) was performed similarly to the assays traditionally used to support efficacy of meningococcal vaccines. In

-----.

The hSBA was performed at -----(b)(4)-----
----- to assess the immune response against a panel of MenB strains (reference to chapter 2.7.2, Table 4.1-1) in the clinical studies V72P10, V72_41, V72P4, V72P5, V72P13 and V72P16. All pipetting steps were done manually which is why the assay is referred to as manual hSBA. Two reports were submitted to support the performance of those assays:

1 page determined to be not releaseable: (b)(4)

Serum bactericidal assay (SBA) for determination of antibodies against serogroup B *Neisseria meningitidis* bacteria, Document No.: 275751, September 2010. (Strains -----(b)(4)---

----- (b)(4) -----

[(b)(4)]

----- (b)(4)

-----(b)(4)-----

sample collections held within the laboratory which had appropriate consent and ethics. Approximately -----(b)(4)-----
----- and used in the validation. These samples were from adults and included pre- and post-vaccination samples from subjects vaccinated with either/or meningococcal A, C, Y and W135 polysaccharide, meningococcal A and C polysaccharide, meningococcal serogroup C conjugate, --- (b)(4)---- OMV vaccine --(b)(4)--, and the New Zealand OMV vaccine MeNZB.

--(b)(4)--

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----- (b)(4) ----- sample stability, Short term stability
(b)(4) samples covering the full range of expected SBA titers (low (b)(4), medium (b)(4) and high (b)(4)) and three negative samples were selected for each target strain. For $\geq 85\%$ of samples the --- (b)(4) --- sample result should be within (b)(4) SBA titer of the median for that sample. --- (b)(4) --- data support the stability of the samples through (b)(4) cycles. Short term stability data also support the storage of samples up to (b)(4) hours at room temperature.

Long-term, sample stability
(b)(4) samples covering the full range of expected SBA titres (low (b)(4)), medium (b)(4) and high (b)(4)) and three negative samples were selected for each target strain. For each of the samples a previously (b)(4) aliquot was (b)(4) and assayed, this was classed as the reference result (day 0). Other --- (b)(4) --- aliquots of the same samples were maintained at --- (b)(4) --- and were assayed after 1, 6 and 12 months. Data were only provided through one month. Long term stability beyond one month has not been demonstrated.

Summary

The assay has been fully validated across the working range. The precision, bias and linearity data, taking into consideration the negative data, support an LLOQ of 8 for the assay against 5/99 and 16 for the assays against H44/76 and NZ98/254, with the limit of detection of 4 for all assays.

Inter-laboratory comparison of the meningococcal capsular group B serum bactericidal antibody assay between Novartis Vaccines -----(b)(4)-----
-----, November 2012 (Strains H44/76, 5/99 and NZ98/254)

In the SBA bridging study sera from infants (V72P9) and adults (C60P1 and V72P5) were used. The participants of these trials received different vaccine formulations and the selected sera were tested against three different MenB strains 44/76-SL, NZ98/254 and 5/99.

The bridging analysis was performed in the years 2006-2009. Sera aliquots of study V72P5 and V72P9 were sent from -----(b)(4)----- . Both studies were previously analyzed in --(b)(4)--- for immunogenicity. Sera from study C60P1 were sent from -----(b)(4)----- . Both laboratories used different plasma complement sources per strain. The reciprocal value of the serum dilution that kills exactly 50% of the bacteria used in the test was determined by interpolation. The assay as validated at (b)(4) reports the highest titer than kills at least 50% of the bacteria. The use of interpolation for the (b)(4) does not reflect the practice at (b)(4).

I defer review of the equivalence analysis for the laboratories to statistical reviewers. No formal acceptance criteria were set. The intended use of the data from each laboratory was not clearly described.

As expected the data suggest higher variability between the laboratories than was demonstrated within each laboratory. In addition, agreement varied depending on the study from which the samples were drawn and the strain used in the assay. In general, better agreement was seen with strain 5-99 than the other two strains. The concordance analyses are difficult to interpret as they depend on the number of samples tested that were close to the cutoff. Of the (b)(4) samples tested for SBA against 5-99, only 11 had median titers between --(b)(4)--. Of the (b)(4) samples tested in the SBA against NZ98-254, 14 had median titers between 2 and 16, and of the (b)(4) samples tested in the SBA against 44-76, 27 had median titers between 2 and 16. Note that the assay for 44-76 had the lowest percent negative agreement at 81%.

The concordance correlation coefficients (CCCs) were estimated by vaccine received for those who received the rMenB or the rMenB + OMV. The CCCs ranged from 0.76 to 0.99. The CCCs consistently higher for samples from subject who received the rMenB + OMV than for those from subjects who received rMenB. Only two CCCs were above 0.9.

In general the data indicate that the assays performed in --(b)(4)-- versus those performed in --- (b)(4) ---- are similar. The data generated in either laboratory could be

used to support functional antibody responses in vaccine recipients. However, the data are not sufficient to support direct comparison between data generated in each laboratory or to support combination of data from the two laboratories.

3.2.2. ~~----(b)(4)-----~~ Human Complement SBA

The ----(b)(4)----- human complement SBA ----(b)(4)--- is an ----(b)(4)----- assay that Novartis has proposed for use in the ----(b)(4)----- vaccine program. The assay was run at -----(b)(4)-----, Novartis Vaccines and ----(b)(4)----- ----- to generate immunogenicity data with an additional NHBA indicator strain ----(b)(4)----- on sera from ----(b)(4)----- trial, V102_03, which contained a rMenB+OMV NZ arm. The assay is considered to be ----(b)(4)----- and data generated with this assay is not considered to be relevant to the demonstration of efficacy in the context of this BLA.

3.2.3. -----(b)(4)----- SBA

The -----(b)(4)----- SBA --- (b)(4)---- is a functional assay developed to -----(b)(4)----- of rMenB+OMV NZ containing vaccines. The assay is designed to be -----(b)(4)----- of MenB. The assay is run at -----(b)(4)-----, Novartis Vaccines and -----(b)(4)----- -----(b)(4)----- . The assay is currently considered --- (b)(4)----- . The (b)(4)--- -- will be used post accelerated approval to generate the pivotal data in the Phase 3 efficacy studies. Review of all the --- (b)(4)--- will be conducted upon completion of the assay qualifications. Those assays are not reviewed under this approval.

3.2.4. (b)(4)

Novartis generated data in several studies using an (b)(4) for the NHBA protein 287-953. The (b)(4) data are not considered relevant to the evaluation of efficacy for this vaccine and therefore the (b)(4) is not reviewed in this BLA.

3.2.5. -----(b)(4)-----

(b)(4)

3.3. Clinical Immunogenicity Data

3.3.1. Overview

Reviewed here are the studies which either the sponsor or CBER considered to be the most relevant to provide data that support the clinical benefit of the vaccine. Ultimately the study found to provide the most relevant immunogenicity data was Study V72_41 as that study population is most similar to the U.S. population with regard to preexisting hSBA titers and the assays used were validated. In addition the data from study V72_29 were considered important as they include information on the possible effects of vaccination on carriage.

The preplanned analyses provided in each of the studies were not used to support effectiveness as the analyses were based on assay parameters (such as the lower limits of quantitation) not supported by the validation data or used definitions not accepted by CBER. Novartis provided a reanalysis in the integrated summary of efficacy (found in amendment 2 to the BLA) based on the pre-BLA CBER request. However the analysis had to be updated to reflect the assay LLOQs. A second reanalysis was requested by CBER (see IR dated 5 September 2014). Novartis' response was submitted in amendment 17. The correctly reanalyzed data from studies V72_41 and V72_29 are found in the table below (data from amendment 17, 1.11.3, Table Q2-1).

Table 3. Percent of subjects with four fold rises after two doses (95% Confidence Interval)

Strain	Study V72_41 n=298-299	Study V72_29 n=188-189
H44/76	98 (95-99)	79 (73-85)
5/99	99 (98-100)	94 (90-97)
NZ98/254	39 (33-44)	67 (60-74)

The percent of subjects with post vaccination hSBA titers above the LLOQ for all three strains tested (H44/76, 5/99, NZ98/254) was also requested. In study V72_41, 63% of individual subjects had titers greater than the LLOQ for all three strains. In study V72_29, 88% of subjects had titers greater than the LLOQ for all three strains.

Overall the data most relevant to the U.S. population demonstrate responses that support the likely clinical benefit of the vaccine.

Correspondence between the sponsor and CBER regarding the clinical endpoints can be found in CBER meeting summary dated 26 June 2014. In addition, Information Requests were sent to the sponsor as described below. Review of the responses is incorporated into the review.

IR dated 5 September 2014

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. NVD (b)(4) lab: 8 for the NZ98/254 strain, and 16 for the H44/76, 5/99, and --(b)(4)-- strains;
- b. HPA --(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 > 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 $\geq \text{LLOQ}$. 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 $\geq \text{LLOQ}$. 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: (tables not reproduced here).

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 ½ 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 ½ 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 ½ 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.

3.3.2. Clinical Studies

V72P10 A Phase 2b/3, Multi-Center, Observer-Blind, Controlled Study of the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine Administered to Healthy Adolescents Aged 11-17 Years According to Different Vaccination Schedules (Chile)

This Phase 2b/3, observer-blind, multi-center, randomized, controlled trial in healthy adolescents aged 11 to 17 years was conducted to assess safety, tolerability and immunogenicity against Novartis rMenB+OMV NZ vaccine administered as 1-dose, 2- dose or 3-dose vaccination schedules. Approximately 1625 subjects were planned to be randomized in an observer-blind manner into one of 8 groups in 1:2:1:2:1:2:3:1 ratio stratified by age group into 11 to 13 years and 14 to 17 years. For the primary vaccination period and persistence (visit-1 to visit-4 and visit-5) these groups were combined into 5 groups; the groups that were combined differed in their schedules only for booster vaccination. Data from approximately 230 subjects in each group were available for immunogenicity analyses.

Primary objective:

To assess the immunogenicity, safety and tolerability of one, two (0,1 or 0,2 schedule) or three doses (0, 1, 2 schedule) of Novartis rMenB+OMV NZ in healthy adolescents, by evaluation of the serum bactericidal activity using human complement (SBA) response at one month after the last rMenB+OMV NZ dose.

From the study groups enrolled into this study, only data from groups 2b and 3b were reviewed for this BLA. These two groups received only two doses of vaccine at schedules of either 0, 1 or 0, 2 month (2b and 3b respectively). Sera were analyzed at the Novartis laboratory using the validated manual hSBA against strains 44-76, 5-99, NZ98-254 and --(b)(4)--. Additional assays against other strains were run but as the ----(b)(4)----- assay was used, these data are not considered sufficiently reliable.

The data indicate that the baseline antibody levels from Chilean subjects may be higher than those in Canadian or other North American subjects (see studies V72_41 or V102_03 (not reviewed here)). As a result the antibody levels achieved post vaccination may overestimate the levels one could expect in a population with lower baseline levels. However, the overall immunogenicity data are consistent with protective responses.

V72_29 A Phase 3 Observer blind Randomized, Multi-center, Controlled study to evaluate the effect of Novartis Vaccine's Meningococcal B recombinant and MenACWY Conjugate vaccines on Pharyngeal Carriage of *N meningitidis* in Young Adults (United Kingdom)

This was a phase-3, multicenter, observer-blind randomized trial that enrolled university students of 18 to 24 years of age in the UK. Subjects were randomized to one of the three treatment arms: rMenB+OMV, MenACWY and control group (Japanese encephalitis vaccine). All subjects received two injections 1 month apart and were followed-up for a total of 12 months. Posterior pharyngeal swabs were collected for culture of *Neisseria* colonies. The colonies were harvested and then transferred to the -----(b)(4)----- laboratory for further analyses.

As mentioned above, blood samples (of 20mL maximum) were collected from a subset of subjects at baseline and at each visit from visit-3 onwards (2 months from first vaccination) for immunogenicity evaluation. At the final visit (visit 6) the subjects in rMenB+OMV and control groups received one dose of MenACWY vaccine as non-test vaccine

Primary objectives

1. To investigate carriage prevalence of virulent sequence types (ST) of *N meningitidis* group B (genogroupable) at one month (Month 2) following administration of two doses of rMenB+OMV NZ, compared to the control group receiving the JE vaccine.
2. To investigate carriage prevalence of *N meningitidis* combined serogroups A, C, W and Y at one month (Month 1) following administration of a single dose of MenACWY conjugate vaccine, compared to the control group receiving JE vaccine.

From the study groups enrolled into this study, only data from group 1 were reviewed for this BLA. This group received two doses of vaccine at schedules of 0, 1 month. The manual hSBA

against serogroup B strains H44/76, 5/99 and NZ98/254 was performed at -----
----- (b)(4) -----
----- using validated assays.

The data indicate that the baseline antibody levels from UK subjects may be higher than those in Canadian or other North American subjects (see studies V72_41 or V102_03). As a result the antibody levels achieved post vaccination may overestimate the levels one could expect in a population with lower baseline levels. However, the overall immunogenicity data are consistent with protective responses.

The analyses for the primary endpoints showed that no effect on carriage was seen after vaccination. At 1 month after second vaccination, the carriage rates were generally similar to the baseline in both vaccine groups (9% in rMenB+OMV and 8% in control groups). No significant difference between the rMenB+OMV and control groups in the prevalence of carriage of group B virulent strains at 1 month after second vaccination was seen ($p=0.3930$).

At 1 month after one dose of MenACWY or after first dose of Ixiaro in the control group, the carriage prevalence was similar to baseline in both vaccine groups (6% in both MenACWY and control vaccine groups). No significant difference was observed in the prevalence of serogroups A, C, W or Y carriage between the group receiving MenACWY and the group receiving control vaccine at 1 month after vaccine dose ($p=0.5928$).

Carriage was assessed throughout the study, up to 11 months post vaccination. Administration of rMenB+OMV did not significantly reduce carriage of meningococcal group B strains in the subjects when assessed at any time throughout the study relative to the control group. However the group vaccinated with rMenB+OMV did significantly lower carriage relative to the control group when all meningococcal strains at any time point were included in the analysis. The differences between the groups were small (carriage was 18.0% in the MenB+OMV group and 20.9% in the control group). Prevention or reduction of carriage is not likely to be a substantive public health benefit of this vaccine.

V72_41 A Phase 3, Randomized, Comparative, Multicenter Observer-Blind Study Evaluating the Safety and Immunogenicity of Novartis rMenB+OMV NZ Vaccine Formulated with OMV Manufactured at Two Different Sites, in Healthy Adolescents Aged 11-17 Years. (Canada and Australia)

This was a Phase 3, multicenter, observer-blind, randomized trial which enrolled healthy adolescents. All subjects received 2 vaccinations one month apart and were followed for a total of 2 months. Subjects were randomized at Visit 1 to one of two treatment arms to receive either two doses of rMenB+OMV NZ vaccine Lot 1 or two doses of rMenB+OMV NZ Lot 2. Blood samples were drawn prevaccination and 2 weeks or 1 month post second vaccination for serologic testing. Total number of subjects enrolled and randomized was 344. Data from approximately 87% of subjects contributed to the per protocol population.

Primary Objective

To demonstrate the equivalence of rMenB+OMV NZ lot 1 to rMenB+OMV NZ lot 2 when administered to adolescents, as measured by human serum bactericidal activity (hSBA) geometric mean titers (GMTs) against 3 *N. meningitidis* serogroup B reference strains (H44/76, 5/99, and NZ98/254) and as measured by -----
----- (b)(4) ----- geometric mean concentrations (GMCs) against vaccine antigen 287-953, approximately 30 days after a primary vaccination course of two doses administered one month apart.

Novartis considered this study a success if, at one month following the second vaccination, the two-sided 95% confidence interval (CI) of the ratio of the hSBA GMTs for each of 3 serogroup B reference strains (H44/76, 5/99, and NZ98/254) and the two sided 95% CI of the ratio of the (b)(4) GMCs against vaccine antigen 287-953 were contained within the interval (0.5, 2.0).

The data here appear to be relevant to the U.S. population as the baselines are similar to what is expected in the U.S. adolescents and young adults. As this study provided the data most likely to reflect the performance of the vaccine in the U.S., these data were considered pivotal to the demonstration of clinical benefit even though the study was designed to demonstrate lot consistency between the manufacturing sites and did not include a placebo control.

The data line listings were reviewed and no aberrant or unusual data were noted.

The clinical endpoints used in this study were the geometric mean titers in each group and the percentage of subjects with titers greater than or equal to 1:5. Due to the need to use the data to show clinical benefit, CBER requested a reanalysis of the data. CBER requested the analysis include the percentage of subjects who had a four fold rise and the percentage of subjects who had post vaccination titers greater than the LLOQ against all three strains tested by hSBA. Four fold rise was defined as follows: for a negative (< 4) pre-immunization titer, the post-immunization titer was at least 16; for a positive (≥ 4 but $< \text{LLOQ}$) pre-immunization titer, the post immunization titer was at least 4-fold the LLOQ; for a positive ($\geq \text{LLOQ}$) pre-immunization titer, the post immunization titer was at least 4-fold the pre-immunization titer. The data from both lots were combined to generate the clinical results.

See summary above for data. The data demonstrate responses that support the likely clinical benefit of the vaccine.

V72P13 A Phase 3, Partially Blinded, Randomized, Multi- Center, Controlled Study to Evaluate Immunogenicity, Safety and Lot to Lot Consistency of Novartis Meningococcal B Recombinant Vaccine When Administered with Routine Infant Vaccinations to Healthy Infants

This study evaluated lot consistency in healthy infants in Europe (Italy, Germany, Austria, Finland and Czech Republic). Subjects meeting the enrollment criteria were assigned to one of five vaccination groups (ratio 4:4:4:3:3). The rMenB lot1 group, the rMenB lot2 group and the rMenB lot3 group received one dose of rMenB+OMV NZ (Lot 1, or Lot 2, or Lot 3, respectively) at 2, 4, and 6 months of age concomitantly with the routinely administered

infant vaccines (Infanrix Hexa and Prevnar). The Routine group received only the routinely administered infant vaccines at 2, 4, and 6 months of age. The MenC+Routine group received the routinely administered infant vaccines plus Menjugate at 2, 4 and 6 months of age. Approximately 45-50% of the subjects were randomly selected from the enrolled population to assess immune response to MenB vaccination. Demographic analysis showed the three groups receiving the MenB vaccine lots were similar.

Primary objectives

- To show the consistency of immune response from 3 lots of rMenB+OMV NZ, by serum bactericidal activity geometric mean titer response (hSBA GMTs), when administered to healthy infants at 2, 4 and 6 months of age, at 1 month after the third vaccination.
- To assess the immunogenicity of 3 doses of rMenB+OMV NZ (3 lots combined) given to healthy infants at 2, 4 and 6 months of age concomitantly with routine infant vaccines, by evaluation of the serum bactericidal activity (hSBA), at 1 month after the third vaccination.

Review of the GMT and reverse cumulative distribution curves (RCDCs) indicate the responses among the lots are not different in the serum bactericidal assay for any of the three strains tested (44/76, 5/99, NZ98/254). Line listings with a readable file format were not provided. Note that the LLOQ used in this assay, a titer of 2, is not supported by the validations. However, due to the overlapping RCDC for each strain, the data are sufficient to support the similarity among the lots.

4. Recommendation

I recommend approval of the group B meningococcal vaccine for use in persons 10 to 25 years of age.

4.1. Product release testing

Immunogenicity Test (b)(4)- potency test)

Due to the limitations of the (b)(4) validation data and the precision of the potency estimates when all (b)(4) data are combined, additional data were requested during review of the BLA. The data overall are consistent and lack any trend indicating changes in the assay or product over time. The assay data do not indicate any major losses in DP potency that would indicate problems with the consistency of manufacturing. The test is likely to detect substantive changes in product potency and can be used as an interim test until Novartis can implement improvements.

4.2. Clinical Immunogenicity

The data from Study V72_41 support responses to the vaccine components consistent with protection against homologous strains. In addition, other studies also demonstrate a consistent response. The data support the likely benefit of vaccination to prevent group B meningococcal

disease. In addition the clinical data from Study V72P13 demonstrate the consistency of responses to multiple lots of vaccine.