Complete Review Memo, July 28, 2014 - GARDASIL 9

Memorandum
Date: July 28, 2014
From: Freyja Lynn, CSO, DBPAP, Committee Member
To: STN 125508/0
GARDASIL9
Human Papillomavirus 9-valent Vaccine, Recombinant
Through: Jay Slater, Director, DBPAP
Subject: Complete Review Memo
Immunoassays to assess responses to pertussis and meningococcal vaccines
Immunogenicity data in Protocol 005 regarding concomitant administration of Adacel and Menactra
Firm: Merck Sharp & Dohme Corp.

Summary

Merck submitted a BLA for licensure of GARDASIL9 (Human Papillomavirus 9-valent Vaccine, Recombinant). As part of the labeling, Merck would like to state that GARDASIL 9 may be administered concomitantly (at a separate injection site) with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)]. In order to support labeling for concomitant administration with meningococcal and TdaP vaccines, Merck submitted data from a study comparing separate versus concomitant administration of Menactra and Adacel with Gardasil9.

The aspects of the BLA reviewed in this memo are the assays to quantitate antibodies to pertussis antigens (pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN) and fimbriae (FIM)) and the serum bactericidal assays to quantitate responses to the meningococcal polysaccharides, groups A, C, W-135, and Y. These assays were used to generate the data in study 005 to support concomitant administration of Gardasil9 with Menactra and Adacel. In addition, the immunogenicity data in the clinical study 005 were reviewed.

Review

Protocol 005 A Phase III Open-Label Clinical Trial to Study the Immunogenicity and Tolerability of V503 (A Multivalent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) Given Concomitantly with Menactra™ and Adacel™ in Preadolescents and Adolescents (11 to 15 Year Olds); Statistical report: Comparison of Neisseria meningitidis immunogenicity when Menactra is administered concomitantly versus nonconcomitantly with 9vHPV vaccine

This study (Protocol V503-005) was an open-label, randomized, multicenter, comparative study to evaluate the tolerability and immunogenicity of the concomitant administration of the first dose of 9vHPV vaccine with Menactra and Adacel versus the

administration of 9vHPV vaccine nonconcomitantly with Menactra and Adacel. The study was designed to enroll 1240 healthy, preadolescent and adolescent boys and girls, 11 to 15 years of age. The subjects were stratified by gender (1:1 ratio) and randomly assigned to 1 of 2 vaccination groups in a 1:1 ratio. Subjects in Group 1 received the 9vHPV vaccine and Menactra and Adacel administered concomitantly on Day 1. Subjects in Vaccination Group 2 received the 9vHPV vaccine on Day 1 and Menactra and Adacel at Month 1. Subjects in both vaccination groups received the second dose of the 9vHPV vaccine at Month 2 and the third dose at Month 6. Serum samples were obtained from subjects in Group 1 immediately prior to vaccination at Day 1, Month 1, and Month 7. Serum samples were obtained from subjects in Group 2 immediately prior to vaccination on Day 1, and at Month 1, Month 2, and Month 7. Sera were analyzed to determine the antibody levels to the vaccine components.

Primary Immunogenicity Objectives regarding Menactra and Adacel:

- To demonstrate that Menactra administered concomitantly with Adacel and a first dose of the 9-valent HPV vaccine induces noninferior immune responses with respect to seroconversion percentages to *Neisseria meningitidis* serogroups A, C, Y, and W-135 compared with the administration of Menactra concomitantly with Adacel
- To demonstrate that Adacel administered concomitantly with Menactra and a first dose of the 9-valent HPV vaccine induces noninferior immune responses to diphtheria, tetanus, and pertussis compared with the administration of Menactra concomitantly with Adacel.

Primary Immunogenicity Hypotheses regarding responses to meningococcal or pertussis antigens:

- The percentages of subjects with a 4-fold or greater rise in antibody titers for *Neisseria meningitidis* serogroups A, C, Y, and W-135 one month post vaccination in subjects receiving Menactra concomitantly with Adacel and a first dose of the 9-valent HPV vaccine will be noninferior to the percentages of subjects receiving Menactra concomitantly with Adacel. The statistical criterion for noninferiority requires that the lower bound of the two-sided 97.5% confidence interval for the difference [Concomitant Group minus Non-concomitant Group] in percentages be greater than -10 percentage points for each Menactra component, i.e. excluding a 10 percentage point decrease.
- The anti-pertussis (anti-pertussis toxin [anti-PT], anti-filamentous haemagglutinin [anti-FHA], anti-fimbrial agglutinogens [anti-FIM], anti-pertactin [anti-PRN]) geometric mean titers (GMTs) one month post vaccination in subjects receiving Adacel concomitantly with Menactra and a first dose of the 9-valent HPV vaccine will be noninferior to the GMTs in subjects receiving Adacel concomitantly with Menactra. The statistical criterion for non-inferiority requires that the lower bound of the two-sided 97.5% confidence interval of the GMT ratio [Concomitant Group/Non-concomitant Group] be greater than 0.67 for each pertussis component, i.e. excluding a 1.5-fold decrease in the GMTs.

Results

Responses to pertussis antigens

The data in Table 11-6 of the clinical study report comparing the percent responders to the pertussis antigens based on four fold rises showed no meaningful difference between responses to FHA, PRN or FIM. However the lower bound of the 95% CI for responses to PT was -16.6 indicating a lower response rate in subjects who received vaccines concomitantly than in those who received vaccines separately. However the

comparisons of the GMTs met the criteria for success (presented in Table 11-4 of the clinical study report). The lower 97.5% CI for the GMT for the responses to PT was 0.69. In general the responses to PT in this age group were low, 28.5 and 35.7 for groups A and B respectively. The reverse cumulative distribution curves are discussed below regarding Merck's responses to IR 9 May 2013 (#8) but indicate no substantive difference between the curves between Groups A and B. No unusual or aberrant data were noted in the line listings.

Responses to meningococcal polysaccharides

The results for the antibody responses to the meningococcal polysaccharides were included as an appendix in the clinical study report due to the lack of an available assay at the time of the report. The results were submitted in the statistical report: "Comparison of *Neisseria meningitidis* immunogenicity when Menactra is administered concomitantly versus nonconcomitantly with 9vHPV vaccine." The percent of subjects with four fold rises meets the success criterion for all serogroups. The reverse cumulative distribution curves are discussed below regarding Merck's responses to IR 9 May 2013 (#8) but indicate no substantive difference between the curves between Groups A and B. No unusual or aberrant data were noted in the line listings.

Clinical Serologic Assays

No data were submitted to support the performance of the assays used to quantitate antibodies to pertussis antigens (pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN) and fimbriae (FIM)) and the serum bactericidal assays to quantitate responses to the meningococcal polysaccharides, groups A, C, W-135, and Y. As a result the following IR was sent to the sponsor.

IR 7 April 2014 (#4)

As we review STN 125508/0, CBER would like to request the following information:

1. Please provide the complete validation reports for the assays to quantitate antibody to the diphtheria, tetanus, pertussis and meningococcal antigens.
2. Please provide data that support the continued assay performance since validation and through the testing of the samples from Protocol 005.

The following documents were received in response to the IR in amendment 0.9:

Measurement of total IgG antibody to *Bordetella pertussis* – pertussis toxin by ELISA; Performance characteristics and validation for the assay performed at ----------(b)(4)----------. 2 March 2007.

Measurement of total IgG antibody to *Bordetella pertussis* filamentous haemagglutinin by ELISA; Performance characteristics and validation for the assay performed at ----------(b)(4)----------. 2 March 2007.

Measurement of total IgG antibody to *Bordetella pertussis* – fimbriae 2/3 by ELISA; Performance characteristics and validation for the assay performed at ----------(b)(4)----------. 11 April 2007.

Measurement of total IgG antibody to *Bordetella pertussis* – outer membrane protein pertactin by ELISA; Performance characteristics and validation for the assay performed at ----------(b)(4)----------. 2 March 2007.

Validation of the serogroup A, C, W135 and Y serum bactericidal antibody assay, number CD0166, 3 August 2011, ----------(b)(4)----------.

Summaries of QC panel run monthly for PT, FHA, PRN and FIM2/3.

Overview of the serum bactericidal antibody assay stability during 2011, number CD0218, 23 January 2012, ----------(b)(4)----------.

Assays to quantitate antibodies to pertussis antigens

Merck indicated that the validation reports for the IgG antibodies to pertussis toxin, (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) had been submitted and reviewed in INDs that predated the BLA supplement for concomitant administration of Gardasil9 with Adacel and Menactra (STN 125126/1516, approved June 2010). The report for IgG antibodies to fimbriae (FIM) was reviewed as part of the data to support: STN 125126/1516. The assays performed to support Gardasil approval for concomitant administration were conducted in late 2007 to early 2008. To my knowledge no review of the assays has been performed since the Gardasil review in 2010, or for any use of the assays beyond 2008. In July 2008, a memo was attached to the validation reports for all four of the pertussis assays indicating that the ----------(b)(4)----------. Also considered were the data that were submitted to demonstrate stability of the assay since validation. According to the reports, the validations for the PT, FHA and PRN assays were conducted prior to 2004 although the exact dates were not provided. The validation for the FIM assay was conducted in January of 2007. All validations predate the change in calculation method. As part of the review of the potential impact of the change in calculation method, several issues with all the existing validation reports were identified. As part of the revalidation needed to address the change in calculation method, the gaps in the existing validations should have been addressed. Upon discussion with the review committee, the specific gaps and issues were included in a letter to the sponsor in the context of the IND in which the relevant study (Protocol 005) was reviewed. The letter also recommends that all the gaps be addressed before the assays are used for future Phase 3 studies generating data that will be used in the label or to base regulatory action. The most important issue identified in the validation for the FIM assay was the lack of data to support the accuracy of the assay at the lower limit of quantitation (LLOQ). The issues for the PT, FHA and PRN assays included insufficient data to support the LLOQ, incorrect analysis of precision and insufficient detail in the report. However, assuming the assays were run under controlled conditions, the provided data do not indicate any substantive issues with the quality of the data generated using the assays.

The stability data found in “Summaries of QC panel run monthly for PT, FHA, PRN and FIM2/3” consisted of charts generated from monthly analysis of 27 samples in the assays. The data showed no indication of aberrant performance but insufficient details were provided to fully assess the data. The mean average ratios for each month were the only data presented. No explanation was provided as to how the ratio was determined. The expected and observed titers for each of the 27 samples were not provided. The CV values for each sample were not provided. Additionally only data from December 2010 to August 2011 were provided. These data were insufficient to

demonstrate the stability of the assay from the time of validation to the sample testing for Protocol 005. See the requests for additional information under the listing of the Information Requests below.

Assays to assess the anti-meningococcal bactericidal activity

The validation report for the serum bacterial activity assay, completed in August 2011, had not been submitted to CBER prior to this BLA. Thus a complete review of the validation was conducted.

Upon discussion with the review committee, the specific gaps and issues identified during review of the validation reports were included in a letter to the sponsor in the context of the IND in which the relevant study (Protocol 005) was reviewed. The most important issues identified with the validation report were the lack of a defined LLOQ and the failure to meet the criterion for inter-operator precision. The letter also recommends that all the gaps be addressed before the assays are used for future Phase 3 studies generating data that will be used in the label or as the basis for regulatory action.

The stability data found in “Overview of the serum bactericidal antibody assay stability during 2011, number CD0218, 23 January 2012, ----------(b)(4)----------” was a summary of technician competence testing for ----------(b)(4)----------.

Based on the gaps in the validation data identified, the following IR was sent to the sponsor.

IR 25 April 2014 (#7)

We acknowledge the receipt of your responses to our Information Request #4, dated April 7, 2014, regarding validation of assays to quantitate antibody to the diphtheria, tetanus, pertussis and meningococcal antigens, which you had submitted via gateway as amendments #09 and #10, dated April 21, 2014 and April 24, 2014, respectively. As we review these amendments, we have the following requests for information:

1. In order to sufficiently support the use of the diphtheria, tetanus, pertussis, and meningococcal assays for their intended purposes we are requesting you provide additional information for the IgG ELISAs for tetanus toxin, pertussis toxin, filamentous haemagglutinin, pertactin and fimbriae, toxin ----(b)(4)----- assay for diphtheria toxin, and for the serum bactericidal assays for the meningococcal groups A, C, W-135 and Y. Please provide for each assay in a readable file format a listing of the assays performed to generate the data for samples from Protocol

005. Please include assay dates, operators and run numbers. For each assay please provide the values for all parameters used to assess system suitability (assay acceptance) including quality control samples, reference curve parameters, bacterial cell counts and any other measure used to assess assay performance. Please include the assays that were rejected due to quality control issues.

Merck indicated by email that they were unlikely to be able to provide the information requested in IR #7 due to the nature of record keeping at the contract laboratory sites. Recognizing the limitations of the availability of the data, the request was simplified and refocused. Critical quality control data were again requested. Analyses of the clinical data in the form of reverse cumulative distribution curves was requested, so that any anomalies in the data might be identified in the absence of specific assay information. See IR #8 below.

IR 9 May 2013 (#8)

We have reviewed the validations and stability data submitted for the assays to assess immune responses to Adacel and Menactra, including the amendment received 8 May 2014. We find these data to be insufficient to demonstrate the performance of the assays to support concomitant administration in study Protocol 005. We acknowledge that the assays were reviewed during the approval of Gardasil, however in some cases changes made to the assays since that review are not sufficiently supported, or new validation reports not adequate to demonstrate suitable performance of the assays. In order to verify that the assays performed adequately during the testing of samples for Protocol 005, we are requesting additional information. The information to respond to comments 1 and 2 should be available from the laboratories as part of their routine assay monitoring and standard operating procedures. Comments 1 and 2 supersede CBER comment 1 in Information Request #7.

1. Please provide the algorithm for batching samples for analysis to prevent bias. Please also describe the means by which assay operators are blinded as to the subject, study group and time point for each sample.
2. Please provide the following information to demonstrate that the assays were adequately controlled during sample testing for Protocol 005.
    a. A description of the system suitability criteria used to accept or reject assay runs including the limits for each criterion and the basis for each criterion.

    b. The trending or tracking data for control samples run in each assay as part of the system suitability. Please include all data, including those from assays that were rejected.

3. Please provide the reverse cumulative distribution curves for pre and post immunization for both groups for the diphtheria, tetanus, pertussis and meningococcal antigens. Please plot all curves for a given antigen on the same figure for ease of comparison between pre and post and between study groups.
4. If you intend to use these assays to assess responses to diphtheria, tetanus, pertussis and meningococcal antigens in future Phase 3 studies, we recommend you address the gaps in the validations. Our detailed review of the validations submitted to the BLA will be provided to you in response to your submission of Protocol 005 in your IND 13447. Please acknowledge.

Merck responded to IR #8 in amendments 0.15, 0.17 and 0.27.
In response to CBER comment 1, Merck verified that the assay operators were blinded as to study group and that both pre-vaccination and post-vaccination samples were drawn at Month 1 thus partially blinding operators as to the expected responses. Samples were shipped in one large shipment to each laboratory with one or two additional minor shipments following in order to send samples received late from clinical sites or to provide additional volume if the original aliquot volume was depleted. Merck confirmed that samples were tested as received with no specific batching. While the methods of blinding the laboratory personnel may be insufficient to prevent bias with regard to pre versus post immunization, the randomization of groups and the blinding of the laboratories to study groups is likely sufficient to prevent bias in the critical comparison between the study groups.
In response to CBER comment 2.a, Merck verified that the SOPs provided in response to IR #4 are the appropriate SOPs in place during sample analysis.
In response to CBER comment 2.b
Pertussis assays: Merck indicated that the ----------(b)(4)----------, responsible for performing the assays to assess responses to the pertussis antigens, has been closed and access to the records limited. They provided a listing of the control and reference performance data for all assays in which samples from Protocol 005 were run. The data submitted indicate that the assays to measure responses to pertussis antigens were under control during the time in which the samples were run.
Meningococcal assays: Merck provided detailed charts of the controls including data from 2003 through 2012. The data support the stability of the assay.
In response to CBER comment 3, Merck provided the reverse cumulative distribution curves as requested. The curves indicate that the response rates for the concomitant versus separate administration groups are entirely overlapping with no apparent anomalous data seen. The curves support the quality of the data generated.
In response to CBER comment 4, Merck will either address the issues raised in CBER's review or find alternate validated assays for any future concomitant use Phase 3 studies.

Recommendation

While gaps in the validation reports for the assays to assess responses to Menactra and Adacel were identified, the additional data submitted, including the control data, indicate that the assays were performing appropriately during analysis of the samples from Protocol 005. Specifically the assays are considered acceptable for the following reasons: 1) the lack of any data that would indicate that the assays were not performing adequately, 2) the absence of any indication that the assays are unstable, 3) the absence of any data in the study that are unusual or anomalous, 4) the internally controlled design of the study and 5) the use of the assays to determine changes in immunogenicity rather than primary efficacy. I recommend that the labeling for concomitant administration of Gardasil9 with Menactra and Adacel be approved.