Statistical Review and Evaluation (Revised Summary and Conclusions) - Menveo

FDA NUMBER:	STN 125300
PRODUCT NAME:	Menveo (Novartis ACYW-135 Vaccine)
SPONSOR:	Novartis Vaccines & Diagnostics, Inc
SUBJECT:	Evaluation of the Immunogenicity, Safety, Reactogenicity, Effectiveness and Lot Consistency of Menveo®
INDICATION:	Immunization of individuals 11-55 years of age, for the prevention of disease caused by N. meningitis serogroups A/C/Y/W-135.
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BACKGROUND

This supervisory memo is being written to address some of the language in the statistical review memo dated January 13, 2010.
I have revised the following section 5 (SUMMARY AND CONCLUSIONS) from the January 13 statistical memo to reflect language that is more objective and appropriate. This revision is also applicable to section 1.2 of the EXECUTIVE SUMMARY section of the 1/13/2010 review. The rationale for this revision includes the following:

1. Whether a post-marketing safety study is needed should be determined by OVRR and the Division of Epidemiology (DE) for this regulatory action;
2. Deference should be made to OVRR and DE to determine the clinical relevance of statistical imbalances in adverse events;
3. While there do appear to be some imperfections in the submitted data, the data limitations should be considered in interpreting the results and reaching conclusions based on them, without any attribution of intent.

The revisions in the following section are in italics.

5. REVISED SUMMARY AND CONCLUSIONS

5.1 Summary of Statistical Results

The objective of this BLA submission was to provide evidence that MenACWY vaccine can be used for "active immunization of individuals 11 through 55 years of age to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W-135 and Y." With regard to immunogenicity and safety of MenACWY, the applicant's approach was to demonstrate non-inferiority of MenACWY as compared to such FDA licensed vaccines as Menactra and Menomune.

The statistical evaluation of the submission was based on three pivotal studies (V59P13, V59P18, and V59P17 (safety pivotal study)) and two supplemental studies. In the case of Study V59P13, all three primary immunogenicity objectives (lot-to-lot-consistency, two non-inferiority hypotheses for two age groups) were met. However, among participants aged 11-18 years, the seroresponse rates for 3 vaccine lots *revealed statistical differences* for each serogroup, particularly for W135 (lot A 74%, lot B 80%, lot C 70%), although they were not consistently high or low for any single lot. Similar remarks are *applicable to* percentages of participants with hSBA titer >1:8. *The following limitations should be considered in interpreting the data from study V59P13*:

1. Without pre-specification in the study protocol of the sample-size re-estimation, *the numbers of subjects in the immunogenicity subsets were increased 6 months after finishing the study enrollment*.
2. After the special second sample selection, the data structure of the first randomization for the immunogenicity testing was not retained for serogroups W and Y. For these groups, the effective randomization ratio for MenACWY vs. Menactra was 3.5:1 *rather than the pre-specified ratio of 3:1.*
3. Immunogenicity populations for serogroups W and Y were slightly younger for the MenACWY group (mean: 22, standard deviation: 12) than for the Menactra group (mean: 27, standard deviation: 14).
4. Each serogroup had its own subset population. Thus, immunogenicity hypotheses were tested on different datasets that contained different numbers of subjects and sometimes different subjects.
5. The vaccine group assignment in two study sites *was unblinded prematurely.* However, a statistical test of possible influence of these two sites on the primary endpoint results was performed by the applicant, and the results revealed that outcomes from these two centers did not have *noticeable* influence on the clinical study outcomes.

The second pivotal Study V59P18 was carried out in only one center in Costa Rica. The study population consisted of healthy adolescents 11 to 18 years of age. Subjects in the study received three types of vaccines: MenACWY, Tdap, and GARDASIL. Based on a pre-BLA agreement between the applicant and CBER, the HPV safety and immunogenicity data for girls were planned to be reviewed as a separate BLA supplement. Therefore, for study V59P18, only immune responses to MenACWY when given sequentially before or after Tdap were assessed by the reviewer. The assessment *revealed* that the co-primary immunogenicity objective #3 (non-inferiority immunogenicity hypotheses based on the seroresponse) was not met. *Thus, the objective of rejecting all three co-primary hypotheses was not met.* Another *feature* of this study was that different serum assay runs were used for different study groups.

Sera from Groups II and III were not assigned at random to assay runs. Whether this had any impact on the results is not known.
Regarding the MenACWY safety profile, based on the pivotal study V59P13, there was a *trend toward increased numbers o*f severe AEs in the MenACWY group. In the case of solicited severe local reactions, the difference is significant (p = 0.018; however, *this analysis was post-hoc, meaning that there is increased potential for false positive findings*). SAEs were reported by 24 (0.93%) subjects (28 adverse events) from the MenACWY group and by 5 (0.59%) subjects (7 adverse events) from the Menactra group. The applicant claimed that none of the SAEs were assessed as related to either of the two study vaccines.
Also in the pivotal study V59P13, eight events that occurred in the MenACWY group appear to have been suicide attempts. No such event was reported in the Menactra control group. Per the reviewer's research, any adequate comparison of suicide attempt rates between this study and the US general public is very difficult.
Additionally, it is worth noting that 2 cases of epilepsy and a case of seizure were observed in the MenACWY group. One miscarriage in the MenACWY group was not included by the applicant as a SAE in study V59P18. Also, 3 spontaneous abortions occurred in study V59P17. One of these spontaneous abortions in the MenACWY group was considered by the investigator as possibly related to the study vaccine and was counted as a SAE.

5.2. Recommendations

OVRR should consider the strengths and weaknesses of the submitted data, as outlined in this review, in determining the basis for regulatory action. Whether any post-marketing studies are needed should be decided by OVRR and CBER's Division of Epidemiology, based on the collective body of evidence.