Information Request Email, April 23, 2014 - GARDASIL 9

RECORD OF EMAIL COMMUNICATION

Submission Type: BLA Submission ID: 125508/0 Office: OVRR
Product: Human Papillomavirus 9-valent Vaccine, Recombinant
Applicant: Merck Sharp & Dohme Corp.

Telecon Date/Time: 23-Apr-2014 04:35 PM Initiated by FDA? Yes
Telephone Number: N/A (email)
Communication Category: Information Request
Author: Laura Montague
Telecon Summary: Clinical information and clarifications requested related to subject disposition, 3 SAE reports, non-US study sites, and spontaneous abortions.
FDA Participants: Laura Montague, Bharat Khurana
Non-FDA Participants: Alison Fisher, Merck
Trans-BLA Group: No
Related STNs: None
Related PMCs: None

Telecon Body:

From: Montague, Laura
Sent: Wednesday, April 23, 2014 4:35 PM
To: alison_fisher@merck.com
Cc: Khurana, Bharat
Subject: STN 125508/0; Information Request #5

Dear Alison,

As review continues on STN 125508/0, we have the following questions from our clinical team:

1. In your clinical study report (CSR) for Study V503-001, you provided four tables of study subject disposition (Module 5.3.5.1.p001-CSR, Tables 10-2, -3, -4, and -5, page 197-200) corresponding to each of four study segments. Please provide one subject disposition table for the entire study period (60 months), which should include the following information:

- Number of subjects who were screened
- Number of subjects who were randomized into to the study
- Number of subjects who completed the 3-dose regimen of the study vaccines

- Number of subjects who completed the study

- Number of subjects discontinued from the study, stratified by reason for discontinuation

  We understand that the trial was case driven and that a sizeable number of subjects had not completed all of the scheduled follow-up when the pre-specified number of cases was reached. Please also include the number of subjects who were still undergoing follow-up at the time that the pre-specified number of efficacy cases was reached.

2. We note in the CSR of Protocol V503-001 that three subjects reported serious adverse events (SAE) after administration of qHPV (all assessed as unrelated to the study treatment) and did not complete the 3-dose regimen of the vaccination. However, the reasons for the discontinuation from the study were not specified in the CSR, and the potential causes for the observed SAEs were not provided. Please provide reasons of discontinuation for these three subjects, and your rationales for assessing the causality of the SAEs as unrelated. The three subjects and SAEs are listed below.

   a. Subject AN 70545 developed tingling, numbness and altered sensitivity to temperature in her right leg a few hours after her second dose. She was diagnosed with multiple sclerosis and did not receive her third dose of qHPV.
   b. Subject AN 17568 developed gastroenteritis, abdominal pain, and fibromyalgia after her second dose of qHPV. She did not receive her third dose of qHPV.
   c. Subject AN 21474 developed spondylitic myelopathy (was later diagnosed as multiple sclerosis) after her second dose and did not receive her third dose of qHPV.

3. According to your response to the question 16 of CBER IR#1 (STN 125508/0.4, Module 1.11.3), Protocols V503-001, -002, -005, -006, and -007 conducted in non-U.S. study sites were not conducted under “the specific requirements of IND 13447”. We acknowledge that these study sites adhered to Good Clinical Practice as specified in 21 CFR 312.120 (b). Please clarify which specific requirements of IND 13447 were not followed by the non-U.S. study sites.

4. We note that for subjects who became pregnant with an estimated date of conception (EDCn) within 30 days of any 9vHPV vaccination, the proportion of pregnancies with known outcome terminating in spontaneous abortion appears to be higher than that for subjects whose EDCn were not within 30 days of vaccination (Appendix 2.7.4: 241 and 242, p908-911).

   a. Please provide your assessment of the imbalance noted for spontaneous abortions when the EDCn was within 30 days of vaccination compared to when the EDCn was not within 30 days of vaccination.
   b. Please provide the criteria used for determining the estimated date of conception for each subject.

c. Please also provide pregnancy outcome summary tables for subjects in study V503-001 who received qHPV and had pregnancies with EDCn within and not within 30 days of any vaccination.

Please provide your response(s) to this information request as amendment(s) to the BLA as soon as possible. Please reference this information request by date and include comment/question numbers.

As always, Dr. Bharat Khurana and I are available if you have questions. Thank you!

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