Information Request Email, June 13, 2014 - GARDASIL 9

RECORD OF TELEPHONE CONVERSATION
Submission Type: BLA Submission ID: 125508/0 Office: OVRR
Product: Human Papillomavirus 9-valent Vaccine, Recombinant
Applicant: Merck Sharp & Dohme Corp.
Telecon Date/Time: 13-Jun-2014 02:25 PM **Initiated by FDA?** Yes
Telephone Number: Email
Communication Categorie(s): 1. Information Request
Author: BHARAT KHURANA
Telecon Summary: Information requested (IR#13) regarding numerical imbalances in cases
FDA Participants: Bharat Khurana and Laura Montague
Non-FDA Participants: Alison Fisher and David Gutsch, Merck
Trans-BLA Group: No
Related STNs: None
Related PMCs: None
Telecon Body:
The following email was forwarded to the sponsor:
From: Khurana, Bharat
Sent: Friday, June 13, 2014 2:25 PM
To: alison_fisher@merck.com; Gutsch, David (david_gutsch@merck.com)
Cc: Montague, Laura
Subject: STN 125508/0; Information Request #13
Dear Alison and David,
As we review STN 125508/0, we have the following Information requests regarding numerical imbalances in cases of spontaneous abortions, multiple sclerosis, type 1 diabetes mellitus, and Raynaud's phenomenon in the 9vHPV group as compared with the qHPV group:

1. We have inquired previously (IR #5, sent on 23 April 2014) about rates of spontaneous abortion (SAB) among subjects in study V503-001 who became pregnant within 30 days before or after any study vaccination. Upon further review, the greatest numerical imbalance in SAB rates comparing the qHPV and 9vHPV treatment groups occurred in the defined risk window of vaccination within 30 days prior to the estimated date of conception (EDCn). Specifically, per our calculations, the SAB rate in 9vHPV recipients who became pregnant within 30 days after any vaccination was 24.6% (14/57 pregnancies) compared with 7.7% for qHPV recipients (5/65 pregnancies). The magnitude of this imbalance persisted regardless of analyzing for non-Latin American vs. Latin American study population and regardless of analyzing for covariate risk factors and possible alternate proximate causes for SAB based on case narratives. We acknowledge that you have previously commented in your response to our IR #5 on the numerical

imbalances in SAB rates observed in study V503-001. Please provide any additional analyses, interpretations, or perspectives that you feel would be helpful to explain these imbalances, in particular for the risk window of EDCn within 30 days after any vaccination.

2. We note an increased number of cases of multiple sclerosis (MS) in the V503-001 9vHPV treatment group (5 cases) compared with the qHPV group (2 cases). Based on the estimated average follow-up period for subjects in this study at the time of database lock, the incidence rate of MS cases among 9vHPV recipients appears to be higher than the range of incidence rates for MS reported in the general population. Please provide the incidence rates of MS in terms of number of cases per 100,000 person-years of follow-up for both the 9vHPV and qHPV treatment groups. Please also provide your interpretation of the incidence rate of MS observed in the 9vHPV group compared with the rate observed in the qHPV group and compared with the rates observed historically in the general population.
3. Please provide your interpretation of the numerical imbalances in cases of type 1 diabetes mellitus and Raynaud's phenomenon between the two treatment groups in Study V503-001.

Please submit your response as an amendment to STN 125508/0 at the earliest possible. As always, please feel free to contact Laura Montague or myself if you have any questions.

Thanks,
Bharat

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