

From: Sweeney, Colleen
Sent: Wednesday, December 14, 2016 12:11 AM
To: Margaretten, Nadine (nadine_margaretten@merck.com)
Cc: Khurana, Taruna; Steele, Matthew
Subject: RE: STN 125592/0 IR

Dear Dr. Margaretten:

We have the following request for additional information regarding your biological license application (BLA):

We note that safety analyses for several Phase 2 and 3 studies were conducted on the Full Analysis Set, defined as all subjects "as randomized." Specifically, Studies P014 and P015 used the Full Analysis Set for safety analyses, and for Study P012, it was decided, after unblinding, to analyze subjects as randomized. However, the pre-specified statistical plan called for safety analyses to be performed based on the actual treatment received.

In light of the above information, we have the following requests:

1. Please explain why the pre-specified plan for Study P012 was revised.
2. For any subjects in any Phase 2 or 3 study who crossed over to a treatment arm to which they were not assigned, please provide the following information:
 - Study name
 - Randomized treatment assignment
 - Actual treatment(s) received by study day
 - All adverse events (AEs) experienced by the subject, including onset by study day, whether the AE was classified as serious, and the AE outcome.
3. Please submit revised proposed labeling with presentations of the safety data that use the as treated population, defined as patients who ever received the investigational therapy regardless of the intended treatment assignment.

Please submit this Final Study Report as an amendment to STN 125592/0.

Thank you.

Captain Colleen Sweeney R.N., M.S., USPHS

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