RECORD OF TELEPHONE CONVERSATION

Submission Information

Application Type	BLA
STN	125614/0.0
Review Office	OVRR
Applicant	GlaxoSmithKline Biologicals / Lic. # 1617
Product	Zoster Vaccine Recombinant, Adjuvanted
Trans-BLA Group:	No

Telecon Details

Telecon Date/Time	06-JAN-2017 03:37 PM
Author	NAIK, RAMACHANDRA
EDR	No
Post to Web	No
Outside Phone Number	
FDA Originated?	Yes
Communication Categories	IR - Information Request
Related STNs	None
Related PMCs	None
Telecon Summary	IR regarding Clinical and BIMO issues, and Assay SOPs
FDA Participants	Ramachandra Naik, Michael Smith and Carmen Collazo-Custodio
Applicant Participants	Jody Gould and Norris Pyle

Telecon Body: E-mail message and the IR attachment pasted below.

RECORD OF TELEPHONE CONVERSATION

From: Naik, Ramachandra
Sent: Friday, January 06, 2017 3:37 PM
To: Jody Gould
Cc: Norris Pyle; Smith, Michael (CBER); Collazo, Carmen
Subject: STN 125614/0: IR regarding Clinical and BIMO issues, and Assay SOPs

Dear Dr. Gould,

Please find attached a request for additional information regarding STN 125614/0 (Zoster Vaccine Recombinant, Adjuvanted). Please provide your responses in an Amendment to STN 125614/0 by January 13, 2017, to comment 9, and by January 20, 2017, to the remaining comments.

Please confirm receipt of this message.

Please let us know if you have any questions or need additional information.
Regards,
Ram

Ramachandra S Naik, Ph.D.
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RECORD OF TELEPHONE CONVERSATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
OFFICE OF VACCINES RESEARCH AND REVIEW
DIVISION OF VACCINES AND RELATED PRODUCT APPLICATIONS

Date: **January 6, 2017**

Pages: **6**

To: **Jody Gould, Ph.D.**
Senior Director
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From: **Division of Vaccines and Related Products Applications**
Office of Vaccines Research and Review
Point of Contact: Ramachandra Naik, Ph.D.
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Telephone: (301)-796-2640 Fax: (301)-595-1124

STN: **125614/0**

Product: **Shingrix (Zoster Vaccine Recombinant, Adjuvanted)**

Subject: **Request for additional information**

Dear Dr. Gould,

Our review of the information provided in your BLA dated October 21, 2016, for Zoster Vaccine Recombinant, Adjuvanted, is ongoing. We have the following comments and request for additional information:

Clinical:

1. Regarding Clinical Study Reports (CSRs):

   Reference is made to the document "Summary of GSK-FDA Pre-BLA Type B Meeting" sent to you on June 23, 2016. Regarding the submission of reports for studies in the immunocompromised populations, CBER had requested the following in FDA Response to Question 7:

> "With regard to studies Zoster-001 and Zoster-015 in the immunocompromised populations, please elucidate what information from these studies you intend to propose for inclusion in the USPI. The data analyses from these studies would need to include overall and age-specific subgroups of ≥ 50 YOA and < 50 YOA. These data would need to be provided in a complete clinical study report encompassing all the data through study end (i.e., no separate annex reports) along with the datasets and SAS analysis programs."

We note that you have submitted annex reports for each of these two studies. Please submit the complete, integrated clinical study reports (CSRs) for Zoster-001 and Zoster-015 to the BLA or specify their location in your original submission dated October 21, 2016.

2. Word versions of the CSRs of Zoster-006, Zoster-022, the Summary of Clinical Safety (SCS) and the Integrated Summary of Efficacy (ISE) would be appreciated to facilitate the review process.

3. In the original BLA submission, Zoster-010 study report bodies are located under the main Zoster-010 tab as well as the Annex-010 tab. Please indicate whether these CSRs are identical, or whether there was other information you intended to include under the Annex-010 tab.

4. Please indicate the location in the study reports for Zoster-006 and Zoster-022 and the Integrated Summary of Safety (main safety pooling) of the comparative tabulations of the pre-existing medical conditions and baseline medications for subjects in the TVC of each vaccination group. If not provided in the study reports, please provide a table for the number and percentage of subjects in each vaccination group with pre-existing medical conditions in ≥ 2% of subjects in one or more vaccination groups by System Organ Class (SOC) and Preferred Term (PT). Please see the abbreviated template provided in Appendix A below for the requested structure of the table.

   Please provide a similar summary for baseline medications. The WHO Drug Dictionary ATC classification terms should be utilized with their appropriate first level group and second level subgroup. Please see the abbreviated template provided in Appendix B below for the structure of the requested table.

5. The WMEDIC dataset appears to include trade names of medications without the corresponding standardized generic medication name. The WHO Drug Dictionary names for medications were not provided in this dataset for Zoster-006, Zoster-022 or the Integrated Summary of Safety. Please specify which dataset contains this information or resubmit the WMEDIC datasets with an additional column containing the appropriate WHO Drug Dictionary name for each medication included in the dataset for Zoster-006, Zoster-022 and the ISS.

6. We acknowledge the Amendment to the BLA dated December 5, 2016, which specifies the tables included in the Integrated Summary of Safety (ISS) which are not linked to the Summary of Clinical Safety (SCS) and for which no discussion was provided in the SCS. As previously stated in our pre-BLA meeting comments, response to Question 12 (May 23, 2016) as well as the teleconference on November 16, 2016, we expected that the ISS would include more comprehensive information in addition to that contained in the SCS. Further, the Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (April 2009) (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm136174.pdf) Section IIIC notes that only in rare instances would a SCS be sufficiently detailed to serve as the narrative portion of the ISS, occurring "…if the application is small and consists of the single study or a number of small studies." Although we have indicated at this time that your application is fileable, please note that for future applications, unless specifically agreed upon with CBER, the ISS should not consist solely of tables but should include discussion of data presented in all tables. Please see the aforementioned Guidance for details. This comment does not require an itemized response.

7. For HZ Ascertainment Committee (HZAC) determinations, you state in Section 5.7.3 of the Zoster-006 Clinical Study Report that classification as a "case of HZ" required a unanimous decision by the HZAC. However, it is unclear how the two other classifications (i.e., "not a case of HZ" or "not able to decide") were made, and what voting options were available for individual HZAC members (i.e., whether "not able to decide" was a voting option for each member). Please clarify the following:

    a. The voting options for each individual member

    b. How the HZAC determination of "not a case of HZ" was made (e.g., also unanimously like "a case of HZ", or majority/non-unanimous vote)

    c. How the HZAC determination of "not able to decide" was made

8. In Section 5.2.9.4.2 (page 116) of the Clinical Overview referring to the ongoing studies of HZ/su in immunocompromised populations, you state that "so far, the IDMCs overseeing 3 (Zoster-002, Zoster-039 and Zoster-041) of the 4 of these ongoing studies have not raised any safety concerns". Please specify what, if any, safety concern was raised by the IDMC for Zoster-028.

9. In Section 6.2 of the Zoster-006 Clinical Study Report, the "number of subjects vaccinated" in Tables 22 (Final HZ efficacy analysis) and 23 [End of Study (EOS) analysis] differ in both vaccination groups. Please clarify why the "number of subjects vaccinated" is higher at the HZ final efficacy analysis than at the EOS analysis and provide the PIDs for the six subjects who appear to be excluded from Table 23.

APPENDIX A

For the tabulation of pre-existing conditions, subjects should be counted a single time for each applicable condition by PT. A subject with multiple conditions within a SOC should be counted a single time for that SOC. The SOCs and PTs included in the table below are examples; the table should be filled out according to the incidence specified.

Subjects in TVC with Pre-Existing Conditions by SOC and PT with Incidence of ≥ 2% (in One or More Vaccination Groups)

	HZ/su n	HZ/su %	Placebo n	Placebo %	Total n	Total %
Subjects in TVC		N/A		N/A		N/A
With one or more prior conditions						
With no reported prior conditions						
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
Anemia						
CARDIAC DISORDERS						
Atrial Fibrillation						
Cardiac Failure						
Mitral Valve Prolapse						

APPENDIX B

For the tabulation of prior medications, every subject should be counted once for each applicable medication. A subject with multiple prior medications within a medication category should be counted once in that category.

Subjects in TVC with Prior Medications
with Incidence of ≥ 2% (in One or More Vaccination Groups)

	HZ/su n	HZ/su %	Placebo n	Placebo %	Total n	Total %
Subjects in TVC		N/A		N/A		N/A
With one or more prior medications						
With no reported prior medications						
ALIMENTARY TRACT AND METABOLISM						
Drugs for acid related disorders						
Omeprazole						
Famotidine						
Drugs used in diabetes						
Glipizide						
Metformin						
CARDIOVASCULAR SYSTEM						
Agents acting on the renin-angiotensin system						
Enalapril						
Lisinopril						
Valsartan						

10. Regarding Financial Disclosures:

We request additional information about the financial disclosure report that was submitted for the clinical investigators and sub-investigators in Section 1.3.4 in your submission dated October 21, 2016. The report states that Dr. Tino Schwarz and Dr. Yoshihito Niki who participated in the two pivotal Phase III studies (110390 and 113077) received a significant amount of honorarium. Please provide in detail the nature and dates of activities that lead to those payments.

11. Regarding incomplete dates provided for the two Phase III studies (110390 and 113077):

    a. The CDISC SDTM DM (Demographics) datasets and the same date recorded on the Legacy Individual Listings show that only the month and year are provided for the birthdates of subjects enrolled at German sites, not the complete dates (month/day/year). Please confirm that the entire birthdates (month/day/year) for those study subjects were provided in the Legacy dataset. If they were not provided, please amend the applicable Legacy datasets for both studies.

    b. Some of the adverse events (AEs) data submitted in the CDISC SDTM AE datasets and the same unsolicited symptoms recorded on the Legacy Individual Listings do not have the complete dates (only the month and year are provided, not month/day/year) or are missing start and end dates. (They were collected after August 2, 2010, which was the study start date for Protocols 110390 and 113077.) Please provide complete dates (month/day/year) and start and end dates, where appropriate, in the Legacy datasets for both studies.

Chemistry, Manufacturing and Control:

12. Please provide SOPs for the following assays in English and in sufficient detail for reproduction:

    a. Purity of gE antigen by (b) (4)

    b. Potency of gE by (b) (4)

Please provide your responses, in an Amendment to STN 125614/0, by January 13, 2017, to comment 9, and by January 20, 2017, to the remaining comments. We recommend that you restate the item and follow it with your explanation or clarification. Use of this format helps organize the relevant information and provides a self-contained document that facilitates future reference. If you have any questions about this communication, please contact Ramachandra Naik, Ph.D. or Michael Smith, Ph.D. at (301) 796-2640.