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	10-FEB-2017 04:07 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 issues
FDA Participants	Ramachandra Naik, Michael Smith and Carmen Collazo-Custodio
Applicant Participants	Jody Gould and Norris Pyle

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

RECORD OF TELEPHONE CONVERSATION

From: Naik, Ramachandra
Sent: Friday, February 10, 2017 4:04 PM
To: 'Jody Gould'
Cc: Norris Pyle; Smith, Michael (CBER); Collazo, Carmen
Subject: STN 125614/0: Clinical IR

Dear Dr. Gould,

Please find attached a request for additional information regarding STN 125614/0 (Zoster Vaccine Recombinant, Adjuvanted). Please confirm receipt of this message, and provide your responses in an amendment to STN 125614/0 by February 17, 2017.

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

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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: **February 10, 2017**

Pages: **5**

To: **Jody Gould, Ph.D.**
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From: **Division of Vaccines and Related Products Applications**
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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:

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Clinical:

1. Regarding study recruitment:

   For studies Zoster-006 and Zoster-022, please provide a brief summary of how subjects were recruited for the study and indicate whether subjects were recruited from nursing homes and/or rehabilitation facilities.

2. Regarding National Clinical Trial (NCT) numbers:

   We acknowledge the NCT numbers that were submitted to the BLA in Module 1.2 of 125614/0. However, we cannot determine which study corresponds to which NCT number. Please provide the NCT number and corresponding study number (e.g., Zoster-022) for each study submitted.

3. Regarding study centers and investigators:

   We acknowledge the submission of 23-NOV-2016 in which contact information was provided for investigators participating in the Zoster-006 and Zoster-022 clinical trials. However, according to the Zoster-006 Clinical Study Report (CSR), 215 centers (Table 6.54) and 268 Principal Investigators (PIs – see page 3) were involved in the Zoster-006 study. However, the CTRINFO dataset (denoted as "raw data" in the data definition file) lists 256 discrete centers, with 245 PIs including centers 74895 and 80997, which were excluded from the Total Vaccinated Cohort (TVC). Please clarify the apparent discrepancy in numbers of study centers and PIs or indicate where we can find the explanation in the submission. Please include the following information in your response:

   a. How many centers did not enroll subjects, vaccinate subjects, or contribute to the TVC?

   b. Reasons for exclusion of these centers in the TVC analysis in Table 6.54 if subjects were enrolled and/or vaccinated at these centers.

   c. The number of PIs associated with the 215 centers listed in Table 6.54.

Regarding protocol deviations at the subject level and subject disposition:

4. Regarding the tabulations of subjects eligible for the modified Total Vaccinated Cohort (mTVC) at the Final HZ efficacy analysis:

   a. In Table 25 of the Zoster-006 Clinical Study Report (CSR) in (p. 251), you included the proportion of subjects of the TVC that participated in the mTVC in the Total column, but you did not include these proportions for each vaccination group or for each reason for exclusion by vaccination group. Please provide the proportions for each row beginning from "Total Vaccinated Cohort" (TVC)

through "modified Total Vaccinated Cohort" with the number in the TVC for each vaccination group as the denominator.

b. Please also provide a similar table including proportions for Table 26 of the Zoster-006 CSR (p. 254).

c. Please provide a table similar to the ones specified in requests 2a and 2b above but by region for the mTVC at the Final HZ efficacy analysis.

d. Please provide a table similar to Tables 6.55 and 6.56 in the Zoster-006 CSR, but for the mTVC at the Final HZ efficacy analysis or specify its location in the submission.

5. Regarding tabulations of subject disposition at the End of Study (EOS):

a. In Table 6.24 of the Zoster-006 CSR (p. 2306), you provided the proportion of subjects in the TVC that were included in the mTVC and ATP cohorts for efficacy in the column designated "Total", but you did not include the proportions for each vaccination group. Please submit a revised Table 6.24 with the proportions provided for the TVC, mTVC and ATP cohort rows for each vaccination group.

b. Tables 6.50 and 6.70 of the Zoster-006 CSR (pp. 2423 – 2424 and 2547 – 2548 respectively) included the proportions of subjects in the mTVC and ATP analysis cohorts relative to the TVC for the column designated "Total" but not for the columns for each age group (Table 6.50) or region (Table 6.70) by vaccination group. Please submit revised Tables 6.50 and 6.70 with these proportions provided for the TVC, mTVC and ATP rows (i.e., not for the rows between the TVC and mTVC, or mTVC and ATP cohort for efficacy) for each age and vaccination group (Table 6.50) and region and vaccination group (Table 6.70).

6. According to Table 6.13 of the Zoster-006 CSR, there were 338 and 276 subjects in the TVC (EOS analysis) in the HZ/su and placebo groups, respectively, who did not receive a second dose. Using the data provided in Table 6.13 of the CSR for Zoster-006, please provide the tabulations and proportions for the following table. The letter 'n' represents the number of subjects in that vaccination group who withdrew from vaccination for that given reason.

Table –XX Number of subjects withdrawn from vaccination (did not receive Dose 2) with reason for withdrawal (TVC – EOS analysis)

	HZ/su N = 338 n (n/N%)	Placebo N = 276 n (n/N%)
Visit not done		
Investigator decision – non-serious solicited AE(s)		
Investigator decision – non-serious unsolicited AE		

	HZ/su N = 338 n (n/N%)	Placebo N = 276 n (n/N%)
Investigator decision – SAE or pIMD		
Investigator decision – protocol violation or outside of time window		
Investigator decision – suspected HZ		
Investigator decision - other		
Subject decision – consent withdrawal not due to an AE		
Subject decision – non-serious solicited AE(s)		
Subject decision – non-serious unsolicited AE		
Subject decision - other		
GSK decision		

7. Please provide the proportions of subjects for each row and column for Table 23 of the Zoster-006 CSR (p. 246). For the calculation of the proportions, the denominator should be the number of subjects vaccinated in the TVC at the EOS analysis for each group (i.e., 7695 for HZ/su, 7710 for Placebo and 15405 for Total).

8. Please also provide similarly revised tables (i.e., including percentages for each row and column with the number of subjects vaccinated in each column as the denominator) for Table 6.37 (p. 2323) and Table 6.57 (p. 2437) of the Zoster-006 CSR.

9. Please provide a pictorial representation of subject disposition for Zoster-006/ZOE-50 (and if not included in the Zoster-022 CSR, for that study as well).

Regarding demographic characteristics:

10. Please provide or indicate where we can find in the Zoster-006 CSR a summary of demographic characteristics by region for the mTVC at the Final HZ efficacy analysis step.

11. Please provide the demographic totals for the following parameters and categories for North America and the Total for the TVC at the EOS analysis adapted from Table 6.72 of the Zoster-006 CSR (p. 2551):

	North America N = 2685	Total N = 15405
Age	N/A	N/A
Mean age at vaccination dose 1		
SD		
Median age at vaccination dose 1		
Gender	N/A	N/A
Male	n (n/N%)	n (n/N%)

	North America N = 2685	Total N = 15405
Female	n (n/N%)	n (n/N%)
Ethnicity	N/A	N/A
American Hispanic or Latino	n (n/N%)	n (n/N%)
Not American Hispanic or Latino	n (n/N%)	n (n/N%)
Geographic Ancestry	N/A	N/A
African Heritage/African American	n (n/N%)	n (n/N%)
American Indian or Alaskan Native	n (n/N%)	n (n/N%)
Asian – Central/South Asian Heritage	n (n/N%)	n (n/N%)
Asian - East Asian Heritage	n (n/N%)	n (n/N%)
Asian – Japanese Heritage	n (n/N%)	n (n/N%)
Asian – South East Asian Heritage	n (n/N%)	n (n/N%)
Native Hawaiian or Other Pacific Islander	n (n/N%)	n (n/N%)
White – Arabic/North African Heritage	n (n/N%)	n (n/N%)
White- Caucasian/European Heritage	n (n/N%)	n (n/N%)

12. Please provide a table similar to that in item #9 for the mTVC at the Final HZ efficacy analysis.

13. Regarding analysis populations:

Please provide or indicate where we can find the number of subjects in the TVC diary card subset by age and vaccination group in Zoster-006 (similar to Table 8 of the Zoster-006 CSR but with the actual, not provisional number of subjects).

We would appreciate the requested tables in Word format.

Please provide your responses, in an Amendment to STN 125614/0. 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.