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

Telecon Details

Telecon Date/Time	06-APR-2017 02:06 PM
Author	NAIK, RAMACHANDRA
FDA Originated?	Yes
Communication Categories	IR - Information Request
Telecon Summary	Clinical and Statistical IR
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: Thursday, April 06, 2017 2:06 PM
To: 'Jody Gould'
Cc: Smith, Michael (CBER); Norris Pyle; Collazo, Carmen
Subject: STN 125614/0: Statistical and Clinical comments

Dear Dr. Gould,

Attached is a request for additional statistical and clinical information regarding STN 125614/0 (Zoster Vaccine Recombinant, Adjuvanted). Please provide your responses, in an amendment to STN 125614/0, by Thursday, April 20, 2017.

Please confirm receipt of this message, and 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: **April 6, 2017**

Pages: **6**

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 requests for additional information:

Statistical:

1. Please provide additional details regarding the HZ efficacy analysis described in Table 33 and Table 7.106 of the Zoster-006 Clinical Study Report:
   (a) Among the 263 subjects who had a confirmed HZ episode up to and including the End of Study Analysis cut-off date, please describe in detail how you determined whether a subject should be included for the HZ vaccine efficacy analysis at the

Final HZ Efficacy Analysis Step and how his/her follow-up time was determined. In your description, please indicate which variables in which datasets were used.

(b) Please provide or indicate where we can find the SAS code used to generate Table 33 and Table 7.106.

(c) Please provide the list of subjects who were excluded from the HZ efficacy analysis at the Final HZ Efficacy Analysis Step.

Clinical:

In this IR, tabulations by MedDRA Preferred Term (PT) refer to outputs similar to Table 10.37 of the Zoster-006 Clinical Study Report (CSR), and tabulations by MedDRA System Organ Class (SOC) refer to outputs similar to Table 10.46 of the Zoster-006 CSR.

2. Please complete the following table for subjects with SAEs in Zoster-006 (TVC – EOS analysis).

Subjects reporting the occurrence of SAEs during select time periods (TVC – Zoster-006 EOS analysis)

	HZ/su N = 7695 n (%)	Placebo N = 7710 n (%)	Total N = 15405 n (%)
Subjects with ≥ 1 SAE reported [30-day (Days 0 – 29) post-vaccination period]	88 (1.1%)	97 (1.3%)	185 (1.2%)
Subjects with ≥ 1 SAE reported (Month 0 – Month 3)			
Subjects with ≥ 1 SAE reported (Month 0 – Month 8)			
Subjects with ≥ 1 SAE reported (Month 0 – Month 14)			

n/% - number/percentage of subjects reporting symptom at least once during the time period

3. Please provide a similar table, but by age group (50 – 59, 60 – 69 and ≥ 70 years of age) and without the "total" column.

4. According to Section 8.3.1 of the Zoster-006 protocol, "the standard time period for collecting and recording serious adverse events (SAEs) will begin at Day 0 and continue until Month 14 for each subject." Please provide, or indicate where in the submission we can find, the tabulations of subjects reporting the occurrence of SAEs classified by MedDRA SOC and by PT for this pre-specified time period of Months 0 – Month 14 (M0 – M14).

5. Please also provide, or indicate where we can find the following for subjects in the TVC of Zoster-006:

   (a) Tables by MedDRA SOC for subjects with SAEs during the following time periods:
   30-day post-vaccination period, M0 – M3, M0 – M8

   (b) Tables by MedDRA PT for subjects with SAEs for the time period M0 – M8

6. For Zoster-022, please provide the following for subjects in the TVC reporting the occurrence of SAEs:

   (a) A table similar to that in item 2

   (b) A table similar to that requested in item 3 with the age groups 70 – 79 and ≥ 80 YOA

   (c) As our review is ongoing, if not already provided, please also provide tables by MedDRA SOC and by PT for subjects in Zoster-022 reporting the occurrence of SAEs during the time periods included in item 2.

7. For Zoster-022, please provide or indicate where we can find a tabulation of subjects with SAEs with causal relationship to vaccination (listings provided in Table 10.91) by vaccination group for the two time periods M0 – M14 and during the whole vaccination period by MedDRA SOC and by PT.

8. In Zoster-006 and Zoster-022 (Section 10.2.7.4), you performed exploratory analyses of interest for SAEs for subjects in the TVC obtained at the EOS analysis. However, these analyses were performed for SAEs occurring during the whole vaccination period. We request that you generate new tables, similar to Tables 10.51 and 10.54 of the Zoster-006 CSR using the pre-specified M0 – M14 time period for the TVCs of Zoster-006, Zoster-022 and the main study pooling.

9. Please complete the following table for subjects reporting the occurrence of potential immune-mediated inflammatory disorders (pIMDs) at the selected time periods for Zoster-006:

Subjects reporting the occurrence of pIMDs during select time periods (TVC – Zoster-006 EOS analysis)

	HZ/su N = 7695 n (%)	Placebo N = 7710 n (%)	Total N = 15405 n (%)
Subjects with ≥ 1 pIMD reported (M0 – M3)			
Subjects with ≥ 1 pIMD reported (M0 – M14)			
Subjects with ≥ 1 pIMD reported (whole post-vaccination period)			

n/% - number/percentage of subjects reporting symptom at least once during the time period

10. For Zoster-006, please provide or indicate where we can find tables for the following:

    (a) A table by MedDRA SOC for subjects with pIMDs from M0 – M3

    (b) Tables by MedDRA SOC and by PT for subjects with pIMDs from M0 – M14

    (c) A table by MedDRA SOC for subjects with pIMDs during the entire study period

11. Please provide the following using the data from Zoster-022:

    (a) A table similar to that in item 9 above

    (b) Tabulations for subjects with pIMDs by vaccination group in Zoster-022 for the time periods in item 9 by MedDRA SOC and by PT if not already included in the Zoster-022 CSR.

12. Please specify where in your submission we may locate tabulations of subjects who died during specified time periods. Your tabulations of subjects with fatal SAEs/SAEs with fatal outcome at particular time periods relative to vaccination in the Zoster-006 and Zoster-022 CSRs include subjects who experienced SAEs with onset during the specified time period that were eventually fatal, but who did not die during the specified time period. For example:

    - Subject 26251 in Zoster-006 who is counted in Table 86 of the Zoster-006 CSR as a subject reporting a fatal outcome from M0 – M3 had an onset of the SAE (hepatocellular carcinoma) 20 days after first vaccination, but died (b) (6) days after the second vaccination.

    - Subject 3656 in Zoster-022 who is counted in Table 63 of the Zoster-022 CSR as a subject reporting a fatal outcome from M8 – M14 had an onset of the SAE (acute monocytic leukaemia) 214 days after the second vaccination, but died (b) (6) days after the second vaccination.

    Please provide the tabulations of subjects who died during select time points as well as tabulations of these subjects by MedDRA SOC and by PT during select time periods (see below).

    (a) Please provide the tabulations for subjects in the TVC who died during select time periods in Zoster-006:

Number and percentage of subjects who died during select time periods
(TVC – Zoster-006 EOS analysis)

	HZ/su N = 7695 n (%)	Placebo N = 7710 n (%)	Total N = 15405 n (%)
Subjects who died in the 30-day (Days 0 – 29) post-vaccination period			
Subjects who died (Month 0 – Month 3)			
Subjects who died (Month 0 – Month 8)			
Subjects who died (Month 0 – Month 14)			
Subjects who died (whole post-vaccination period)			

n/% - number/percentage of subjects reporting symptom

(b) Please provide the tabulations of subjects who died in the Zoster-006 TVC, classified by MedDRA SOC and by PT if not already provided, for the time periods in 12 (a)

(c) Please provide the table above by age group (50 – 59, 60 – 69 and ≥ 70 YOA) without "total" column .

(d) Please provide additional tables for subjects who died within the 30-day post-vaccination period and the M0 – M14 period by age by MedDRA SOC and by PT

(e) Please ensure that it is clear from table titles that tables generated for items 12 and 13 (and potentially 13) reflect the tabulations of subjects who died at the particular time period

13. The data requested in item 12 are requested for subjects in the TVC of Zoster-022. Please use age groups 70 – 79 and ≥ 80 years for the tabulations by age group for Zoster-022.

14. We request that you submit revised tables referencing subjects who died in the TVC of the main pooling analysis during the 30-day time period and up to one year post-vaccination in the ISS/SCS, provided by MedDRA SOC and by PT. It should be clear from the table title that the death(s) occurred during specified time periods.

15. Please evaluate whether similar tabulations of subjects with fatal SAEs who died within specified time periods affect other outputs in the ISS/SCS, for example, your tabulations of subjects who died at particular time periods relative to vaccination by age group and for North American subjects, as well as the tabulations for the broader pooling analysis. If so, they will need to be re-tabulated and re-submitted.

16. In the telecon (March 6, 2017) summary and IR sent on March 17, 2017, we notified you in item 6 (b) that the tabulations of Grade 3 unsolicited AEs during the 30-day post-vaccination period in the ISS included subjects with Grade 3 SAEs but not Grade 1 and 2 SAEs. Additionally, we asked for tabulations of subjects with non-serious unsolicited AEs and Grade 3 non-serious unsolicited AEs during the 30-day

post-vaccination period for the TVCs of Zoster-006, 022 and the main pooling analysis.

We would also like the tabulations of subjects reporting Grade 3 and above (i.e., including all SAEs) unsolicited events during the 30 day post-vaccination period by MedDRA SOC and by PT for the TVCs of Zoster-006, Zoster-022 and the main pooling analysis. Please indicate in the titles of these tables that the subjects had Grade 3 and above (including all SAEs) unsolicited AEs during that period.

17. Please provide a table similar to Table 25 in the SCS but for the TVCs of Zoster-006 and Zoster-022.

18. We requested specific tabulations of subjects with events during pre-specified time periods by MedDRA SOC in this and other IRs. Additionally, you should ensure that MedDRA SOC outputs are provided for major protocol-specified events by time period (e.g., medically attended events M0 – M8, unsolicited AE during the 30-day post-vaccination period) for the TVCs of Zoster-006, Zoster-022 and the SCS/ISS.

19. Please provide information as the nature of your SMQs, including whether they were broad or narrow, or customized. For example, the Cardiac Arrhythmias SMQ can be either broad or narrow and has several sub-SMQs.

20. According to Section 5.7.2.3 of the Zoster-006 and Zoster-022 protocols, the investigator was to "review and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study in the eCRF". Please provide a dataset for past medical history conditions for subjects in Zoster-006 and Zoster-022. Please include the following:
    - PID
    - Age
    - a flag for subjects in the TVC
    - Treatment variable with the codes HZ/su and Placebo

21. We would appreciate Word versions of the tables requested above.

Please provide your responses, in an Amendment to STN 125614/0, by Thursday, April 20, 2017. We recommend that you restate each 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.