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-MAR-2017 11:15 AM
Author	NAIK, RAMACHANDRA
FDA Originated?	Yes
Communication Categories	IR - Information Request
Telecon Summary	Clarification regarding number of subjects with events occurring from first dose to 30 days post last vaccination period and other clinical issues.
FDA Participants	Paula Agger, Carmen Collazo-Custodio, Meghan Ferris, Rong Fu, Tsai-Lien Lin, Ramachandra Naik, and Michael Smith
Applicant Participants	Fernanda Tavares Da Silva, Mohamed El Idrissi, Jody Gould, Lidia Oostvogels, Norris Pyle, Tamzin Tanner, Carla Vinals, and Toufik Zahaf

***Telecon Body*:**

The following topics were discussed during the teleconference:

1. Regarding item 3 discussed during the teleconference held on February 23, 2017, CBER stated that it used the "wunsol" dataset to confirm the numbers of subjects in the HZ/su group who reported at least one serious adverse event (SAE) and a fatal SAE, and we are looking forward to GSK's assessment. GSK stated that they are targeting submission of the response to item 3 by March 17, 2017. CBER noted that they had confirmed the numbers of subjects discussed in the teleconference of February 23, 2017.

   Post-meeting note:
   GSK submitted the aforementioned information in amendment 13, dated March 13, 2017.

2. CBER made reference to the following tables of the Integrated Summary of Safety (ISS):

   (a) Table 52 (page 461): Percentage of subjects reporting the occurrence of serious adverse events from the first administered dose up to 30 days post last vaccination period (Total Vaccinated Cohort)

(b) Table 297 (page 3336): Percentage of subjects reporting the occurrence of serious adverse events from the first administered dose up to 30 days post last vaccination period (Total Vaccinated North American Cohort)

(c) Table 110 (page 1911): Percentage of subjects reporting the occurrence of potential Immune Mediated Diseases from the first administered dose up to 30 days post last vaccination period (Total Vaccinated Cohort)

CBER stated that after analysis of datasets, we could not confirm the numbers of subjects provided in the tables for that time point and asked GSK to reanalyze. GSK stated that they will reanalyze and submit the response document as an amendment to their BLA.

3. CBER asked for clarification as to whether the P_IMD_L variable (defined in the ISS WUNSOL data definition file as potential pIMDS) represents pIMDs as determined by the investigator and if P_IMD is GSK-determined. GSK replied that CBER is correct in assigning/referring these two variables.

4. CBER explained that in Section 2.2.3 of the Summary of Clinical Safety (SCS), information on North American subjects with SAEs during the whole post-vaccination period was provided. As previously discussed, that time point was not pre-specified in the protocol for collection of non-fatal, unrelated SAEs. Therefore, please provide the following information:

   (a) CBER asked GSK to provide an assessment of SAEs in this population during the 365 days post-vaccination period. GSK agreed to provide the information in an amendment to their BLA.

   Post-meeting note:

   (b) Please also provide a table similar to Table 30 in the SCS, but for North American subjects in the TVC of the main safety pooling analysis with SAEs (regardless of causality) during the 365 day post last vaccination period. Please ensure that subjects are counted only once in an SOC if they have more than one event in that SOC during the specified time period.

5. Regarding inclusion criteria about age in two pivotal studies, CBER noted that several subjects not meeting the inclusion criteria for age in two pivotal efficacy studies were actually included in the TVC or mTVC analyses. For example, for study Zoster-006, in subjects ≥50 years of age (YOA), 1 subject (placebo) aged 48 years was included in TVC and mTVC, and for study Zoster-022, in subjects ≥70 YOA, 3 subjects (2 placebo, 1 HZ/su) aged 69 years and 1 subject aged 62 years (placebo) were included in the TVC, and the 3 subjects who received placebo were included in the mTVC for efficacy. Please clarify why these subjects were included in TVC and mTVC analyses of these studies. GSK agreed to provide their clarification in an amendment to their BLA.

CBER indicated that we also had a few requests for information which we will be providing in writing. The requests are below.

***Information Requests*:**

6. We request the following additional information to supplement Section 2.1.5.1 (Unsolicited AEs in the main safety pooling analysis) of the SCS:

   (a) Please provide or indicate where we can find a table similar to Table 18 of the SCS (subjects with at least one symptom and subjects with events classified by SOC) for the following:

      (i) Subjects with unsolicited AEs within the 30-day post-vaccination period (TVC – main pooling analysis)

      (ii) Subjects with unsolicited AEs within the 30 days post-vaccination period with a medically attended visit (TVC – main pooling analysis)

      (iii) Subjects with unsolicited AEs with a medically attended visit from first dose up to Month 8

   b) It appears that the tabulation of subjects in the TVC of the main pooling analysis with Grade 3 unsolicited symptoms during the 30 day post-vaccination period (Table 38 of the ISS) includes subjects with Grade 3 SAEs, but not Grade 1 or 2 SAEs. Please complete the following table for the numbers of subjects with non-serious unsolicited AEs (any grade) and Grade 3 non-serious unsolicited AEs during the 30-day post-vaccination period. Please also provide tables similar to Table 18 of the SCS and Table 38 of the ISS for subjects with non-serious unsolicited AEs (any grade) during the 30 day post-vaccination period. If your tabulations of unsolicited AEs were assessed similarly (i.e., including Grade 3 SAEs but not Grade 1 or 2 SAEs) in the CSRs for subjects in the TVC of studies -006 and -022, please submit the requested tables (the table below and tables similar to Table 18 in the SCS and Table 38 in the ISS) for unsolicited non-serious AEs and unsolicited Grade 3 non-serious AEs in these two studies individually, as well.

Example Table:

Table XX - Subjects reporting at least one non-serious unsolicited symptom (any grade and Grade 3) within the 30 day post-vaccination period (TVC – Main pooling analysis)

	HZ/su 50 – 69 N = 5887 n (%)	HZ/su **≥ 70** N = 8758 n (%)	Placebo 50 – 69 N = 5887 n (%)	Placebo **≥ 70** N = 8773 n (%)	Overall HZ/su N = 14645 n (%)	Overall Placebo N = 14660 n (%)
Subjects reporting occurrence at least one non-serious unsolicited symptom						
Subjects reporting occurrence of at least one Grade 3 non-serious unsolicited symptom						

n (%) – number and percentage of subjects reporting the symptom at least once

7. In order to better assess events which occurred in subjects included in the broader pooling analysis of the ISS who were not participants in Zoster-006 and Zoster-022, we request the following including only those subjects:

   (a) A table similar to Table 18 in the SCS for subjects reporting SAEs in the 30-day post vaccination period

   (b) A table similar to Table 18 in the SCS for subjects reporting SAEs during the 365 day post last vaccination period

   (c) A table similar to Table 59 in the ISS for subjects reporting SAEs in the 30-day post vaccination period

   (d) A table similar to Table 59 in the ISS for subjects reporting SAEs in the 365 day post vaccination period

   (e) A table similar to Table 18 in the SCS for subjects with fatal SAEs during the 365 day post-vaccination period

   (f) A table similar to Table 59 in the ISS for subjects with fatal SAEs during the whole post vaccination period

8. Please provide the following additional tables for Zoster-006:

   (a) A table similar to Table 60 of the Zoster-006 Clinical Study Report (CSR) with tabulations by age (50-59, 60-69, and ≥ 70 years of age) and vaccination group. For each solicited local event, include only rows for all grades and Grade 3/severe events and the sections for Dose 1, Dose 2 and overall/subject (not the section for overall/dose). Please exclude the 95% confidence interval columns.

(b) A table similar to Table 61 of the Zoster-006 CSR with tabulations by age (50-59, 60-69 and ≥ 70) and vaccination group. For each solicited general event, include only all grade and Grade 3 events, and the sections for Dose 1, Dose 2 and overall/subject (not the section for overall/dose). Please exclude the 95% confidence interval columns.

9. Regarding your revisions to Section 2.1.3 of the ISS in the submission of March 13, 2017 (response to CBER's February 23, 2017 IR), we note that the comparative analysis of SAEs in the main safety pooling was not provided for the first vaccination up to one year post last vaccination time point as "only data for the whole post-vaccination follow-up period are available" (page 8 of the submission of March 13, 2017; STN 125614, Amendment 13). However, we request that you submit these analyses, as it would appear that the data for SAEs from first vaccination up to one year post last vaccination are available in the datasets.

10. Please provide or indicate where we can find a table similar to Table 10.9 of the Zoster-006 CSR which includes the duration of fever (regardless of route and not limited to the 7 day post-vaccination period) by dose and overall per dose for both vaccination groups (TVC – End of study analysis), similar to that below. Should a similar tabulation not appear in the Zoster-022 CSR, please provide that as well.

Solicited symptom	Dose	Group	N	Mean	Min	Q1	Median	Q3	Max
Temperature/(°C)	Dose 1	HZ/su							
		Placebo							
	Dose 2	HZ/su							
		Placebo							
	Overall/dose	HZ/su							
		Placebo							

11. We note that you have provided a tabulation of the number of days with local symptoms (Table 10.15) and general symptoms (Table 10.16) not limited to the (7-day) solicited post-vaccination period in the Zoster-006 CSR. Please provide or indicate where we can find in the Zoster-006 CSR tabulations for the number of days with Grade 3 local and general symptoms, similar to Tables 10.19 and 10.20 but not limited to the solicited post-vaccination period.

Word copies of the tables requested in items 1, 6 to 8, 10 and 11 above would be appreciated.

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