RECORD OF TELEPHONE CONVERSATION

Submission Information

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

Telecon Details

Telecon Date/Time	23-FEB-2017 01:00 PM
Author	COLLAZO-CUSTODIO, CARMEN
EDR	Yes
Post to Web	Yes
Outside Phone Number	610-917-4086
FDA Originated?	Yes
Communication Categories	IR - Information Request
Related STNs	None
Related PMCs	None
Telecon Summary	Teleconference between CBER and GSK to discuss several items related to the presentation of the safety data in the BLA submission.
FDA Participants	Paula Agger, Carmen Collazo, Meghan Ferris, Ramachandra Naik
Applicant Participants	Mohammed El Idrissi, Brecht Geeraerts, Lidia Oostvogels, Norris Pyle, Fernanda Tavares Da Silva, Tamzin Tanner, Carlota Vinals, Toufik Zahaf

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Telecon Body:

The following topics were discussed during the teleconference:

1. Regarding Table 18 of the Summary of Clinical Safety (SCS) it appears that the "n" for the System Organ Class (SOC) rows may be the number of events in that SOC instead of, as indicated by the footnote, the number of subjects with at least one event in that SOC. For example, using the WUNSOL dataset, CBER noted that n=189 for "cardiac disorders" appeared to be the number of events, not the number of subjects with an event in that SOC. CBER mentioned that a similar analysis was performed for one SOC row in Table 10.46 of the Zoster-022 study report and the reviewer was able to corroborate that the number was the number of subjects with at least one event in that SOC. CBER asked GSK to do the following:

    a. To verify the numbers provided in Table 18 of the SCS with "n" being the numbers of subjects with at least one event in each SOC for the SOC rows (i.e., subjects with multiple events in an SOC would be counted only once for that SOC). If there are errors, to revise the table for the whole post-vaccination follow-up period.

    b. To provide a similar table to Table 18 for the time point from the first administered dose up to 365 days post last vaccination.

    c. To provide a similar table to Table 18 for the time period from the first administered dose up to 30 days post last vaccination.

    Post-discussion note: *If it is confirmed that the numbers for "n" in Table 18 reflect the number of events instead of the number of subjects reporting the symptom at least once, we request that you please conduct a quality check of tables with similar outputs and provide revised tables, as necessary.*

2. CBER noted that the comparative analysis of fatal and non-fatal SAEs in Section 2.1.3.1 and much of the descriptive analysis of the SAEs in Section 2.1.3.1.2 were conducted on SAEs (fatal and non-fatal) which occurred during the whole post-vaccination follow-up period. However, according to the Zoster-006 and Zoster-022 protocols, SAEs that were not fatal and not considered vaccine-related were to be collected and recorded only until Month 14. Therefore, the collection of SAEs that were not fatal and not considered vaccine-related from Month 14 to the end of the reporting period may have been inconsistently collected and recorded, as it was not required by the protocol, and thus the data may not be robust. CBER asked GSK to remove the parts of Section 2.1.3 which refer to SAEs during the whole post-vaccination time period. Further, although it is preferable to use protocol pre-specified time points consistently throughout this application, it is acceptable to revise your analysis of the SAEs (such as in Section 2.1.3.1.1) from

the first dose to 365 days post last vaccination time point, which appears to be used frequently in the SCS.

Post-discussion note: *Along with providing a revised Table 19 using the first administered dose to 365 days post last vaccination time point, CBER would appreciate a similar table for the first dose up to 30 days post last vaccination period.*

3. CBER made reference to Tables 53 (page 470), 54 (page 496), 60 (page 549), and 61 (page 555) of the Integrated Summary of Safety (ISS). CBER noted that in the HZ/su group 1,880 subjects experienced at least one SAE (fatal or non-fatal) during the whole post-vaccination follow-up period (Table 54), and 1,482 subjects experienced at least one fatal or non-fatal SAE from the first administered dose up to 365 days post last vaccination period (Table 53). Therefore, 398 subjects experienced at least one SAE (fatal or non-fatal) during the timeframe between 365 days post last vaccination to the end of the follow-up period. However, 634 subjects in the HZ/su group experienced at least one fatal SAE during the whole post-vaccination follow-up period (Table 62), whereas 153 subjects experienced at least one fatal SAE from the first administered dose up to 365 days post last vaccination period (Table 60), for a total of 481 subjects experiencing a fatal SAE in the timeframe between 365 days post last vaccination and the end follow-up period. It is unclear how the number of fatal SAEs (481) during a time period could be higher than the number of fatal and non-fatal SAEs (398) during the same time period. CBER would appreciate your comments regarding this, even though we have requested that references to SAEs during the whole post-vaccination follow-up period be removed from SCS Section 2.1.3.

   Post-discussion note: *In addition, it appears unlikely that 1,482 subjects would experience an SAE (fatal or non-fatal) in one year and only 398 would experience an SAE (fatal or non-fatal) during a period of several subsequent years.*

4. CBER noted that the some of the data tables provided in the Clinical Study Report for Zoster-006 (e.g., Section 10.2.7) do not have denominators and proportions and alerted GSK that we will likely be requesting revision of these or similar tables to include denominators and proportions. The same may apply to tables presented in other clinical study reports.

5. CBER noted that the SAE data on the Total Vaccinated Cohort in the clinical study reports appear to be presented as pre-specified in the protocol (up to Month 14), but the SAE data in the ISS are presented from the first vaccination up to Day 365. Although our review is ongoing, if not provided, CBER may request that you provide the analysis of SAEs on the pooled population of subjects ≥ 70 years using the pre-specified Month 14 time point.

Post-discussion note: *This may be necessary for other safety endpoints for the pooled population ≥ 70 years of age if the time points in the ISS do not conform to the time points in the study reports and safety tabulations on the pooled population at the time points pre-specified in the protocol are not provided in the Zoster-022 study report.*

CBER asked GSK to provide items 1-3 (listed above) in an amendment to the BLA as soon as possible. Since CBER's review of the application is still ongoing, it was agreed to have these revisions provided as a response to CBER's request for information with the expectation that the SCS and the ISS will need to be updated to reflect these changes at a later point during the review cycle. This advice was given to avoid having to ask GSK to submit a revised document every time CBER has a request while the review is still in progress.

Summary of Action Items

Item	Actions	Owner
Table 18 of the Clinical Summary of Safety (SCS)	1. Verify the numbers provided in Table 18 of the SCS. If there are errors, to revise the table for the whole post-vaccination follow-up period. 2. Provide a similar table to Table 18 for the time point from the first administered dose up to 365 days post last vaccination. 3. Provide a similar table to Table 18 for the time period from the first administered dose up to 30 days post last vaccination.	GSK
Section 2.1.3: *Other Serious Adverse Events* (page 80) of the SCS	Remove reference to SAEs during the whole post-vaccination follow-up period in this section. Revise Table 19 (page 84) to capture the analysis of SAEs collected from first vaccination until 365 post last vaccination and provide a similar table for the time point from first vaccination up to 30 days post last vaccination.	GSK

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Item	Actions	Owner
Tables 53 (page 470), 54 (page 496), 60 (page 549), and 61 (page 555) of the Integrated Summary of Safety	Evaluate the reason for having more fatal SAEs than SAEs (fatal and non-fatal) reported in the timeframe between 365 days post last vaccination and the end of the follow-up period	GSK
Tables similar to those in Section 10.2.7 of the Zoster-006 study report	Revise some tables to include denominators and proportions	CBER will likely ask GSK
SAE data on the Total Vaccinated Cohort presented as per protocol (up to Month 14)	Harmonize the SAE data on subjects ≥70 years from both studies at the M14 time point (if not already pooled and provided in the Zoster-022 study report).	CBER will likely ask GSK