Submission Information

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

Telecon Details

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Author	SMITH, MICHAEL
EDR	No
Post to Web	Yes
Outside Phone Number	
FDA Originated?	Yes
Communication Categories	IR - Information Request
Related STNs	None
Related PMCs	None
Telecon Summary	Summary of the 4/28/2017 CBER-GSK teleconference regarding clinical issues

FDA Participants	Paula Agger, Clinical Reviewer, OVRR/DVRPA/CRB2 • Carmen Collazo-Custodio, BLA Chair, Team Leader, OVRR/DVRPA/RRB3 • Marion Gruber, Director, OVRR • Meghan Ferris, Team Leader, OVRR/DVRPA/CRB2 • Rong Fu, Statistical Reviewer, OBE/DB/VEB • Andrea Hulse, Branch Chief, OVRR/DVRPA/CRB2 • Philips Krause, Deputy Director, OVRR • Ramachandra Naik, Regulatory Project Manager, OVRR/DVRPA/RRB3 • Michael Smith, Regulatory Project Manager, OVRR/DVRPA/RRB3 • Wellington Sun, Director, OVRR/DVRPA • Elizabeth Sutkowski, Branch Chief, OVRR/DVRPA/RRB3
Applicant Participants	• Ozzie Berger, VP, Head Regulatory Affairs RDC US • Dominique Descamps, Vice President, Head Clinical RDC Belgium • Brecht Geeraerts, Senior Manager, Clinical RDC Belgium • Jody Gould, PhD, Senior Director, North American Regulatory Affairs • Barbara Howe, VP and Director, Vaccines Medical and Clinical, US • Lidia Oostvogels, Director, Clinical and Epidemiology Project Leader Herpes Zoster Vaccine, Clinical RDC Belgium • Kimber Poffenberger, VP and Head, North American Regulatory Affairs • Amy Scott-Billman, VP and Head, Global Regulatory Affairs • Tamzin Tanner, Senior Manager, Global Regulatory Affairs • Fernanda Tavares, Director, Head of Safety Evaluation and Risk Management • Carla Vinals, Director, Global Regulatory Lead Herpes Zoster vaccine • Toufik Zahaf, Senior Manager, Lead Statistician Herpes Zoster Vaccine

Telecon Body:

Teleconference summary: CBER and GSK made introductions, and then CBER informed GSK that due to systemic network issues, we had not conducted a full review of the document that was e-mailed to CBER on April 27, 2017 (please refer to the attached slide deck entitled *"Clarification call on CBER-identified errors/omissions in the HZ/su BLA"*). GSK understood and it was agreed that GSK would go through the document with CBER during the call. GSK assured CBER that rigorous data Quality Control (QC) analyses were performed on the BLA prior to it being submitted. However, they agreed that several errors were made in tables that were generated manually. GSK said they would submit an overview document that will outline everything that will be revised, including the impact on downstream documents.

GSK started going through the document with CBER asking clarification questions or commenting as needed. The text below in italicized font refers to the specific text in a slide.

Slide 3:

- *All statistical outputs at the time they are generated*
- *All CSRs at the time they are generated*
- *Modules 2.5, 2.7.3 & 2.7.4*

Regarding the first two bullet points above, CBER asked for the meaning "at the time they are generated." GSK responded that the documents were "QC checked" and finalized after the studies were completed and the documents were generated (i.e., the documents were not changed after that or revised prior to the BLA being submitted).

Regarding the third bullet point above, CBER noted that only module 2 is referenced and asked if other modules were checked. GSK said that all modules were checked, not just module 2.

Slide 4:

In reference to Question 9 of Information Request (IR) provided to GSK on March 17, 2017, GSK identified an error in the statistical outputs and committed to provide the corrected information. GSK *confirmed that the conclusions do not change as a result of the corrections.*

Slide 5:

GSK acknowledged that several summary tables do not include proportions and proposed the following:

*To provide additional tables (as done for Z-006 in Question 4 & 5 of IR (10 Feb)) for Z-022, Main pooling, Broader pooling and Z-007**
**considered as a pivotal study and it is not included in the Broader pooling)*

CBER asked if the additional tables will only be for the ones already requested or for all tables. GSK said it would only be for the tables already requested, but similar tables will be submitted for studies Zoster-006, Zoster-022, the main pooling, the broader pooling, and Zoster-007. CBER noted that it would make sense to have GSK go through the submission, identify all summary tables that do not include denominators and proportions, and provide these revised tables to the BLA. GSK stated that they will have an internal discussion regarding the timeframe to generate these tables and get back to CBER. CBER later commented that we may not need all tables, but we need to discuss this internally and get back to GSK.

Slide 6:

Regarding several key outputs that were not provided by SOC, CBER noted that for future applications GSK should consider submitting tables with both SOCs and PTs included in each table as analysis by SOC was only provided for some multi-page tables of PTs.

GSK proposed to *provide any additional analyses (by SOC), that CBER has identified as relevant for meaningful review of the safety data.* CBER concurred with this proposal.

Slide7:
Regarding the analyses not presented on pre-specified time periods, GSK indicated that the whole post-vaccination period was pre-specified in the Statistical Analysis Plan of the ISS. However, GSK acknowledged CBER's request to conduct the comparative analysis for M0-14 rather than for the whole post-vaccination period. GSK performed the analyses requested by CBER and submitted it to the BLA. GSK concluded that t*he update to the section of the SCS had no impact on the conclusions*.

Slide 8:
GSK proposal:

Provide additional downstream analyses (by age, region and causality) for the Main pooling (365 days after the last dose) as well as for the overall and downstream analyses for Z-006 and Z-022 (M0-14).

CBER concurred with GSK's proposal. CBER asked if GSK could also submit outputs and tabulations for subjects with SAEs who are included in the broader pooling only (e.g., only these subjects, not for all subjects included in the main pooling and the broader pooling combined) for the 365 days timeframe after receiving the last vaccine dose. GSK said they will submit this information to the BLA.

Slide 10:
Regarding issues with SMQ analyses of most common SAEs for studies Zoster-006 and -022, GSK proposed:

To perform additional analyses as per CBER request for Main pooling Unsolicited AEs (30 days), SAEs (365 days after last vaccination), and Medically attended AEs (M0-8). This will be done for the same selected SMQs as described above i.e. Cardiac and Cerebrovascular SMQs, as narrow search in MedDRA 18.

CBER noted at least one irregularity regarding cardiac arrhythmia SMQ using MedDRA version 18 and the dataset (this was discussed in detail during the April 20, 2017, teleconference) and requested that if re-submitted, GSK be more specific about the nature of the SMQ (broad, narrow, and if utilized, which level) and ensure that the results of the query are consistent with the MedDRA version being used.

Slide 11:
GSK proposal:

In order to rapidly close out technical questions on GSK's statistical methodology, GSK would like to suggest regular direct contact (through teleconferencing) between CBER and GSK statistical teams.

CBER agreed to this proposal and reminded GSK that these teleconferences would need to be coordinated and scheduled through the BLA Chair and RPMs.

Slide 12:
Regarding the SCS and ISS, GSK requested confirmation as indicated below:

Following submission of the above response, GSK considered this issue closed and that there was no need to update the SCS/ISS. Dose CBER agree?

CBER agreed.

Slide 14:
GSK was requested to clarify the observed apparent discrepancy in number of any SAEs and
fatal SAEs over the entire follow-up period.

As GSK believes these tables are correct, GSK does not plan to perform any additional analyses for the specified tables or any tables for downstream analyses.

Question to CBER:
Does CBER agree that the response provided was acceptable and there are no further actions for GSK?

CBER did not agree that all of the tables are correct and further noted that the text in the SCS clearly states that the referenced table contained the tabulations of subjects who died during the specified time period, but the table included counts of subjects who experienced an SAE that was eventually fatal, but not during the time specified in the title of the table. GSK responded that that is correct, the subjects in the table had SAEs occurring during that time period which were fatal SAEs, but some subjects died later. CBER stated that the numbers and proportions of subjects who died during time periods relative to vaccine administration are important safety tabulations and asked for these tabulations for particular time periods (e.g., 30 days post vaccination time period and the 365 day time period). CBER noted that GSK used the terminology "time windows" in the statistical section of the protocol and they did not specifically define the timeframe when safety endpoints were captured. GSK said they would redo their analysis based on when the deaths occurred and submit this information and any related downstream information to the SCS. CBER also asked GSK to identify the program used to calculate this analysis and GSK agreed to provide this information. CBER noted that after GSK does this analysis, this might be an occasion when the GSK and CBER clinical and statistical teams could have a teleconference to discuss this information before it is submitted to the BLA.

Slide 15:

Question to CBER:

For other IRs on fatal SAEs, which approach should be used (date of SAE onset versus date of death)?

CBER responded that for other IRs, we would like to see tabulations of subjects who died during time periods relative to study product administration.

Slides 16 and 17:
Selected Major Protocol-specified event analysis *Unsolicited Symptoms* • *Within 30 days post-vaccination Unsolicited Symptoms – Grade 3* • *Within 30 days post-vaccination*

Proposed time period for

With regard to the tabulations of subjects with Grade 3 unsolicited AEs, CBER asked GSK to submit tabulations of subjects with Grade 3 and above unsolicited AEs occurring during the pre- specified time period which would include subjects with Grade 3 unsolicited AEs and all SAEs during that time period; as CBER had noted that subjects with Grade 3 SAEs, but not with Grade
1 or 2 SAEs were included in the tabulations submitted in the BLA. GSK agreed to CBER's request. Furthermore, CBER noted they had also requested in a previous IR additional tabulations of subjects with Grade 3 non-serious unsolicited AEs during the pre-specified time period.

CBER asked GSK to clarify the meaning of "not for related" and GSK clarified that it means
"for all," both related and unrelated.

Post-teleconference note: CBER plans to discuss with GSK which of these tabulations they refer to on slide 16.

Slide 19:
Quantity of downstream analyses and time to generate

- *Based on the above, the table count for the additional analyses is* ***~700 tables***

  Note: this does not yet include the analyses for SMQs mentioned in the minutes received from CBER on 25 April 2017.
- *Overall timeframe: ~6-8 weeks*

Does CBER agree that the extent of the additional analysis is sufficient to allow meaningful review?

CBER stated that they will discuss the amount of tables that will need to be submitted to the BLA and get back to GSK during the Mid-cycle communication (MCC) that is scheduled for May 3, 2017. GSK should prioritize sending revised tables with information regarding deaths and SAEs with the revised timeframes M0-14 to the

BLA. GSK stated that they will get back to CBER after discussing a timeframe for prioritizing the submission of these tables. GSK also requested that CBER let them know if there is another subset of tables that they could prioritize and CBER understood.

CBER asked GSK if they performed a safety analyses by gender. In addition, CBER asked if GSK conducted a safety and efficacy analyses by ethnicity or region. GSK replied that these analyses were not conducted, and stated that they analyzed safety only by region.

CBER commented that GSK still needs to respond to CBER's statistical IR regarding vaccine efficacy and GSK agreed.

CBER also noted that it appears a major amendment is likely for this application given the information to be provided. The timing of the pending amendment(s) and the amount of information (number of pages/tables) in them will also impact the timing of the AC and other late cycle items. However, the review team stated that they will do their best to review the application and to update GSK on this situation later during the review of the BLA.

Action Items:

1. CBER commented that we may not need all the tables referenced during the discussion of slide 5, but we will need to evaluate this internally and get back to GSK. In the meantime, GSK will provide a timeframe for submission of these tables.

2. GSK will prioritize generating tables regarding deaths and SAEs within the pre-specified timeframe and consider having a teleconference between the clinical teams prior to submitting the information to the BLA (slide 14). CBER also requested information about what program GSK will use to calculate the tabulations for deaths by time and GSK agreed to provide this information.

3. CBER will provide feedback on GSK's approaches for downstream analyses (slides 16-18) during the MCC teleconference.

4. CBER will send GSK an agenda for the MCC on Monday, May 1, 2017, but some of the issues listed will not be as granular. The MCC agenda was sent to GSK on May 1, 2017. CBER will provide GSK with feedback on GSK's proposal and additional guidance during the MCC which will help GSK in planning for its response.

5. CBER and GSK agreed to exchange summaries of this teleconference.

Post-teleconference notes:

1. Please provide subgroup analyses of safety by sex, race and ethnicity according to the protocol pre-specified safety endpoints and at the protocol specified endpoint time periods. Please ensure that all outputs include a summary of all observations

(imbalances vs no imbalances) and what if any conclusions can be drawn from the analyses. Please perform the analyses on the TVC of the main pooling (e.g., this does not need to be provided separately for Zoster-006 and Zoster-022). For safety evaluations by sex, please include analyses by age and sex using the following age groups 50 – 59, 60 – 69 and ≥70.

2. Please provide subgroup analyses of the primary efficacy endpoints for Zoster-006, Zoster-022 and the pooled analysis by race and ethnicity.