Our Reference: BLA STN 125614/0 June 1, 2017

GlaxoSmithKline Biologicals
ATTENTION: Jody Gould, Ph.D.
14200 Shady Grove Road
VR1500
Rockville, MD 20850

Dear Dr. Gould:

Attached is a copy of the summary for your May 3, 2017, Mid-Cycle Communication teleconference with CBER. This memorandum constitutes the official record of the teleconference. If your understanding of the teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to submission STN 125614/0 in your future submissions related to the subject product.

If you have any questions, please contact Ramachandra Naik, Ph.D. and CDR Michael Smith, Ph.D., at (301) 796-2640.

Sincerely,

Wellington Sun, M.D.
Director
Division of Vaccines and
Related Products Applications
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research

Mid-Cycle Communication (MCC) Teleconference Summary

Application type and number:	STN 125614/0
Product name:	Shingrix (Zoster Vaccine Recombinant, Adjuvanted)
Proposed Indication:	Prevention of herpes zoster (shingles) in adults aged 50 years and older
Applicant:	GlaxoSmithKline Biologicals
Meeting date & time:	May 3, 2017, 1:30 PM
Committee Chair:	Carmen Collazo-Custodio, Ph.D.
RPMs:	Ramachandra Naik, Ph.D. and CDR Michael Smith, Ph.D.

Attendees:

CBER:
Paula Agger, Clinical Reviewer, OVRR/DVRPA/CRB2
Deepa Arya, Epidemiology/Pharmacovigilance Branch Chief, OBD/DE/AEB
Carmen Collazo-Custodio, BLA Chair, Team Leader, OVRR/DVRPA/RRB3
Doran Fink, Clinical Team Leader, OVRR/DVRPA/CRB2
Meghan Ferris, Clinical Team Leader, OVRR/DVRPA/CRB2
Rong Fu, Statistical Reviewer, OBE/DB/VEB
Marion Gruber, Director, OVRR
Ravi Goud, Epidemiology/Pharmacovigilance Reviewer, OBD/DE/AEB
Andrea Hulse, Branch Chief, OVRR/DVRPA/CRB2
Tsai-Lien Lin, Statistical team leader, OBE/DB/VEB
Ramachandra Naik, Regulatory Project Manager, OVRR/DVRPA/RRB3
Laurie Norwood, Deputy Director, OCBQ/DMPQ
Rebecca Reindel, Clinical Reviewer, OVRR/DVRPA/CRB2
Michael Smith, Regulatory Project Manager, OVRR/DVRPA/RRB3
Wellington Sun, Director, OVRR/DVRPA
Elizabeth Sutkowski, Branch Chief, OVRR/DVRPA/RRB3
Shuang Tang, Product Reviewer, OVRR/DVP/LDV
Jeremy Wally, DMPQ Reviewer, OCBQ/DMPQ/BII

Applicant:
Ozzie Berger, VP, Head Regulatory Affairs RDC US
Dominique Descamps, Vice President, Head Clinical RDC Belgium
Brecht Geeraerts, Senior Manager, Clinical RDC Belgium
Jody Ann Gould, Senior Director, North American Regulatory Affairs, Vaccines
Barbara Howe, VP and Director, Vaccines Medical and Clinical, US
Linda Kramer, Head RA Facilities, Global Regulatory Affairs
Lidia Oostvogels, Director, Clinical and Epidemiology Project Leader Herpes Zoster Vaccine, Clinical RDC Belgium
Kimber Poffenberger, VP and Head, North American Regulatory Affairs
Norris Pyle, Senior Regional Expert Zoster US CMC
Amy Scott-Billman, VP and Head, Global Regulatory Affairs

Jens-Ulrich Stegmann, VP Clinical Safety & PV, Vaccines
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

Agenda and Discussion Summary: The agenda was sent to GSK on May 1, 2017, and it is listed below, followed by the summary of the discussion for each item in italics.

1. Any significant issues/major deficiencies, categorized by discipline, identified by the review committee to date.

   a. **Pre-licensure Inspection**: The Team Biologics inspection of the manufacturing site in (b) (4)/Rixensart, Belgium (FEI 3002875226) held in (b) (4) . Please note that we are currently not planning on conducting any pre-licensure inspections of applicable manufacturing sites for this BLA.

      Discussion Summary: *GSK asked CBER to update them if there are any changes and CBER agreed.*

   b. **Clinical**: Reference is made to the teleconferences held on April 20, 2017, and April 28, 2017, between GSK and CBER representatives in which we discussed serious issues that have been discovered during the clinical review of the BLA that adversely affected the meaningful review of the BLA. Many of the issues found are regarding the review of the safety data/information for studies Zoster-006 and Zoster-022, the Integrated Summary of Safety, and the Summary of Clinical Safety. CBER would like to continue these discussions with GSK during the Mid-Cycle Communication Teleconference.

      Discussion Summary: *As noted above, teleconferences were held on April 20 and 28, 2017, between CBER and GSK regarding the clinical review of the BLA, specifically concerning the safety data/information. Additionally, GSK e-mailed CBER a slide deck on April 27, 2017, that was discussed during the April 28, 2017, teleconference. CBER sent GSK summaries for both teleconferences and there were five action items and two post-teleconference notes listed on page 7 of the April 28, 2017, summary. The first three action items and the two post-teleconference notes were discussed during the MCC.*

      The first three action items listed in the April 28, 2017, teleconference summary were discussed during the MCC (for clarity in these minutes, the format of these first three items has been changed from "1, 2, 3" to "i, ii, iii"):

i. 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.

Discussion Summary: *GSK stated that it would take a substantial amount of time to generate all these tables, but noted that approximately two weeks would be added to the timeframe that was discussed during an earlier teleconference if they limit the tables to 1) demography, with downstream effects on analyses by region and 2) withdrawals, with downstream effects on analyses by region and age. CBER agreed that the demography tables lacked proportions, but stated that some of the safety tables also lacked proportions and asked GSK for a proposal for including proportions in key safety tables. GSK stated that they would have to look into this and couldn't provide a timeline at this time. In addition, GSK indicated that they will look at all the proposed outputs and prioritize in which order to generate and submit them.*

ii. 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.

Discussion Summary: *GSK stated they could submit the analyses of the following: SAEs with fatal outcomes with deaths occurring at time periods relative to vaccination with tabulations by age, race and causality during the week of May 24th. GSK will submit a proposal to CBER first and a teleconference with the clinical review team might follow to ensure the correct analyses and documents are submitted.*

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

Discussion Summary: *CBER stated the fatal SAEs with death occurring within the 30 days post-vaccination and one year post-vaccination were not included in the BLA and they requested the numbers and proportions of subjects that died within 30 days and within a year of receiving the vaccine. Regarding Grade 3 unsolicited AEs within 30 days post-vaccination, CBER requested the tabulation of Grade 3 unsolicited non-serious AEs only (i.e., not Grade 3 and above/Grade 3 non-serious and serious) to decrease the amount of information being submitted. CBER also asked that GSK apply this request to the information presented on slide 17 regarding main pooling and broader pooling. CBER asked for clarification on what GSK meant when they*

used the term "not for related" on slide 17. GSK stated that they meant for all related and unrelated SAEs.
CBER then stated that some analyses were already performed and asked GSK the reason for presenting them again (mainly deaths and Grade 3 AEs) in the slides that were referenced during the April 28, 2017, teleconference. GSK replied that the PTs were included in the tables previously submitted, but now they plan to include the SOCs along with the PTs.

Two post-teleconference notes were listed in the April 28, 2017, teleconference summary and these two items were discussed during the MCC (for clarity in these minutes, the format of these two items has been changed from "1, 2" to "i, ii,"):

i. 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.

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

Discussion Summary: *GSK stated that they have started performing the analyses and suggested submitting the requested information in a staggered approach.*

1a. The analyses on SAEs with fatal outcomes with deaths occurring at time periods relative to vaccination with tabulations by age, race and causality will be submitted May 24th.

iia. The analyses on all other AEs and pIMDs (about 300 tables), will be submitted June 9th.

iiia. The analyses on medically attended events, including unsolicited AEs and symptoms (about 180 tables), will be submitted June 16th.

iva. The analyses using SMQs and downstream effects were initially proposed by GSK to be submitted at the end of June, but after further discussion, CBER requested that this be omitted and GSK agreed.

CBER suggested having a small group teleconference in the near future to discuss the priorities and narrow the scope of what is being submitted; for example, subgroup analyses by sex, race and ethnicity as these are required analyses.

Post-Mid-Cycle Communication Note: A teleconference has been scheduled for Monday, May 8, 2017, 12:00 PM for the clinical team to discuss the pending submission.

2. Information regarding major safety concerns.

Clinical: Due to the review issues identified so far and discussed with GSK, CBER has not been able to complete a meaningful review of some portions of the safety information submitted to the BLA at this stage of the review cycle. CBER is evaluating imbalances identified for several conditions (please refer to item 3 below). We may identify additional AEs requiring CBER evaluation once the aforementioned data issues are resolved.

Discussion Summary: *See discussion under item 3 below.*

3. Preliminary review committee thinking regarding risk management.

Pharmacovigilance: CBER has identified imbalances for the following diseases: temporal arteritis, optic ischemic neuropathy, gout, osteonecrosis, and amyotrophic lateral sclerosis. We are continuing to evaluate these findings and their implications.

Discussion Summary: *CBER stated that they continue to investigate these findings and their implications, which may bring to light other imbalances as the review progresses. GSK understood and asked if there will be any IRs on these imbalances. CBER replied that no IRs are planned at this time, but wanted to bring this to GSK's attention.*

4. Any information requests sent and responses not received

a. 4/6/2017 Clinical and Statistical Information Request (IR)

Discussion Summary: *GSK stated they could either respond to the IRs themselves or by topic and staggered submissions. CBER replied that it would be better to keep the responses together by topic. CBER asked if GSK could reply to the April 6th IR regarding vaccine efficacy as soon as possible and GSK replied that they would. GSK stated that they would submit the rest of their responses to the April 6th and April 18th IRs together.*

b. 4/18/2017 CMC IR

Discussion Summary: *GSK stated that they plan to submit their responses to this IR on May 5th.*

c. 4/18/2017 Statistical IR

Discussion Summary: *GSK stated that they plan to submit their responses to this IR on May 16th.*

5. Any new information requests to be communicated

IRs related to the CMC, Clinical, and Pharmacovigilance disciplines will be provided to GSK

Discussion Summary: *There was no additional discussion on this item.*

6. Proposed date(s) for the Late-Cycle meeting (LCM)

a. The LCM between you and the review committee is currently scheduled for August 31, 2017, 1:00 PM.

Discussion Summary: *There was no additional discussion on this item.*

b. We intend to send the LCM meeting materials to you by August 25, 2017.

Discussion Summary: *There was no additional discussion on this item.*

c. If these timelines change, we will communicate updates to you during the course of the review.

Discussion Summary: *There was no additional discussion on this item.*

7. The Vaccines and Related Biological Products Advisory Committee meeting is scheduled for September 13, 2017.

Discussion Summary: *There was no additional discussion on this item.*

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.

None.

Discussion Summary: *There was no additional discussion on this item.*

At the end of the teleconference, CBER stated that GSK has presented safety information across many studies and requested that GSK develop an approach to link the revised tables and text to the original tables and text so there will be a seamless way to see both the old and new information and what was revised. GSK stated that they would send CBER their proposal. GSK then stated that during the teleconference held on April 28, 2017, CBER noted that a major amendment was likely for this application and asked if CBER still thought that this was the case. CBER replied that it was difficult to judge at this time and this decision will be informed by GSK's final agreed upon proposed outputs and actual timelines for the proposed submissions.

Action Items:

1. CBER and GSK will have a teleconference on Monday, May 8, 2017, at 12:00 PM, to discuss what tables and information will be included in the next submissions. GSK will then submit their proposal for the submission of safety information and results of safety analyses and CBER will review it in a timely manner and get back to GSK. CBER will indicate if the proposal covers everything they are looking for or if something else should be added or revised and resubmitted to the BLA.

2. The analyses on SAEs with fatal outcomes with deaths occurring at time periods relative to vaccination with tabulations on age, race and causality will be submitted May 24th.

3. The analyses on all other AEs and pMIDs (about 300 tables), will be submitted June 9th.

4. The analyses on medically attended events, including unsolicited AEs and symptoms (about 180 tables), will be submitted June 16th.

5. GSK will respond to the April 6, 2017, statistical IR regarding vaccine efficacy as soon as possible.

6. GSK will respond to the rest of the April 6, 2017, and the April 18, 2017, statistical IRs in one submission on May 16, 2017.

7. GSK will respond to the April 18, 2017, CMC IRs on May 5, 2017.