BLA 125614/0

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

September 27, 2017

Dear Dr. Gould:

Attached is a copy of the memorandum summarizing your August 31, 2017, Late-Cycle Meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

If you have any questions, please contact Ramachandra Naik, Ph.D. or CAPT Michael Smith, Ph.D. at 301-796-2640.

Sincerely,

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

LATE-CYCLE MEETING SUMMARY

Meeting Date and Time:	August 31, 2017, 1:00 PM
Meeting Location:	WO-Bldg 71, Room 1206
Application 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. By preventing herpes zoster, SHINGRIX reduces the overall incidence of postherpetic neuralgia.
Applicant Name:	GlaxoSmithKline Biologicals
Meeting Chair:	Carmen Collazo-Custodio, Ph.D.
Meeting Recorders:	Michael Smith, Ph.D. and Ramachandra S. Naik, Ph.D.

FDA ATTENDEES

Paula Agger, M.D., M.P.H., Clinical Reviewer, OVRR/DVRPA
Sudhakar Agnihothram, Ph.D., Regulatory Project Manager, OVRR/DVRPA
Nabil Al-Humadi, Ph.D., Pharm-Tox Reviewer, OVRR/DVRPA
Steven Anderson, Ph.D., Director, OBE
Deepa Arya, M.D., M.P.H., M.B.A, Branch Chief, OBE/DE
Noel Baichoo, Ph.D., CMC Reviewer, OCBQ/DBSQC
Lokesh Bhattacharyya, Ph.D., Lab Chief, OCBQ/DBSQC
Denis Cato, Chief BMB, OCBQ/DIS
Haecin Chun, M.S., BIMO Reviewer, OCBQ/DIS
Carmen Collazo-Custodio, Ph.D., BLA Chair, Team Leader, OVRR/DVRPA
Alfred Del-Grosso, Ph.D., CMC Reviewer, OCBQ/DBSQC
Karen Farizo, M.D., Associate Director for Medical Policy & Vaccine Safety, OVRR
Meghan Ferris, M.D., M.P.H., Team Leader, OVRR/DVRPA
Rong Fu, Ph.D., Statistical Reviewer, OBE/DB
Hana Golding, Ph.D., Lab Chief, OVRR/DVP/
Ravi Goud, M.D., M.P.H., Epidemiology Reviewer, OBE/DE
Marion Gruber, Ph.D., Director, OVRR
Dale Horne, Ph.D., Branch chief, OBE/DB/VEB
Andrea Hulse, M.D., Branch Chief, OVRR/DVRPA
Telba Irony, Ph.D., Deputy Director, OBE,
James Kenney, D.Sc., Lab Chief, OCBQ/DBSQC
Philips Krause, M.D., Deputy Director, OVRR
Loris McVittie, Ph.D., Deputy Director, OVRR/DVRPA
Randa Melhem, Ph.D., OCBQ/DMPQ
Ramachandra Naik, Ph.D., Regulatory Project Manager, OVRR/DVRPA

Laurie Norwood, M.S., Deputy Directory, OCBQ
Tao Pan, Ph.D., CMC Reviewer, OCBQ/DBSQC
Keith Peden, Ph.D., Branch Chief, OVRR/DVP
Scott Proestel, M.D., Director, OBE/DE
Rebecca Reindel, M.D., Clinical Reviewer, OVRR/DVRPA
Michael Smith, Ph.D., Regulatory Project Manager, OVRR/DVRPA
Wellington Sun, M.D., Director, OVRR/DVRPA
Elizabeth Sutkowski, Ph.D., Branch Chief, OVRR/DVRPA
Shuang Tang, Ph.D., Product Reviewer, OVRR/DVP
Jeremy Wally, Ph.D., DMPQ (Facilities, CCIT, Inspector) Reviewer, OCBQ/DMPQ
Claudia Wrzesinski, Ph.D., Pharm-Tox Reviewer, OVRR/DVRPA
Marina Zaitseva, Ph.D., DVP, Product Reviewer, OVRR/DVP

APPLICANT ATTENDEES

Ozzie Berger, Regulatory Affairs Head - US R&D Center, Global Regulatory Affairs
Emmanuelle Espié, Senior Epidemiology Lead Zoster, R&D Clinical and Epidemiology
Jody Gould, Senior Director, Regulatory Affairs, North American Region
Jacqueline Miller, Vice President and Head, US Clinical R & D
Lidia Oostvogels, Director, Clinical and Epidemiology Project Leader Herpes Zoster Vaccine, Clinical RDC Belgium
Norris Pyle, Associate Director, Regional CMC Expert, Regulatory Affairs, North American Region
Harry Seifert, Senior Director, Pharmacovigilance Alliance, Vaccine Clinical Safety & Pharmacovigilance
Jens-Ulrich Stegmann, Vice President, Head, Clinical Safety and Pharmacovigilance
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
Catherine Cohet, Senior Epidemiology Expert, R&D Clinical and Epidemiology
Benedicte Dupasquier, Director, Labeling Development, Global Regulatory Affairs
Toufik Zahaf, Senior Manager, Lead Statistician Herpes Zoster Vaccine
Arnaud Didierlaurent, Director and Head of Adjuvant Platform R & D Belgium
Kimber Poffenberger, Vice President, Head, North American Regulatory Affairs
Sophie Dandois, Manager, Global Regulatory Affairs
Gilbert Liebaut, Head, Platform Technologies, Global Regulatory Affairs

BACKGROUND

GlaxoSmithKline Biologicals (GSK) submitted BLA 125614/0 on October 21, 2016, for SHINGRIX (Zoster Vaccine Recombinant, Adjuvanted).

Proposed indication: SHINGRIX is a recombinant, adjuvanted vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older. By preventing herpes zoster, SHINGRIX reduces the overall incidence of postherpetic neuralgia.

PDUFA goal date: October 20, 2017

In preparation for this meeting, FDA issued the Late-cycle Meeting (LCM) Materials on August 22, 2017. In addition, FDA issued Advisory Committee Briefing Materials on August 17, 2017, and the FDA Errata to the Briefing Materials on August 30, 2017.

The Agenda items presented during the LCM are restated below followed by a summary of the discussion that occurred during the meeting in italics (under the sub-heading *LCM Discussion*).

DISCUSSION

1. Discussion of Substantive Review Issues

The following substantive review issues have been identified to date:

a. Product Testing

i. The review of the $AS01_B$ adjuvant lot release assay for the determination of the relative abundance of (b) (4) by the (b) (4) method is pending. CBER sent an Information Request (IR) on August 3, 2017, and responses are anticipated by September 1, 2017. The applicant will be asked to discuss a timeline for their response.

LCM Discussion:

GSK stated that CBER sent an Information Request (IR) in July 2017 regarding the validation report for the determination of the relative abundance of (b) (4) *in the $AS01_B$ adjuvant by the* (b) (4) *method. In this IR, CBER requested validation of this method for parameters such as accuracy, linearity, and range. GSK noted that the method is stability indicating and added that the* (b) (4) *are not impurities but part of a* (b) (4) *GSK informed CBER that the method was validated for its intended use. CBER then sent another IR on August 3, 2017, requesting validation data on accuracy, linearity, and assay range. GSK submitted their responses, including validation results for accuracy, linearity and range, in their August 29, 2017, submission to the BLA. CBER noted that review of the submission is in progress but the information appears to be acceptable. In addition, CBER determined the*

Limit of Quantitation (LOQ) from the data provided by the applicant, and concluded that all results reported by GSK are well above the LOQ, hence valid.

ii. During CBER's in-support testing, (b) (4) out of (b) (4) lots of gE antigen Final Containers have failed the total protein content by (b) (4) assay [results are out of specification (OOS)]. CBER needs to investigate these OOS results and initiated a collaborative interaction with GSK, including a telecon, to discuss this matter given that we are late in the review cycle.

- CBER requested additional samples and reagents on August 18, 2017, and CBER expects to receive these no-later-than the week of August 28, 2017.
- CBER held a telecon with GSK and discussed this matter on August 22, 2017.

LCM Discussion:

GSK stated that CBER received the samples, reagents and standards on August 30, 2017, and noted that they believe the problem might be in the standard that CBER initially used for the assay.

CBER thanked GSK for sending the samples, reagents and standards so quickly and mentioned that we already completed testing. However, CBER noted that there was some confusion regarding the "dose" in the proposed specification, and asked what "dose" meant. GSK replied that a dose would be the entire content of the vial. CBER thanked GSK for the clarification and stated that based on the definition of dose provided by GSK, the results of the second test were (b) (4) *, but if the dose was o.5 mL, then the concentration would be* (b) (4) *, which would barely pass the specification.*

CBER will send GSK an IR regarding this issue to request that GSK officially clarifies what a dose is in the context of the assay.

Post-meeting Note:

In an e-mail communication received on September 1, 2017, Mr. Norris Pyle from GSK made a correction that the dose is defined as 0.5 mL and the value is reported per the 0.5 mL dose (i.e., target 50 µg), and not the full content of the vial.

b. Clinical

i. Discussion on the proposed indication and review of the Prescribing Information (PI) are pending. Labeling meetings have been scheduled and the target date for sending labeling comments to GSK is no later than September 21, 2017.

This item was not discussed during the LCM.

ii. In study Zoster-015, Grade 3 local symptoms of fatigue, myalgia, and shivering were each reported by >20% of HIV-infected subjects < 50 years of age. These issues will be discussed with the applicant during review of the PI.

LCM Discussion:

Prior to the LCM, GSK informed CBER that they would like to obtain clarification on the reason for discussing Zoster-015 since the study was conducted in immunocompromised subjects and this population is not the subject of the BLA. Subjects aged < 50 years are not part of the indicated age range (i.e., SHINGRIX is intended for use in adults aged 50 years and older).

GSK stated they would like clarification from CBER on this question because the intended population for this vaccine is subjects ≥ 50 years of age who are not immunocompromised. CBER stated that this was a general comment for GSK and noted that section 8.6 on the draft PI, entitled "Immunocompromised Individuals," mentions subjects with HIV infection who received SHINGRIX. CBER further stated that internal labeling discussions are still ongoing and we will get back to GSK with any potential additional comments. GSK mentioned that the subjects in study Zoster-015 received three doses and more reactogenicity was observed in subjects receiving the later doses, but the current dosing schedule is for only two doses. GSK added that greater reactogenicity is observed in younger subjects and the three dose schedule in study Zoster-015 was the main driver for these reactogenicity events.

iii. In study Zoster-033, the overall incidence of herpes zoster (HZ) in subjects with a prior history of HZ over the 14-month study duration was higher than expected, although none of the cases included laboratory confirmation of disease and the incidence of HZ was not a pre-specified study endpoint. These issues will be discussed with the applicant during review of the PI. GSK has proposed a clinical study (Zoster-062) to formally evaluate the use of SHINGRIX in subjects with previous HZ.

LCM Discussion:

Prior to the LCM, GSK informed CBER that they would like to discuss the study design for Zoster-062 submitted to IND 13857 on March 17, 2017 (Sequence No. 0285, Amendment 286). CBER has not provided feedback to GSK on the proposed study design.

GSK provided a brief update on Zoster-056, the ongoing "cross-over" study where placebo recipients in Zoster-006 and Zoster-022 are offered vaccination with SHINGRIX and then followed for safety outcomes. In this study, the occurrence of suspected HZ (self-reported or medically diagnosed) is collected throughout the whole study period and is a secondary endpoint.

To date, 286 subjects with a confirmed case of HZ in Zoster-006 or Zoster-022 have been enrolled in the study. Of these subjects, only one subject has now reported a case of suspected HZ, clinically confirmed by the investigator.

In addition, GSK mentioned that Dr. Myron Levin (who was the chair of the adjudication committee for the pivotal studies Zoster-006 and Zoster-022) and Dr. Gershon (who was the chair of the IDMC for the same pivotal studies) reviewed the suspected HZ cases in the Zoster-033 study. Dr. Levin concluded that 7 of the 9 cases were not HZ. However, Dr. Gershon arrived at different conclusions. GSK will share the written opinions of these experts with CBER.

Post-Meeting Note:

GSK provided additional information on this topic in BLA amendment 46 (Sequence Number 46) received by CBER on September 25, 2017.

c. Epidemiology/Pharmacovigilance

Imbalances of optic ischemic neuropathy, polymyalgia rheumatica, temporal arteritis, gout and arthralgia were identified during the review of the pre-licensure clinical data. After CBER's feedback on the proposed Pharmacovigilance Plan (PVP), GSK submitted a proposal for a revised PVP, and an outline for a Targeted Safety Study (TSS), which is not a required postmarketing study). Reviewers are drafting a response to provide feedback on GSK's proposed PVP.

LCM Discussion:

Prior to the LCM, GSK informed CBER that they would like to discuss CBER's comments that were sent on August 29, 2017, regarding the PVP, specifically the items below:

- Case definitions
- Wording of new potential risks CBER requested in the PVP

GSK asked for clarification on the conditions to be monitored in the PVP. CBER stated there seems to be two issues: 1) amending the PVP, including clarification on the conditions monitored, and 2) the specific conditions monitored in the TSS.

GSK agreed to revise the PVP as described in the feedback provided by CBER on August 29, 2017. Specifically, osseous and ocular pathology would be added as separate potential risks, as this will facilitate monitoring and analysis. GSK expressed interest in creating a consensus list of conditions to be monitored in each of these two groups with CBER input, and CBER agreed to this.

GSK and CBER agreed that the ability of the TSS to adequately monitor the conditions of interest depended on many factors, and that all the details could not be discussed during the meeting. The possibility of enriching the study population to include more elderly individuals was briefly discussed, and GSK and CBER agreed that ability to study specific populations will depend on vaccine uptake, and the availability of data in specific age ranges. CBER and GSK also agreed that the case definitions will be important to ensure the conditions of interest can be reliably identified. The possible observation of certain conditions due to their association with advanced ages, and the potential to disentangle noise from signal in these situations with a comparator group was briefly discussed.

CBER asked if GSK could strive to submit the revised PVP by September 6, 2017, and a preliminary concept protocol for the TSS by September 20, 2017. GSK replied that they will try to provide the revised PVP by September 6, 2017. GSK agreed to try to meet these timelines. In addition, GSK and CBER discussed the possibility of scheduling a conference call to discuss the various aspects of the TSS.

Post-meeting Note:

GSK provided responses to CBER's comments dated August 29, 2017, in BLA amendment 40 (Sequence Number 40) received by CBER on September 7, 2017. CBER held a conference call with GSK on September 19, 2017, to discuss the updated PVP and the proposed TSS. In addition, GSK provided a protocol outline for the TSS in BLA amendment 47 (Sequence Number 47) received by CBER on September 26, 2017.

2. Information Requests

The following IRs are outstanding:

a. March 13, 2017, IR regarding the release data on (b) (4) gE FC lots filled under the (b) (4) filling duration (also formally requested in the IR of June 5, 2017, item 6)

GSK Response submitted August 24, 2017

b. August 2,2017, IR regarding process-related impurities for the gE and AS01 drug product final containers

GSK Response submitted August 29, 2017

c. August 3, 2017, IR regarding validation data on accuracy, linearity and limit of quantification of (b) (4) distribution by the (b) (4) method

GSK Response submitted August 29, 2017

d. August 18, 2017, IR requesting additional samples and reagents for protein content using the (b) (4) method

Samples received on August 30, 2017

e. August 22, 2017, IR regarding review of the Carton and Containers

Response in progress

LCM Discussion:

GSK stated they have already responded to the first four IRs listed above (a-d) and they do not anticipate any issues with CBER's comments on the Carton and Containers.

Post-meeting Note:

GSK provided responses to CBER's comments on the Carton and Containers in BLA amendment 43 (Sequence Number 43) received by CBER on September 20, 2017.

3. Discussion of Upcoming Advisory Committee Meeting

LCM Discussion:

Prior to the LCM, GSK provided CBER with a table of information that GSK might consider referencing at the VRBPAC meeting if the committee asks specific questions (refer to Attachment 1). Some of the items listed were not submitted to the BLA.

GSK asked CBER if they had any concerns regarding this information. CBER replied that we did not have any objection to the strategy proposed in the table and thanked GSK for providing this list. GSK also noted that they received confirmation from CBER that they have 90 minutes for the presentation at the VBRPAC meeting.

4. Postmarketing Requirements/Postmarketing Commitments

Two PMCs are under consideration at this time:

a. Study Zoster-062 to formally evaluate the use of SHINGRIX in subjects with previous HZ

b. A TSS to evaluate the safety of SHINGRIX in adults aged 50 years and older in a real time setting in the US

LCM Discussion:

Regarding feedback on the concept protocol for study Zoster-062 submitted to IND 13857, CBER stated that we look forward to having discussions with GSK about the design of this study after the BLA Action Due Date of October 20, 2017.

5. Major Labeling Issues

Review of the PI is ongoing and inclusion of the statement, "By preventing herpes zoster, SHINGRIX reduces the overall incidence of postherpetic neuralgia," in the INDICATIONS AND USAGE section is under discussion.

This item was not discussed during the LCM.

6. Review Plans

- CBER is currently reviewing the PI and the target date for sending labeling comments to GSK is no later than September 21, 2017.
- CBER will take an action on this application no later than October 20, 2016.

LCM Discussion:

Regarding the date of October 20th, it was clarified that CBER will take an action on this application no later than October 20, 2017.

Post-meeting Note:

CBER's comments on the PI were provided to GSK on September 21, 2017.

7. Applicant Questions

Prior to the LCM, GSK informed CBER that they would like to discuss the three items listed below:

- **Can CBER share their current thoughts on our approach to reactogenicity in the proposed label?**

  LCM Discussion:

  GSK asked if CBER had any questions or comments on the reactogenicity of SHINGRIX as it relates to the PI. CBER replied that we are discussing the best way to present these data in the PI. CBER also noted that the reactogenicity decreases in older vaccine recipients and because of this, CBER may be suggesting revisions to tables 1 and 2 of the PI. Following a question by GSK, CBER added that these proposed revisions will be included in the PI to inform health care providers about the decrease in reactogenicity with age.

- **In CBER's VRBPAC Briefing Document, it is mentioned that the dosing schedule is 0 and 2 months. Based on our clinical data, GSK has proposed 0 and 2 – 6 months in the draft PI. GSK requests clarification of CBER's position with respect to the dosing schedule.**

LCM Discussion:

GSK asked if CBER had any comments on the dosing schedule that will be in the PI and CBER stated we are still discussing this internally. GSK asked if there were concerns regarding the data on the second dose being 2-6 months after the first dose. CBER replied that there are no concerns about the demonstration of non-inferiority of the humoral immune response to SHINGRIX when administered on M0/M6 as compared to a M0/M2 schedule, but the description of the timing of the second dose as proposed in the draft PI will need to be discussed during labeling negotiations.

- **GSK's responses to IRs from CBER in some cases have implications for the contents of BLA modules. GSK would like to discuss the path forward for aligning with CBER on the best way and timing for updating BLA modules.**

LCM Discussion:

GSK asked CBER about updating the modules in the BLA. For example, documents in module 2 and the summary of clinical safety, due to the four large submissions GSK made during the review of the BLA. GSK requested feedback from CBER on how and when this should occur. CBER cautioned GSK about resubmitting data to CBER while the BLA is still being reviewed. CBER stated that GSK could consider submitting appendices or tables that list the most relevant items that were updated or revised during the review of the BLA.

CBER asked GSK to submit their proposal for updating the modules and CBER will review it and provide feedback.

Post-meeting Note:

GSK provided a proposal for updating clinical modules in BLA amendment 46 (Sequence Number 46) received by CBER on September 25, 2017.

8. Wrap-up and Action Items

- The discussions surrounding the PI are ongoing and CBER will send comments to GSK no later than September 21, 2017.
- GSK will submit their responses to CBER's comments on the carton and container labels.
- CBER will send GSK an IR to clarify the term "dose"
- GSK will submit their revised PVP around September 6, 2017, and then submit their concept protocol for the TSS around September 20, 2017.
- GSK will submit their proposal to update the BLA modules in the eCTD format and CBER will provide guidance after reviewing the proposal.

- CBER will provide feedback on the concept protocol for study Zoster-062 after the Action Due Date of October 20, 2017.

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.

Attachment 1

Data not in the original BLA	Planned use @ VRBPAC	Plan to share with CBER	Context of Use / Comments	Shared publically (ACIP, e.g.)
Summary of revised PVP	Briefing document (high level) Core presentation slide deck	Summary of revised PVP elements sent to CBER via email on August 11. FDA feedback received on August 29. To be discussed and agreed with the Agency and/or confirmed at the late cycle meeting (August 31)	As agreed with CBER, high level information shared in the Briefing Document (submitted on August 11).	No
Long term follow up data (safety and immuno) – 9 years	Back up VRBPAC slides	ACIP slides that included these data were submitted to IND 13857 on March 16, 2017 (Seq. No. 0284) The data have not been reviewed in detail by CBER; data are available for submission to IND for CBER's information.	To be used to answer a question and support that there has been no waning observed as yet.	ACIP meeting – February 2017
Preclinical data in non human primates to evaluate the systemic effect of AS01 to further clarify what was observed in mice.	Briefing Document- Back-up slides	The data were shared at the type C meeting on AS01 (Nov 3rd, 2015) A publication is in preparation -	Provides additional information on the nature and kinetics of the inflammatory response induced by the vaccine. In this model a systemic effect of AS01 was found to be self-limited, with a transient increase in Il-6 and IFN-γ (peak at Day 1) at low levels, suggestive of a spill-over from local activation. Overall, the nature and kinetics of the inflammatory profile of AS01 as described in the non-clinical models are consistent with the reactogenicity profile of HZ/su observed in clinical studies.	Poster at Keystone symposium "The Modes of Action of Vaccine Adjuvants", 2014, Seattle.

Data not in the original BLA	Planned use @ VRBPAC	Plan to share with CBER	Context of Use / Comments	Shared publically (ACIP, e.g.)
Zoster -001 and 015 data (immuno and safety – immunocompromised population)*	Back up slides	Submitted in the original BLA – October 2016	Since this is an indication of interest GSK will use these data only to answer a question from the VRBPAC. If these data are shown, GSK will reiterate that full data in this population are not in the initial BLA or reviewed by FDA, and will be the subject of a future application.	No
Zoster-048 data (Shingrix after Zostavax)	Back up slides	ACIP slides that included these data were sent to CBER on June 16, 2017. The data have not been reviewed in detail by CBER; data are available for submission to IND for CBER's information.	Data will be shown only in response to a question to show that this study was considered and conducted. If these data are shown, GSK will reiterate that full data in this population are not in the initial BLA or reviewed by FDA, and will be the subject of a future application.	ACIP meeting – June 2017
Summary of exposure and safety outcomes of studies of AS01-containing vaccines	Briefing Document and back up slide	A BLA amendment that included these data was submitted on July 26, 2017 (Seq. No. 0031).	Data will be shown only in response to a question regarding overall exposure or experience with AS01 adjuvant.	No
Summary of correlate of protection analysis results	Back up slides	The data have not been reviewed in detail by CBER; data are available for submission to IND for CBER's information.	Data will be shown only in response to a question to indicate we have considered this and are analyzing our data. GSK will remind the panel that efficacy data is available and used for BLA. If these data are shown, GSK will reiterate that these data are not in the initial BLA or reviewed by FDA.	No
Preliminary mice data on uric acid production at Injection sites with various adjuvants, including AS01	Back up slides	The existence of the data is disclosed in the answer to Question 1 of CBER's June 30 IR, submitted on July 26, 2017 (Seq. No. 0031).	Data will be shown only in response to a specific question regarding preclinical evaluation of uric acid production.	No

Data not in the original BLA	Planned use @ VRBPAC	Plan to share with CBER	Context of Use / Comments	Shared publically (ACIP, e.g.)
Clinical data on serum cytokines and HBs-specific CD4 T cell responses following administration of HBs/AS01B in healthy subjects (ECR-002)	Back up slides	Publication (Burny et al, Frontiers Immunology, 2017) is available for submission to the IND for CBER's information.	The data describes the level of cytokines detected after immunization of an AS01-containing vaccine. The Analysis showed a transient increase of some cytokines/markers at low levels (IFN-g, CRP and IL-6) and absence of others (IL-1beta, TNFa), showing that systemic effect is transient and self-limited.	Yes - Published
More detailed analysis of the mode of action of QS-21 and the synergy between QS-21 and MPL in ASO1	Briefing doc	Publications (Detienne, 2016; Welsby, 2017 and Coccia, 2017) are available for submission to the IND for CBER's information.	Publications provide more detailed analysis of the MOA of QS-21 but include the data provided in the BLA. They described the role of macrophages and caspase-1 pathway in QS-21 response (Detienne, 2016) and molecular mechanism on how QS-21 activates human dendritic cells (Welsby, 2017). Coccia et al describes the molecular and cellular mechanism of synergy between QS-21 and MPL. It includes the data presented in the BLA on the role of INFg in this synergy to promote CMI response.	Yes - published
Data from study Zoster-056 – subjects with clinical cases of HZ who have been revaccinated	Back up slides	Summary of data being prepared.		

*These data were submitted in the original BLA.