U.S. FOOD & DRUG ADMINISTRATION

Memorandum

DATE: September 27, 2017

TO: Carmen Collazo, BLA Committee Chair
Paula Agger, Clinical Reviewer
Rebecca Reindel, Clinical Reviewer
Ramachandra Naik, RPM
Michael Smith, RPM

FROM: Haecin Chun
Bioresearch Monitoring Branch
Division of Inspections and Surveillance
Office of Compliance and Biologics Quality

THROUGH: Dennis Cato, Chief, Bioresearch Monitoring Branch

THROUGH: Carrie M. Mampilly, Director, Division of Inspections and Surveillance

SUBJECT: Amended Bioresearch Monitoring Final Discipline Review Memo
BLA: STN 125614/0
PRODUCT: Zoster Vaccine Recombinant, Adjuvanted (Shingrix)
SPONSOR: GlaxoSmithKline Biologicals

REVIEW SUMMARY

Bioresearch Monitoring (BIMO) inspections were conducted at five foreign clinical sites in support of this Biologics Licensing Application (BLA). The inspections did not reveal significant problems that impact the data submitted in the application.

BACKGROUND

GlaxoSmithKline Biologicals (GSK) submitted this BLA to obtain a marketing approval for "Zoster Vaccine Recombinant, Adjuvanted (Shingrix) for use in adults 50 years of age and older." The following two pivotal phase III protocols were identified for BIMO inspection:

- A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' gE/AS01B vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years and older [110390 (ZOSTER-006)]

- A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety and immunogenicity of GSK Biologicals' gE/AS01B vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 70 years and older [113077 (ZOSTER-022)]

According to the sponsor, ZOSTER-006 and ZOSTER-022 were multicenter studies conducted in 18 countries, with 63 study sites in the United States (U.S.) and 193 sites outside of the U.S: a total of 219 study sites screened and enrolled study subjects for both protocols. The sponsor intiated the study of both protocols on the same day, and the clinical study sites conducted the study for each Protocol simultaneously. A total of 16161 study subjects were enrolled in ZOSTER-006, of which 16136 subjects were randomized to either of two treatment groups: the study vaccine or placebo. ZOSTER-022, enrolled a total of 14816 study subjects of which 14803 subjects were randomized to either of the two treatment groups.

The Bioreseach Monitoring Branch (BMB) member and the review committee selected five foreign clinical investigators conducting ZOSTER-006 and ZOSTER-022. These clinical investigators were selected based on subject enrollment, previous inspectional history and an evaluation of the data submitted in the BLA. The inspection of the general study conduct at each of the study sites was performed in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators.

Additionally, the information and data submitted in the BLA were compared to source documents at each clinical study site during the inspection for either ZOSTER-006 or ZOSTER-022. The BIMO inspection assignment also included specific questions concerning the clinical study. This data review at the inspected sites represented approximately 6.6 % (n=1063) of enrolled subjects for ZOSTER-006 and approximately 4.4% (n=648) for ZOSTER-022.

INSPECTION FINDINGS

No significant inspectional findings were noted from the BIMO inspection. However, the following issues were reported in the Establishment Inspection Reports (EIRs) and were discussed with the relevant review committee members:

- One FDA investigator who inspected two of the five study sites noted that the inspected study sites did not have records of the vaccine reconstitution time
- No signed Form FDA 1572 (Statement of Clinical Investigator) documents were available at the five inspected foreign sites

The table below summarizes the BIMO inspections at five foreign study sites selected for Protocols Zoster-006 and ZOSTER-022:

Protocol	Site ID	Study Site Location	Form FDA 483 Issued	Final Classification
110390 (ZOSTER-006)	76849	Taipei, Taiwan	No	No Action Indicated
	79857	Hradec Kralove, Czech Republic	No	No Action Indicated
113077 (ZOSTER-022)	78504	Valencia, Spain	No	No Action Indicated
	80520	Helsinki, Finland	Yes	Voluntary Action Indicated
	80932	Sao Paulo, Brazil	Yes	Voluntary Action Indicated

SPONSOR ISSUES

No significant sponsor or monitoring issues were noted at the inspected study sites; however, the following issue was discussed with the relevant review committee members:

- During the inspection, FDA investigators noted that the five inspected study sites had no signed copies of Form FDA 1572 (Statement of Investigator).

Additionally, BMB included the following items in the review committee's information request (IR) letter that was issued to the sponsor on January 06, 2017:

- Financial disclosure – See the detail info in the "Financial Disclosure" section
- Incomplete study subject demography – For the entire study subjects enrolled at all clinical sites in Germany, the sponsor only provided month and year for their birth date (month/year)
- Adverse events (AE) dataset – The fields to enter start and end dates were lacking entries. The AE start and end dates were either missing or not filled in with the full date (month/day/year)

The sponsor addressed the requests by amending their BLA on January 20 and January 27, 2017, and BMB reviewer discussed the responses with the review committee.

FINANCIAL DISCLOSURE

The Clinical Investigator Compliance Program directs the FDA investigator to ask the clinical investigator if and when he/she disclosed information about his/her financial interests to the sponsor and/or interests of any sub-investigators, spouse(s) and dependent children, and if and when the information was updated. The information submitted to the BLA was verified for each of the inspected clinical sites.

An Information Request was issued to the sponsor on January 06, 2017, where BMB reviewer and the review committee asked the sponsor to provide more detailed information about the nature and dates of activities that lead for those clinical investigators to receive the honoraria. The sponsor amended the BLA with atheir response on January 27, 2017. BMB and the clinical reviewers concluded that the sponsor adequately provided the requested information and their response did not reveal any conflict of interests that would impact the data submitted in the BLA.

ADMINISTRATIVE FOLLOW-UP

Information letters were issued to the four clinical investigators. Information letter to one other clinical investigator will be issued after a minor administrative matter is resolved.

Should you have any questions or comments about the contents of this memo or any aspect of Bioresearch Monitoring, please contact me at (240) 402-8038.

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Haecin Chun
Consumer Safety Officer