Memorandum

DATE: January 18, 2018

TO: Mikhail Ovanesov, Ph.D., Chair
Bindu George, M.D., Clinical Reviewer
Jean Gildner, 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 Mampilly, Director, Division of Inspections and Surveillance

SUBJECT: Bioresearch Monitoring Final Discipline Review Memo – Addendum

BLA: 125586/0
PRODUCT: Coagulation Factor Xa (Recombinant), Inactivated (Andexanet alfa)
SPONSOR: Portola Pharmaceuticals Inc.

REVIEW SUMMARY:

Bioresearch Monitoring (BIMO) issued two clinical investigator inspection assignments in support of the original Biologics License Application (BLA) when it was first received on December 18, 2015. Subsequently, two additional BIMO inspections of clinical investigators were conducted after the sponsor submitted a response to a Complete Response Letter (CRL) dated August 17, 2016. These inspections did not reveal significant problems that impact the data submitted in the application.

BACKGROUND

The BIMO and clinical reviewers for this application selected two domestic clinical sites to be inspected for clinical study 14-505, *A phase 3/4b Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who have Acute Major Bleeding*. The two sites were selected based on several factors, including subject enrollment, previous inspectional history and an evaluation of the data submitted in the BLA.

The confirmatory study, Protocol 14-505 was an on-going study at the time of the response submission; therefore, the BIMO inspection assignments were issued with the datasets that the

sponsor provided based on the data cut-off date of April 20, 2017. This portion contained the data of 185 enrolled subjects from 27 clinical study sites: 23 sites were in the United States and four were foreign study sites. The two domestic sites selected for BIMO inspections represented approximately 18% of the enrolled subjects.

The inspections were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. Information submitted in the BLA was compared to source documents at this site for selected study subjects. Additionally, the inspection assignment included specific questions concerning the clinical study mentioned above.

INSPECTION SITES

The following table summarizes the BIMO inspections for Protocol 14-505:

Study Site Number	Site Location	FDA Form 483	Final Classification
3	Boston, MA	Not Issued	No Action Indicated
24	Sarasota, FL	Not Issued	No Action Indicated

INSPECTIONAL FINDINGS

Study Site #24: None of the informed consent forms signed by the study subjects included the required clinicaltrials.gov statement. The site made the correction before the inspection was complete; therefore, a Form FDA 483 was not issued for this finding at the end of this inspection.

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, including if and when the information was updated. The information submitted to the BLA was verified for each of the inspected clinical sites.

SPONSOR ISSUES

The BIMO inspections did not reveal sponsor related issues. Application review issues related to financial disclosure and the tabulation datasets submitted in the application were adequately addressed by the sponsor.

ADMINISTRATIVE FOLLOW-UP

Information letters were issued to all parties inspected in support of the BLA submission.

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

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Haecin Chun
Consumer Safety Officer