MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE: June 23, 2016

FROM: Haecin Chun
Erin McDowell
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Division of Inspections and Surveillance
Office of Compliance and Biologics Quality

THROUGH: Patricia Holobaugh, Bioresearch Monitoring Branch Chief

THROUGH: Gilliam Conley, Director, Division of Inspections and Surveillance

TO: Mikhail Ovanesov, Chair
Lisa Faulcon, Clinical Reviewer
Thomas Maruna, RPM

SUBJECT: Bioresearch Monitoring Final Discipline Review Memo
SPONSOR: Portola Pharmaceuticals Inc.
PRODUCT: Coagulation Factor Xa (Recombinant), Inactivated (Andexanet alfa)
BLA: 125586/0

FINAL SUMMARY STATEMENT

The Bioresearch Monitoring (BIMO) inspection of two clinical investigators in support of this Biologics Licensing Application (BLA) did not reveal substantive problems that would impact the data submitted in the application.

BACKGROUND

CBER Bioresearch Monitoring (BIMO) issued two domestic inspections for the following two Phase 3 protocols identified by the review committee in support of this BLA:

- A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study in Older Subjects to Assess Safety and the Reversal of Apixaban Anticoagulation with Intravenously Administered Andexanet alfa (Protocol 14-503)
- A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study in Older Subjects to Assess Safety and the Reversal of Rivaroxaban Anticoagulation with Intravenously Administered Andexanet alfa (Protocol 14-504)

These two clinical trials were designed as two-part studies: Part 1 and Part 2, which evaluated a different dosing regimen of andexanet alfa (andexanet). A total of 66 subjects were enrolled in trial 14-503 and 48 of these subjects were treated with andexanet. A total of 80 subjects were enrolled in trial 14-504 and 53 subjects were treated with andexanet.

Each study was conducted at a single study site in the United States, and the BIMO inspections were conducted at these two sites that enrolled subjects. The inspections were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. Information related to the selected study subjects that were submitted in the BLA was compared to source documents at this site. Additionally, the inspection assignment included specific questions concerning the two clinical studies mentioned above.

INSPECTION SITES

The following table summarizes the clinical study sites where Bioresearch Monitoring inspections were conducted:

PROTOCOL	SITE NUMBER	SITE LOCATION	FORM FDA 483	FINAL CLASSIFICATION
14-503	001	Celerion Tempe, Az	Not Issued	No Action Indicated
14-504	001	West Coast Clinical Trials, Inc. Cypress, CA	Not Issued	No Action Indicated

INSPECTIONAL FINDINGS

The following two items were observed regarding the electrocardiogram (ECG) records from the inspected sites: the ECG data were not stored electronically as per the study protocol; and multiple unscheduled ECG readings were collected from a number of study subjects at both clinical sites. The analyses for each of these unscheduled ECG recordings were not well documented.

SPONSOR ISSUES

An Information Request (IR) letter was issued to Portola Pharmaceuticals Inc. on April 06, 2016 to address the following items for Protocol 14-504:

- Clarify the discrepant study site ID and its location
- Verify the disposition of all study subjects who participated in 14-504
- Clarify the discrepant account of study subjects in two reports submitted in the application: the Clinical Overview Report and the Protocol 14-504 Study Report
- Assess the integrity of the submitted ECG data

The sponsor submitted a written response to the IR letter in an amendment on April 20, 2016. The response was discussed with the clinical reviewer and it was concluded that the sponsor adequately addressed the items above.

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.

ADMINISTRATIVE FOLLOW-UP

Information letters were issued to the clinical investigators at all sites 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.

Haecin Chun Consumer Safety Officer	Erin McDowell Consumer Safety Officer