MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE February 15, 2017

FROM Dennis T. Cato, Bioresearch Monitoring Branch
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THROUGH Patricia Holobaugh, Chief, Bioresearch Monitoring Branch
Carrie Mampilly, Director, Division of Inspections and Surveillance

TO

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SUBJECT Bioresearch Monitoring Discipline Review Memo

BLA/STN:	125606/0
IND:	14992
Sponsor:	CSL Behring GmbH
Product:	C1 Esterase Inhibitor (Human) (Subcutaneous)

EXECUTIVE SUMMARY

Bioresearch Monitoring (BIMO) inspections were issued for one foreign and two domestic clinical study sites conducting Study CSL830_3001 under IND 14992. All three of the inspections have been completed and the Establishment Inspection Reports (EIRs) were received and reviewed. A Form FDA 483 was issued to one of the two domestic clinical study sites inspected. The second domestic study site and the foreign study site did not receive a Form FDA 483 at close of the inspection, and no significant deviations from applicable regulations were noted. Final inspectional correspondences were issued to all of the inspected sites. The inspections did not reveal problems that impact the data submitted in this Biologics Licensing Application (BLA).

REVIEW SUMMARY

BIMO inspections were performed at one foreign and two domestic clinical study sites conducting Study CSL830_3001 in support of BLA STN: 125606/0, CSL Behring, C1 Esterase Inhibitor. The pivotal study entitled: *A Double-blind, randomized, placebo-controlled, cross-over study to evaluate the clinical efficacy and safety of subcutaneous administration of human plasma-derived C1-Esterase inhibitor in the prophylactic treatment of hereditary angioedema*, was conducted under IND 14992. The primary objectives of the study were to demonstrate the clinical efficacy of subcutaneous (SC) CSL830 in the prophylactic treatment of Hereditary Angioedema (HAE), and to compare the clinical efficacy of 2 doses of SC CSL830. The inspections have been completed and the EIRs were received. A review of the three EIRs did not reveal problems that impact the data submitted in the BLA.

BACKGROUND

Clinical Investigator Inspection Assignments were issued for one foreign and two domestic clinical investigators in support of this BLA. The study sites inspected enrolled a total of 19 subjects, which represented approximately 16.5 percent of all subjects (N=115) enrolled in the CSL830 study. There were a total of 38 Clinical Study Sites in 10 countries, enrolling a combined total of 115 Subjects.

Bioresearch monitoring inspections are conducted in accordance with the FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The inspection assignments included specific questions related to the study protocol, and verification of the study data on efficacy and safety endpoints submitted by the sponsor in the BLA.

PROTOCOL AUDITED

A Double-blind, randomized, placebo-controlled, cross-over study to evaluate the clinical efficacy and safety of subcutaneous administration of human plasma-derived C1-Esterase inhibitor in the prophylactic treatment of hereditary angioedema. (CSL830_3001)

The table below summarizes the inspection results:

Site Number	Study Site	Location	Number of Subjects	Classification
8400143	Institute for Asthma and Allergy	Chevy Chase, Maryland	10	No Form FDA 483 - NAI
8400185	Bernstein Clinical Research Center, LLC	Cincinnati, Ohio	6	Form FDA 483 issued - VAI
1240023	Gordon Sussman Clinical Research Inc.	Ontario, Canada	3	No Form FDA 483 - NAI

NAI = No Action Indicated; VAI = Voluntary Action Indicated

FINANCIAL DISCLOSURE

The Clinical Investigator Compliance Program directs the FDA investigator to ask the clinical investigator if and when s/he disclosed information about her/his 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. Each inspected study site had a copy of the financial disclosure forms on hand for the clinical investigators and sub-investigators.

INSPECTIONAL FINDINGS

Sponsor/Monitor Issues

A review of the establishment inspection reports did not revealed any sponsor related issues that may affect the data submitted in the application.

Clinical Investigator (CI) Study Site Issues

A review was conducted of testing records, regulatory binders, study specific standard operating procedures, and general study conduct. In addition, source documents, including records of adverse

events, protocol deviations, and subject dispositions were reviewed and the information contained was compared to the data tables submitted by the sponsor in the application. Individual site observations are listed below:

Site 8400143: Institute for Asthma and Allergy: A Form FDA 483 was not issued at close of this inspection, and the inspection received a final classification of NAI.

Site 8400185: Bernstein Clinical Research Center, LLC: A Form FDA 483 was issued at close of this inspection. A review of the inspection report revealed minor deviations involving (b) (4) Activity levels that the Clinical Investigator determined was not clinically significant, and the reporting of this suspected deviation to the IRB. In a letter responding to the Form FDA 483, the Clinical Investigator provided additional information that added clarity to the issues reported on the Form FDA 483.

Site 1240023: Gordon Sussman Clinical Research Inc.: A Form FDA 483 was not issued at close of the inspection, and a review of the inspection report revealed no deviation from applicable regulations. The inspection received a final classification of NAI.

BIMO ADMINISTRATIVE FOLLOW-UP

Information letters were issued for all clinical sites inspected. Please contact me should you have any questions about this memo or any aspect of Bioresearch Monitoring.

Dennis T. Cato
Consumer Safety Officer

CC:

CBER BIMO Notification – Access/Chron
eMRP – EDR: STN 125606/0
ORA BLT BIMO
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ORA CIN BIMO
Yvette M. LaCour-Davis, FDA Investigator
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