

Summary of Bioresearch Monitoring Inspections - Berinert,

DATE:

FROM:

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Division of Inspections and Surveillance

Office of Compliance and Biologics Quality

THROUGH: Patricia Holobaugh, Chief, Bioresearch Monitoring Branch, HFM-664

TO:

Felice D'Agnilo, HFM-34

Chair, BLA Licensing Committee

SUBJECT: Summary of Bioresearch Monitoring Inspections

SPONSOR: CSL Behring GmbH

PRODUCT: C1 Esterase Inhibitor, Pasteurized (human)

BLA: STN 125287/0

Summary

The bioresearch monitoring inspections of three clinical investigators did not reveal any problems that impact the data submitted in the Biologics Licensing Application (BLA).

Background

Inspections of three clinical sites were requested in support of the BLA and were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The inspection assignment included specific questions on the following study protocol entitled *Human Pasteurized C1 Esterase Inhibitor Concentrate (CE1145) in Subjects with Congenital C1-INH Deficiency and Acute Abdominal or Facial HAE Attacks*.

The inspections were conducted at three clinical sites and represented 32% of the total subjects enrolled in the study submitted in the BLA. The data audit portion of the inspection focused on the verification of the study data on safety and efficacy endpoints submitted by the sponsor in the BLA for all the enrollees at two of the inspected sites (Centers #6 and #8) and for about 50 % the total number of enrollees at Center #12 that were randomly and equitably selected from the total enrollees. The following table identifies the inspection results.

Inspection of clinical sites and outcome

Study site /Site #	Location	Form FDA 483 issued	Final classification
Creighton University Center #6	Omega, NE	No	NAI

Study site /Site #	Location	Form FDA 483 issued	Final classification
Allergy Clinic of Tulsa, Inc./Center #8	Tulsa, OK	No	NAI
Family Allergy and Asthma Center/Center #12	Atlanta, GA	Yes	VAI

VAI-Voluntary Action Indicated NAI-No Action Indicated

Inspectional findings

Clinical investigator issue: Center#6

Failed to prepare and maintain adequate records of drug disposition. [21 CFR § 312.62(a)].

For subject #-b(6)-, the investigator did not maintain adequate records of drug disposition and study drug use and disposition records indicated that the subject received study drug from 3 (10ml) vials instead of 4. The investigator acknowledged that 3 (10 ml) vials from Batch #11561711A were used inadvertently by the pharmacist to make up a total dosing of 33.0 ml for this subject although four vials were required.

Sponsor issue:

We note that at Center #8 one subject traveled more than 300 miles after the symptoms started to obtain treatment for the HAE attack from the clinical investigator as part of the study. Documentation was not available at the site for the duration of time between the attack and the study drug treatment. The sponsor reported in the submitted data that all nine subjects enrolled at this site had a minor protocol deviation where the time from start of attack until start of treatment was greater than 5 hours. However, the data submitted by the sponsor does not indicate actual duration of time between the attack and the treatment. We note that the data submitted by the sponsor in the BLA indicates, in addition, that 5 of 9 subjects at Center 6 and 15 of 22 subjects at Center 12 also had the above minor protocol deviation.

BIMO actions

Close-out letters were issued to the clinical investigators. Should you have any questions or comments about this memo or any aspect of Bioresearch Monitoring, please contact me at 301-827-6188.

Bhanu Kannan