Bioresearch Monitoring Final Review memo - CINRYZE

Date: January 30, 2008

From: Robert L. Wesley, Bioresearch Monitoring, HFM-664 Division of Inspections and Surveillance Office of Compliance and Biologics Quality

Through: Patricia A. Holobaugh Bioresearch Monitoring Branch Chief, HFM-664

To: Nannette Cagungun, HFM-380, RPM
Felice D'Agnillo, HFM-370, Chair

Subject: Bioresearch Monitoring Final Review memo

STN: BLA 125267/0

Sponsor: Lev Pharmaceuticals, Inc.

Product: C1 Esterase Inhibitor For Prophylactic and Acute Treatment of subjects with HAE

SUMMARY STATEMENT

The bioresearch monitoring inspections of three clinical investigators did not reveal significant problems that impact the data submitted to the BLA. Deviations from the protocol were noted at two of the clinical sites, none of which affected data integrity.

BACKGROUND

Inspections and data audits of the following three clinical investigators were conducted in support of the BLA.

Clinical Investigator	Site	Location	No. of Subjects	FDA-483	Classification
Martha V. White, MD	#07	Wheaton, MD	6	Yes	VAI
William R. Lumry, MD	#13	Dallas, TX	7	No	NAI
Timothy J. Craig, MD	#05	Hershey, PA	7	No	NAI

INSPECTIONAL FINDINGS

Major focus of the inspections was to compare data points from the BLA with source documents and subject's case report forms at each site. Data points included Inclusion/Exclusion criteria, SAEs/AEs, HAE attacks, diaries, and infusion rate.

The inspections of the three clinical investigators revealed the following deviations from the applicable federal regulations.

1. **Failure to ensure that the investigation is conducted according to the signed investigator statement and the investigational plan. [21 CFR § 312.60].**

Site #05 Dr. Timothy Craig

a. Following infusion of test article, pain assessments for two subjects did not begin within the time period required by the protocol.
b. Two subjects, who had C1q levels not meeting inclusion criteria, were enrolled into the study, based on waivers granted by the sponsor.

Site #07 Dr. Janet White

One subject, who was randomized to receive a placebo, was given the study drug.

2. **Failure to ensure that informed consent was obtained according to the provisions of 21 CFR Part 50. [21 CFR § 312.60].**

Site #07 Dr. Janet White

a. One subject signed the assent form for minors, and one subject signed an out dated consent form.

Site #13 Dr. William Lumry

During the inspection, the study coordinator, who was responsible for obtaining informed consent, stated that she gave prospective subjects the consent form to read and sign in the waiting room, and that she and the CI were available to answer questions after the subjects had read and completed the form. Under the process described by the study coordinator, subjects may have been reluctant, forgotten to, or not felt they had the opportunity to ask questions about the study or the complex 16 page consent form that contained technical language.

SPONSOR FINDINGS

There were no sponsor issues noted during the inspections.

BIMO ADMINISTRATIVE FOLLOW-UP

Letters describing the inspectional findings were issued to each of the clinical investigators. Should you have any questions or comments about this memorandum or any aspect of Bioresearch Monitoring, please contact me at (301) 827-6348.

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Robert L. Wesley
Consumer Safety Officer