BIMO Final Summary Review Memo, November 15, 2013 - RAGWITEK

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

DATE November 15, 2013
FROM Dennis T. Cato, Bioresearch Monitoring Branch, HFM-664
Division of Inspections and Surveillance
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Through: Patricia Holobaugh, Chief, Bioresearch Monitoring Branch HFM-664
TO Elizabeth Valenti HFM-481 Chair, Review Committee
Colleen Sweeney HFM-481 RPM
Ronald Rabin HFM-422 Clinical
SUBJECT Bioresearch Monitoring Final Summary Review Memo
Original BLA/STN: 125478/0
Sponsor: Merck Sharp & Dohme Corp.
Product: Short Ragweed Pollen Allergen Extract

SUMMARY
Bioresearch monitoring inspections were conducted for three clinical sites. The inspection reports for all sites were received and reviewed, and did not reveal problems that impact the data submitted in the application.

PROTOCOLS AUDITED
A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study Evaluating the Efficacy and Long-Term Safety of Ragweed (*Ambrosia artemisiifolia*) Sublingual Tablet (SCH 39641) in Adult Subjects With a History of Ragweed-Induced Rhinoconjunctivitis With or Without Asthma. (P05233)

BACKGROUND
Clinical Investigator Inspection Assignments were issued for three domestic clinical investigators in support of this Biologics License Application (BLA). The inspections were 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 endpoints submitted by the sponsor in the BLA. The following table identifies the inspection results:

Summary of Inspection Results for all Clinical Sites Audited

Site Number	Study Site	Location	Number of Subjects	Classification	483 Issued?
01	Clinical Research Institute	Minneapolis, Minnesota	19	NAI	No
80	Abraham Research, PLLC	Crescent Springs, Kentucky	08	NAI	No
91	Clinical Research of the Ozarks, Inc.	Columbia, Missouri	17	VAI	Yes

Classification – 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 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. All inspected sites had copies of the financial disclosure forms for the clinical investigators and sub investigators.

INSPECTIONAL FINDINGS
Sponsor Issues
A review of the EIRs from the three clinical investigator study sites did not reveal any sponsor or monitoring issues.

Clinical Investigator (CI) Site Issues
A review was conducted of testing records, regulatory binders, study specific standard operating procedures, and general study conduct. In addition, source documents were reviewed and compared to the data tables submitted by the sponsor in the application. Individual site observations are listed below:

Study Site 01: The inspection did not result in the issuance of a Form FDA 483 and received a final classification of NAI.

Study Site 80: The inspection did not result in the issuance of a Form FDA 483 and received a final classification of NAI.

Study Site 91: The inspection resulted in the issuance of a Form FDA 483. The findings included protocol violations and documentation errors. Specifically, the following deviations were not report to the IRB as required by the IRB Investigator Handbook: Analysis for hematocrit was not performed at visit 9 as required for two subjects, and for one subject, one tablet could not be accounted for as required for the test article

accountability; Additionally, for all 17 study subjects enrolled through visits 2-1, 2-2, 2-3, subjects were not documented as observed for the required 30 minutes after dosing, and in several instances, study comment cards, which documented the use of rescue medications, adverse events, and missed doses were not signed and dated as reviewed for compliance. The inspection received a final classification of VAI.

OTHER ISSUES

Sponsor/Monitor and Clinical Investigator surveillance inspection assignments were previously issued for Study P05233 at the Sponsor and Study Sites 63, 64, and 67. Observations at the individual sites are as follows:

Sponsor/Monitor: The inspection was conducted at the Merck and Company, Inc., Springfield, New Jersey 07081 location by the NWJ-DO between April 17, 2012 and May 02, 2012. At close of the inspection, a Form FDA 483 was issued for failing to conduct study site monitoring visits within the time frame of six to eight weeks as is specified in the sponsor's Site Monitoring Visit Plan. The inspection received a final classification of VAI.

Site 63: CBER BIMO issued the inspection assignment as a result of notification received by the Agency that the sponsor had discontinued the clinical investigator based on evidence of serious Good Clinical Practice non-compliance issues. The inspection was conducted by the NY-DO and at close of the inspection a Form FDA 483 was issued. After receipt and review of the EIR, the inspection received a final classification of OAI (Official Action Indicated) and an Untitled Letter was issued to the clinical investigator. The observations cited are as follows:

- Failure to fulfill the general responsibilities of an investigator;
- Failure to obtain legally effective informed consent from a subject or the subject's legally authorized representative;
- Failure to prepare and maintain accurate and complete case histories for subjects enrolled in the study, with respect to observations and data pertinent to the study;
- Failure to maintain source documents and records pertinent to an investigation for a period of two years following approval of a marketing application or discontinuance of the investigation and notification of the FDA, and;
- Failure to assure that an IRB complying with the applicable regulatory requirements would be responsible for the initial and continuing review and approval of a clinical study.

The sponsor reported that all 5 subjects from Study Site 63 were excluded from the Full Analysis Set (FAS) and the All Subjects as Treated Set (ASaT).

Site 64: CBER BIMO issued the inspection assignment as a result of a complaint received by the Agency. At close of the inspection, the allegations in the complaint could not be substantiated and a Form FDA 483 was not issued. The inspection received a final classification of NAI.

Site 67: CBER BIMO issued the inspection assignment as a result of a complaint received by the Agency. At close of the inspection, the allegations in the complaint could not be substantiated and a Form FDA 483 was not issued. The inspection received a final classification of NAI. It is important to note that Study Site 67 was cited by the Sponsor-assigned Clinical Site Monitor for multiple GCP inadequacies.

BIMO ADMINISTRATIVE FOLLOW-UP
Information letters were issued for all study 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:
HFM-664 Access/Chron
EDR STN 125478/0

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Reviewed: Holobaugh: 11/15/2013