U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Oeyama-Moto-Medical Group Foundation, LLC 3/29/16

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Silver Spring, MD 20993

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 16-HFD-45-03-02

Benedict S. Liao, M.D.
Sponsor Representative
Oeyama-Moto Medical Group Foundation
3106 East Garvey Avenue South
West Covina, California 91791-2344

Dear Dr. Liao:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at Oeyama-Moto Medical Group Foundation (Oeyama-Moto) between August 11 and September 29, 2015, by Mr. Uttaniti Limchumroon, Mr. Greg Keshishyan, and Ms. Quynh-Van Tran, representing FDA. The purpose of this inspection was to review **(b)(4)** conduct as the sponsor of a clinical investigation ["**(b)(4)**"] for the investigational drug **(b)(4)**.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Mr. Limchumroon and Mr. Keshishyan presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your October 12, 2015, written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and your October 12, 2015, written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We wish to emphasize the following:

1. You violated a clinical hold by allowing a clinical investigator to give subjects an investigational drug after FDA issued an order to delay a proposed investigation [21 CFR 312.42(a)].

A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug.

Your IND application (IND **(b)(4)**), which contained the inspected study, was placed on Full Clinical Hold during a teleconference on December 5, 2012, for unreasonable and significant risk of illness or injury to human subjects, and for insufficient information to assess risks to subjects of the proposed study [21 CFR 312.42(b)(2)(i)]. As a follow-up to this teleconference, FDA sent you a Full Clinical Hold Letter dated December 20, 2012, in which FDA reiterated that no studies under IND **(b)(4)** could be initiated or resumed, and delineated the following reasons for placing the IND on clinical hold:

- Insufficient information to assess risks to human subjects [21 CFR 312.42(b)(2)(i)]
- Unreasonable and significant risk of illness or injury to human subjects [21 CFR 312.42(b)(2)(i)]
- Plan or protocol is deficient in design to meet its stated objectives [21 CFR 312.42(b)(2)(ii)]
- Investigator brochure is misleading, erroneous, or materially incomplete [21 CFR 312.42(b)(2)(i)]

FDA issued a Continue Full Clinical Hold Letter dated August 13, 2013, stating that the removal of the clinical hold was unwarranted. Based on a subsequent review of your submissions, FDA issued a Remove Full Clinical Hold Letter dated May 9, 2014, which permitted you to initiate the clinical investigation under IND **(b)(4)**.

You violated the Full Clinical Hold order when a clinical investigator administered the investigational drug **(b)(4)** to six subjects participating in an investigation that was currently subject to a clinical hold. Specifically, Subjects L-3 and L-10 received investigational drug on May 3, 2014; and Subjects L-5, L-6, L-7, and L-8 received investigational drug on May 7, 2014. All of these subjects received investigational drug before the clinical hold was removed on May 9, 2014.

In your October 12, 2015, written response to the Form FDA 483, you indicated that you submitted the Phase 2 study protocol on or about March 24, 2014, and that you were in constant contact with the Office of Hematology and Oncology Products Regulatory Project Manager, who “communicated with us and hinted to us that if we

did not receive rejection within 30 days, then we can proceed with the Study in early May 2014." You also referred to the statement on the Form FDA 1571 in which you agreed not to begin the study until thirty days after FDA's receipt of the IND unless you received earlier notification by FDA that the study may begin. You explained that you therefore "piled up patients to begin this clinical Study in the first week of May 2014" and had subjects sign informed consent documents. However, you stated that study drug was not administered, in case subjects changed their minds about participating in the study.

Your written response is inadequate because study records show that the six subjects noted above received investigational drug before the clinical hold was removed on May 9, 2014, despite your statement otherwise. Your written response is also inadequate because you have not provided a corrective action plan to prevent the recurrence of similar violations in the future.

2. You failed to ensure proper monitoring of the clinical investigations [21 CFR 312.50 and 312.56(a)].

FDA regulations require that sponsors ensure proper monitoring of clinical investigations and ensure that their clinical investigators conduct the investigations in accordance with the general investigational plan and the protocols contained in the IND application. Our investigation found that you failed to ensure proper monitoring because there are no monitoring records associated with the inspected study.

In your October 12, 2015, written response to the Form FDA 483, you indicated that you monitored the progress of the study through your Institutional Review Board (IRB) and documented this in the IRB meeting minutes.

Your written response is inadequate because an IRB cannot assume the sponsor's responsibility to ensure proper monitoring of clinical investigations. In addition, please note that a sponsor may transfer its obligation to monitor a study to a contract research organization. Any such transfer of obligations shall be described in writing [21 CFR 312.52].

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to explain the violations noted above adequately and promptly may result in regulatory action without further notice. If you believe that you have complied with FDA regulations, include your reasoning and any supporting information for our consideration.

If you have any questions, please contact Douglas B. Pham, Pharm.D., J.D., at

301-796-1955; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Douglas B. Pham, Pharm.D., J.D.
Branch Chief (Acting)
Compliance Enforcement Branch
Division of Enforcement and Postmarketing Safety
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Building 51, Room 5348
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,

{See appended electronic signature page}

David C. Burrow, Pharm.D., J.D.
Office Director (Acting)
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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/s/

DAVID C BURROW
03/29/2016

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