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

Benedict S. Liao, M.D. 3/29/16

Department of Health and Human Services

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

WARNING LETTER
MAR 29, 2016

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref.: 16-HFD-45-03-03

Benedict S. Liao, M.D.
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 your clinical site between August 11 and September 29, 2015. Mr. Uttaniti Limchumroon, Mr. Greg K. Keshishyan, and Ms. Quynh-Van Tran, representing FDA, reviewed your conduct of a clinical investigation ("**(b)(4)**") for the investigational drug **(b)(4)**, performed for **(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 6, 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 6, 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 failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

As a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plan. The investigational plan requires that subjects have between 1 and 15 measurable tumor(s) (i.e., between 0.2-10 cm in size) in order to be eligible for the study, and that laboratory tests, including thyroid stimulating hormone (TSH) and alpha-fetoprotein (AFP), be conducted every four weeks, and computed tomography (CT) and/or positron emission tomography (PET) scans be conducted every three months. You failed to adhere to these protocol requirements. Specifically:

a. You failed to follow the protocol for subject eligibility when you enrolled Subject L-36, who did not have a measurable tumor at baseline. Subject L-36 received investigational drug on July 22, 2014, even though the subject did not meet this protocol requirement.

b. You failed to conduct TSH and AFP laboratory tests at required time intervals (i.e., every 4 weeks) for the following subjects during the noted time periods:

i. Between May 3, 2014, and November 15, 2014, you failed to conduct any required TSH and AFP laboratory tests for Subject L-10.

ii. Between May 3, 2014, and December 17, 2014, you failed to conduct any required TSH and AFP laboratory tests for Subject L-20.

iii. Between May 7, 2014, and December 3, 2014, you failed to conduct any required TSH and AFP laboratory tests for Subject L-21.

iv. Between May 6, 2014, and January 28, 2015, you failed to conduct any required TSH and AFP laboratory tests for Subject L-35.

v. Between May 29, 2014, and December 12, 2014, you failed to conduct any required TSH and AFP laboratory tests for Subject H-67.

We acknowledge that the finding noted in Item 1.a. above (Subject L-36) and the AFP findings in Item 1.b. above (Subjects L-10, L-20, L-21, L-35, and H-67) were not included on the Form FDA 483 you received, and that therefore, your written response does not address these findings.

c. Between July 8, 2014, and February 17, 2015, you failed to conduct a CT and/or PET scan at any of the required time intervals (i.e., every 3 months) for Subject L-36.

In your October 6, 2015, written response to the Form FDA 483, you indicated that because **(b)(4)** is nontoxic, you did not see the need to follow the protocol strictly. In addition, you stated that some subjects were noncompliant with the protocol instructions to have laboratory tests and CT scans performed. You also indicated that for subjects who did not have thyroid carcinoma, TSH assessment was

unnecessary; and that for all subjects, appropriate cancer markers were used instead [e.g., prostate-specific antigen (PSA) for subjects with prostate cancer]. You also stated that some subjects had CT scans every 4 months instead of every 3 months, and some subjects were followed by vaginal colposcopy in addition to pelvic and rectal ultrasound examinations, rather than by CT scan, PET scan, or both.

Your written response is inadequate because you must adhere to protocol-required assessments despite the presumed safety of the investigational drug, and study subjects' purported responses to it. Although you followed subjects with cancer-specific blood markers, the protocol requires all subjects to undergo the following laboratory tests: complete blood count, chemistry-7, chemistry-24, liver and renal function, carcinoembryonic antigen, cancer antigen 125, cancer antigen 153, cancer antigen 199, TSH, AFP, "and other tumor markers." Further, you have not provided a corrective action plan to prevent the recurrence of similar violations in the future.

Your failure to perform protocol-required laboratory tests and scans jeopardizes subject safety and welfare, and compromises the validity and integrity of the data collected at your site.

2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

As a clinical investigator, you are required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include records demonstrating that subjects met protocol-specified inclusion and exclusion criteria. You failed to maintain adequate and accurate case histories that included these records. Specifically:

a. You failed to maintain study records demonstrating that Subjects L-10, L-21, L-26, and L-36 met the protocol-specified inclusion criterion of failure to be helped by two separate regimens of conventional radiation therapy and/or chemotherapy before study enrollment.
In your October 6, 2015, written response to the Form FDA 483, you indicated the following:

- Subjects L-10 and L-26 received 6 courses of carboplatin/Taxol®.
- Subject L-21 received the doxorubicin hydrochloride/Adriamycin®, bleomycin, vinblastine sulfate, and dacarbazine (ABVD) regimen every 3 to 4 weeks from August 2012 through February 2013 at other hospitals, and you obtained those records.
- Subject L-36 received 6 courses of mitomycin/Taxol®.

We are unable to perform an informed evaluation of your response because you did not submit documentation of these subjects' prior courses of chemotherapy. Failure

to maintain study records for the above-mentioned inclusion criterion compromises significantly the validity and integrity of data collected at your site; without these study records, we cannot confirm these subjects' eligibility for enrollment in the study. In addition, you have not provided a corrective action plan to prevent the recurrence of similar violations in the future.

b. You failed to maintain study records demonstrating that Subjects L-3, L-10, L-20, L-21, L-35, and H-67 met the following protocol-specified laboratory eligibility criteria:

- Inclusion criteria of platelet count greater than 100,000/mL, hemoglobin greater than 9.0 g/dL, and no "significant abnormal hepatic and/or renal function."
- Exclusion criteria of hemoglobin less than 9.0 g/dL and white blood cell count less than 4.0 k/μL, platelet count less than 100,000/μL, and international normalized ratio greater than 1.5.

In your October 6, 2015 written response to the Form FDA 483, you indicated the following:

- Laboratory tests for Subject L-3 were performed at affiliated facilities. You tried to collect the laboratory reports but may have misplaced them.
- Laboratory tests for Subjects L-10, L-20, and H-67 were performed by your clinic and/or affiliated facilities. You tried to collect the laboratory reports but may have misplaced them.
- You may have misplaced some of the laboratory reports for Subject L-21, so you tried to recover them and place them in the subject's record.
- You had some of the laboratory reports for Subject L-35 and tried to obtain the missing ones.

We are unable to perform an informed evaluation of your response because you did not submit any laboratory reports maintained at your site. In addition, you have not provided a corrective action plan to prevent the recurrence of similar violations in the future.

Your failure to maintain adequate and accurate case histories jeopardizes subject safety and welfare, and compromises the validity and integrity of data captured at your site.

3. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].

As a clinical investigator, you are required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. You failed to comply with this requirement. Specifically, for all subjects at your site who enrolled in the study and received low-dose and/or high-dose **(b)(4)**, you failed to maintain any drug disposition records.

In your October 6, 2015, written response to the Form FDA 483, you indicated that you have General History and Physical Examination Summary Forms that provide

treatment planning, the study-drug dose and quantity to be given to each subject, and study-visit frequency. You also provided calculations of the overall number of tablets and bottles given to subjects and remaining in the warehouse, and you provided records stating subjects' planned treatment groups and projected number of tablets over certain time periods.

We are unable to perform an informed evaluation of your response because you did not submit documentation showing how many tablets were actually given to and returned by each subject, with corresponding dates and dosage strengths. In addition, you have not provided a corrective action plan to prevent the recurrence of similar violations in the future.

Your failure to maintain adequate and accurate drug accountability records compromises the validity and integrity of the data at your site.

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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