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

Gross, Howard M. M.D. 6/29/15

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.: 15-HFD-45-06-02

Howard M. Gross, M.D.
Dayton Clinical Oncology Program
3123 Research Boulevard
Suite 150
Dayton, OH 45240

Dear Dr. Gross:

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 November 19, 2014, and January 14, 2015. Mr. Richard W. Berning, representing FDA, reviewed your conduct of the following clinical investigations:

- Protocol **(b)(4)** of the investigational drug **(b)(4)**, performed for **(b)(4)**; and

- Protocol **(b)(4)** of the investigational drug **(b)(4)**, performed for **(b)(4)**. and **(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. Berning presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your January 28, 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 written response dated January 28, 2015, 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 investigations are conducted in accordance with the investigational plan. The investigational plan for Protocol **(b)(4)** required you to ensure that study subjects met the protocol inclusion and exclusion criteria before their enrollment. You failed to adhere to these requirements. Specifically:

a. For Protocol **(b)(4)**, you failed to ensure that study subjects met the protocol inclusion and exclusion criteria before their enrollment.

i. Protocol **(b)(4)** specified that for subjects with proteinuria ≥ 2+ or urine protein creatinine ratio ≥ 0.5, a 24-hour urine protein should be obtained and the level must be <1 gram of protein in 24-hour urine to be eligible for enrollment. Subject 2102 had a protein level of 37.1 mg/dl, which is clinically considered 2+ protein (≤100 mg/dl). However, a 24-hour urine test was not performed. This subject was randomized into the clinical investigation on May 17, 2012.

ii. Protocol **(b)(4)** specified that subjects receiving chronic therapy with nonsteroidal anti-inflammatory agents or other antiplatelet agents, including clopidogrel, will not be enrolled into the clinical investigation. Subject 2100 was taking Plavix (clopidogrel) between January 3, 2012, and March 2, 2012. However, this subject was randomized into this clinical investigation on February 6, 2012.

In your January 28, 2015, written response to the violations noted in Item 1.a., you agreed that Subjects 2102 and 2100 did not meet the eligibility criteria. You indicated that as part of your corrective action plan, you developed a standard operating procedure (SOP), "Second Eligibility Check," which specifies that study staff will verify that eligibility criteria are met prior to enrollment.

Your response is inadequate because, although you stated that your SOP "Second Eligibility Check" has been put into effect and that your research coordinators are well aware of this requirement, you failed to provide documentation that your research staff have been adequately trained in this SOP. Without such documentation, we are unable to determine whether your corrective action plan appears sufficient to prevent similar violations in the future.

The eligibility criteria for each clinical investigation are designed to optimize interpretability of collected data and to minimize foreseeable harm to enrolled subjects. Enrollment of subjects who do not meet the eligibility criteria jeopardizes subject safety and welfare, and raises concern about the validity and integrity of the data collected at your site. Particularly concerning to us is that two of the five subjects randomized into Protocol **(b)(4)** at your site were enrolled despite their being ineligible for the clinical investigation.

b. Protocol **(b)(4)** specified that **(b)(4)** will be administered over 90 (±10) minutes, and that subjects will be observed post-administration for at least 30 minutes. After this observation period,

(b)(4)/placebo will be administered. Any infusion-related symptoms must have resolved before the administration of **(b)(4)**/placebo.

i. You administered the study drugs in reverse order for one subject. For Subject 006, **(b)(4)**/placebo infusion was followed by **(b)(4)** infusion at the following study visits: Cycles 4, 7, and 10-12.

Failure to follow the protocol-specified order of study drug administration has the potential to affect both data integrity and subjects' safety and welfare.

ii. You failed to adhere to the required 30-minute observation period before administering **(b)(4)**/placebo for all subjects enrolled in this clinical investigation at the following study visits:

1. For Subject 001: Cycles 1 and 2
2. For Subject 003:

a. Cycles 2-7 and 9-14
b. Cycle 8: No observation period was performed; **(b)(4)**/placebo was administered one minute before the **(b)(4)** infusion was stopped.

3. For Subject 006: Cycles 2 and 3
4. For Subject 007: Cycles 10-14

In your January 28, 2015, written response to the violations noted in Item 1.b. above, you confirmed that the order of administration of study drugs was reversed for five of Subject 006's treatment cycles. You also confirmed that observation periods were not followed for multiple treatment cycles for four subjects. You indicated that as part of your corrective action plan, you trained study staff to review protocol orders and infusion requirements with infusion nurses before starting study drug administration.

Your response is inadequate because it does not contain sufficient detail. Specifically, it is unclear whether study staff and infusion nurses would be adequately trained on protocol requirements before initiating the study, or only before study drug administration for each subject. As a result, we are unable to determine whether your corrective action appears sufficient to prevent similar violations in the future.

Failure to adhere to protocol requirements for study drug administration, including reversing the order of administration of study drugs and failure to follow the protocol-specified observation period, compromises subject safety and welfare significantly, and raises concerns about the validity and integrity of the data collected at your site.

c. Protocol **(b)(4)** required coagulation profile laboratory tests to be performed at baseline; at Cycles 4, 8, and 9-x; at the summary visit; and at the 30-day follow-up visit. For Protocol **(b)(4)**, the coagulation profile included prothrombin time (PT or INR) and partial thromboplastin time (PTT). You failed to perform coagulation profile laboratory tests for four of the five subjects that received study drug at the following specified intervals:

i. For Subject 2100: Cycles 4 and 8-17
ii. For Subject 2102: Cycle 4
iii. For Subject 2104: Cycles 4, 8, and 13-17

iv. For Subject 2105: Cycles 1,4, 8-15, 17, 19, 20, 22, and 23

d. Protocol **(b)(4)** required that liver function tests be performed at screening; during the anthracyclines treatment period; within 3 days prior to Day 1 of Cycles 1-5, 9, and 18; and at safety follow-up at the end of treatment. For Protocol **(b)(4)**, the liver function tests include ALP; ASAT; ALAT; LDH; and total, direct, and indirect bilirubin. You failed to perform all or certain liver function tests for all of the subjects enrolled at the following specified intervals:

i. For Subject 001, at screening and Cycles 1 and 2: direct and indirect bilirubin
ii. For Subject 003:
    1. At Cycle 1: all liver function tests
    2. At Cycles 2-5, 9, and 18: direct and indirect bilirubin
    3. At Cycle 3: ASAT, ALAT, and ALP
    4. At Cycles 2, 4, and 9: LDH
iii. For Subject 006:
    1. At Cycles 6 and 9: all liver function tests
    2. At Cycles 1, 2, 4, and 5: direct and indirect bilirubin
    3. At Cycle 2: LDH
iv. For Subject 007, at screening and Cycles 2-5: direct and indirect bilirubin

e. Protocol **(b)(4)** required that biochemistry laboratory tests be performed at screening; during the anthracyclines treatment period; within 3 days prior to Day 1 of Treatment Cycles 1-9, 13, and 18; and at safety follow-up at the end of treatment. For Protocol **(b)(4)**, biochemistry laboratory tests included serum creatinine, blood urea nitrogen (BUN), and electrolytes (phosphorus, calcium, magnesium, sodium, potassium, and chloride). You failed to perform all or certain biochemistry laboratory tests for three of the four subjects enrolled at the following specified intervals:

i. For Subject 003:
    1. At Cycles 1 and 7: all biochemistry laboratory tests
    2. At Cycle 3: serum creatinine, BUN, calcium, chloride, sodium, and potassium
    3. At Cycles 4, 6, and 8: phosphorus
    4. At Cycles 6 and 8: magnesium
ii. For Subject 006:
    1. At Cycle 9: all biochemistry laboratory tests
    2. At Cycles 2, 5, and 6: phosphorus
iii. For Subject 007:
    1. At Cycles 2, 8, and 9: phosphorus
    2. At Cycle 8: magnesium

In your January 28, 2015, written response to the violations noted in Items 1.c., 1.d., and 1.e. above, you confirmed that protocol-required laboratory tests were missed for subjects enrolled in the clinical investigations for Protocols **(b)(4)** and **(b)(4)**. You indicated that as a part of your corrective action plan, you have added a “clinical trials link” to your site’s electronic medical record (EMR) to provide access to study information for study staff. You further indicated that you will review with study staff the process of accessing study information and the importance of following the study calendar.

Your response is inadequate because you did not provide sufficient information to enable us to evaluate the adequacy of your corrective action plan for use in any future clinical research that you may conduct. It is unclear how adding a "clinical trials link" to your site's EMR will ensure that protocol requirements will be met for studies conducted at your site. You did not provide any details of a corrective action plan to prevent similar violations from occurring in the future, nor have you provided sufficient details regarding your plan to implement additional measures and procedures to address the inspection findings. Without these details, we are unable to determine whether your corrective action plan appears sufficient to prevent similar violations in the future.

As detailed above, you failed to conduct the investigation in accordance with the investigational plan. Specifically, your enrollment of subjects who do not meet eligibility criteria; your failure to adhere to protocol requirements for study drug administration; and your failure to perform protocol-required laboratory tests jeopardize subject safety and welfare, and raise concerns about 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. For Protocol **(b)(4)**, these case histories include source documents recording serious adverse events. For Protocol **(b)(4)**, a serious adverse event was defined as an adverse event requiring inpatient hospitalization. You failed to maintain adequate and accurate case histories with respect to these study records.

Specifically, a telephone record shows that on June 6, 2012, your study coordinator was made aware that Subject 001 had been hospitalized. However, a progress note shows that the study coordinator was notified on June 13, 2012, of Subject 001's hospitalization. There is no documented explanation for this discrepancy.

This is particularly concerning to us because Protocol **(b)(4)** required that serious adverse events be reported to the sponsor within 24 hours of your becoming aware of the event. The sponsor was notified of this serious adverse event on June 15, 2012. However, because of the discrepancy in the date of your awareness of the event, we were unable to evaluate whether you adhered to this protocol requirement.

We acknowledge that this violation, as written, was not included on the Form FDA 483 that you received.

Your failure to maintain adequate and accurate case histories, including the aforementioned discrepancies in the dates on documentation related to serious adverse events, raises concerns about the validity and integrity of data captured 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 address the violations noted above adequately and promptly may result in regulatory action without further notice. If you believe you have complied with FDA regulations, include your reasoning and any supporting information for our consideration.

If you have any questions, please contact Allen Lou at 301-796-5652; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Allen Lou
Acting Branch Chief
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 5260
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,

{See appended electronic signature page}

Sean Y. Kassim, Ph.D.
Director
Office of Scientific Investigations
Office of Compliance
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U.S. Food and Drug Administration

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/s/

SEAN Y KASSIM
06/29/2015

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