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

Cheta Nand, M.D. 3/10/16

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-45-03-01

Cheta Nand, M.D.
2630 N. Columbia Center Boulevard
Richland, Washington 99352-4853

Dear Dr. Nand:

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 October 6 and October 30, 2015. Ms. Tracy K. Li and Ms. Sherri N. Rohlf, representing FDA, reviewed your conduct of the following clinical investigations:

- Protocol **(b)(4)**, "**(b)(4)**," of the investigational drug **(b)(4)**, performed for **(b)(4)**
- Protocol **(b)(4)**, "**(b)(4)**," of 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, Ms. Li and Ms. Rohlf presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your November 19, 2015, written response to the Form FDA 483, and your written response dated December 18, 2015.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and your written responses dated November 19, 2015, and December 18, 2015, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical

investigations. We wish to emphasize the following:

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 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 this requirement. Specifically:

1. Protocol **(b)(4)** specified that subjects were to be treated with atorvastatin, simvastatin, or rosuvastatin, and that no dose should be lower than atorvastatin 20 mg, rosuvastatin 20 mg or simvastatin 40 mg. It also stated that all subjects must be on a stable dose at least 6 weeks before screening.

For example, you failed to follow the investigational plan when you randomized subjects 1004, 1023, and 1037 on July 31, 2014; September 3, 2014; and September 15, 2014, respectively, despite these subjects' receiving a dose of simvastatin lower than 40 mg. For at least six weeks before screening, Subjects 1004, 1023, and 1037 were on stable doses of simvastatin 20 mg once daily.

In your November 19, 2015, written response to the Form FDA 483, you agreed that Subjects 1004, 1023, and 1037 were on 20 mg of simvastatin and were randomized into the study in error. You indicated that as part of your corrective and preventive action plan, your study staff will complete continuing education training regarding NIH and GCP practices, which you will lead. You also noted that study records will undergo a two-step verification process to monitor for completion, quality, and accuracy.

We are unable to undertake an informed evaluation of your written response because you did not provide a corrective action plan that, if properly carried out, would prevent this type of violation in the future. Specifically, you did not provide any details or descriptions of a corrective action plan to prevent similar violations in the future, nor did you provide sufficient details about your plan to implement additional measures and procedures to address the inspection findings regarding your failure to ensure the eligibility of enrolled subjects.

2. Protocol **(b)(4)** specified that subjects with creatinine kinase (CK) values > 3.0 times the upper limit of normal (ULN) at screening cannot be enrolled into this clinical investigation. However, the protocol also permitted a measurement of > 3.0 times ULN to be repeated once during screening. If the repeat measurement was < 3.0 times ULN, the subject was eligible for enrollment.

Protocol **(b)(4)** also specified that if at any study visit after screening, a subject experiences unexplained CK values > 5 times ULN, that subject must return for a repeat CK, preferably within 48 hours of when results are made available to the investigator. If the repeat testing confirms the elevated CK value, without associated muscle pain, muscle tenderness, and/or muscle weakness, or new-onset renal

dysfunction, the subject may continue to receive investigational drug if the sponsor's medical monitor provides approval.

a. You failed to follow the investigational plan when Subject 1014 was randomized on August 22, 2014, with a CK of 1074 U/L, which is > 3 times ULN (198 U/L), at screening on August 4, 2014. You initialed the laboratory report on August 6, 2014, and noted that "↑CK is not visible – clinically on lab values it might be, but not by looking at the patient." Regardless of your clinical evaluation, the protocol required either that you repeat the CK test, which you did not do, or that you not enroll the subject, as required by this exclusion criterion.

b. You failed to follow the investigational plan when Subject 1014 did not undergo a repeat CK test, preferably within 48 hours, despite having an unexplained (i.e., not associated temporally with recent trauma, intramuscular injections, heavy exercise, or physically strenuous activity) elevated CK value > 5 times ULN at the randomization visit (992 U/L on August 22, 2014).

c. You failed to follow the investigational plan when Subject 1014 did not undergo a repeat CK test, preferably within 48 hours, despite having an unexplained elevated CK value > 5 times ULN at Visit 11/Day 365 (3168 U/L on September 10, 2015). We acknowledge your handwritten note on September 18, 2015, which appears to state that the subject was called to schedule a repeat test, but the subject was unable to schedule a repeat test due to the subject's work schedule.

In your November 19, 2015, written response to the Form FDA 483, you indicated that you determined Subject 1014's elevated CK values not to be clinically significant because the subject was highly active, does regular weight training, and did not present with any clinical symptoms. You noted that your study coordinator had received verbal confirmation from a study monitor that Subject 1014 was eligible to be randomized on the study, based on your determination that the elevated CK value was not clinically significant.

In addition, you indicated that as part of your corrective and preventive action plan, your study staff will complete continuing education training regarding NIH and GCP practices, which you will lead. You noted that study records will undergo a two-step verification process to monitor for completion, quality, and accuracy. You also noted that verbal conversations with the study monitor will be followed up with e-mail correspondence to document the verbal conversations.

We are unable to undertake an informed evaluation of your written response because you did not provide a corrective action plan that, if properly carried out, would prevent this type of violation in the future. Specifically, you did not provide any details or descriptions of a corrective action plan to prevent similar violations in the future, nor did you provide sufficient details about your plan to implement additional measures and procedures to address the inspection findings regarding your failure to ensure the eligibility of enrolled subjects.

3. Protocol **(b)(4)** specified that subjects must have a fasting triglyceride (TG) value of $\leq$ 400 mg/dL at the second screening visit within 7 days ($\pm$ 3 days) of randomization.

a. You failed to follow the investigational plan when Subject 1005 was randomized on July 31, 2014, despite having a TG value of 456 mg/dL at the second screening visit on July 24, 2014, which exceeded the fasting TG value for subject eligibility.

b. You failed to follow the investigational plan when Subject 1006 was randomized on August 4, 2014, despite having a TG value of 701 mg/dL at the second screening visit on July 28, 2014, which exceeded the fasting TG value for subject eligibility.

In your November 19, 2015, written response to the Form FDA 483, you agreed that Subjects 1005 and 1006 were randomized into the study with exclusionary TG levels. You noted that your study coordinator had received verbal confirmation from a study monitor to allow Subjects 1005 and 1006 to continue on the study. You indicated that study coordinators have been re-educated on following inclusion/exclusion criteria and acceptable reporting timelines. You also stated that as part of your corrective and preventive action plan, your study staff will complete continuing education training regarding NIH and GCP practices, which you will lead. You noted that study records will undergo a two-step verification process to monitor for completion, quality, and accuracy. You also noted that verbal conversations with the study monitor will be followed up with e-mail correspondence to document the verbal conversations.
We are unable to undertake an informed evaluation of your written response because you did not provide a corrective action plan that, if properly carried out, would prevent this type of violation in the future. Specifically, you did not provide any details or descriptions of a corrective action plan to prevent similar violations in the future, nor did you provide sufficient details about your plan to implement additional measures and procedures to address the inspection findings regarding your failure to ensure the eligibility of enrolled subjects.

4. Protocol **(b)(4)** specified that subjects cannot be enrolled into this clinical investigation with tests positive for hepatitis B surface antigen (HBsAg), HB core antibody (HBcAb), or hepatitis C antibody indicative of present or prior infection. However, the protocol permitted the enrollment of subjects who test positive for HBcAb if the subject tests negative for HBsAg and positive for antibody to HB surface antigen.

You failed to follow the investigational plan when Subject 1007 was randomized on August 12, 2014, despite testing positive for HBcAb, negative for HBsAg, and negative for antibody to HB surface antigen at screening.

In your November 19, 2015, written response to the Form FDA 483, you agreed that Subject 1007 was enrolled into the study in error, based on the subject's having tested positive for HBcAb. You indicated that, upon learning that the subject was ineligible, the study coordinator reported the protocol deviation to the IRB and

attempted to get the subject to return all study medication. You noted that all site staff were re-educated on the importance of closely monitoring laboratory values and following all inclusion/exclusion criteria. You stated that, as part of your corrective and preventive action plan, your study staff will complete continuing education training regarding NIH and GCP practices, which you will lead. You noted that study records will undergo a two-step verification process to monitor for completion, quality, and accuracy. You also noted that verbal conversations with the study monitor will be followed up with e-mail correspondence to document the verbal conversations.

We are unable to undertake an informed evaluation of your written response because you did not provide a corrective action plan that, if properly carried out, would prevent this type of violation in the future. Specifically, you did not provide any details or descriptions of a corrective action plan to prevent similar violations in the future, nor did you provide sufficient details about your plan to implement additional measures and procedures to address the inspection findings regarding the enrollment of ineligible subjects.

5. Protocol **(b)(4)** specified that subjects with known **(b)(4)** equivalents at the highest approved dose of statins have a fasting low-density lipoprotein cholesterol (LDL-C) value of $\geq$ 70 mg/dL (1.81 mmol/L) at both screening visits, and that the value at the second screening visit (within 7 days of randomization, $\pm$ 3 days) must not be lower or higher than 20% of the initial fasting LDL-C value.

You failed to follow the investigational plan when Subject 1026 was randomized on September 19, 2014, despite having an LDL-C value of 125 mg/dL at the second screening visit on September 12, 2014, which is higher than 20% of the initial LDL-C value (97 mg/dL on September 5, 2014).

In your November 19, 2015, written response to the Form FDA 483, you agreed that Subject 1026 had elevated LDL levels. You noted that you reviewed the results and made a notation for the study coordinator to review the eligibility criteria pertaining to LDL values. You further noted that your study coordinator failed to review the lab reports and consequently randomized the subject without a second review of the eligibility criteria.

You stated that all site staff were re-educated on the importance of closely monitoring laboratory values and following all inclusion/exclusion criteria, along with review of reporting timelines per protocol. Your site audited the lab values for all the study subjects to re-check LDL values for compliance with the protocol. In addition, you indicated that as part of your corrective and preventive action plan, your study staff will complete continuing education training regarding NIH and GCP practices, which you will lead. You noted that study records will undergo a two-step verification process to monitor for completion, quality, and accuracy.

We wish to emphasize that as the clinical investigator, it was your ultimate responsibility to ensure that these studies were conducted properly and in compliance with FDA regulations to protect the rights, safety, and welfare of study subjects and to ensure the integrity of study data. We are unable to undertake an

informed evaluation of your written response because you did not provide any details or descriptions of a corrective action plan to prevent similar violations in the future, nor did you provide sufficient details about your plan to implement additional measures and procedures to address the inspection findings regarding the enrollment of ineligible subjects.

6. Protocol **(b)(4)** specified that subjects must be at a high or very high risk of incurring a **(b)(4)**, as defined either by known **(b)(4)** equivalents, or by the presence of multiple (that is, three or more) listed risk factors. The protocol defined having known **(b)(4)** equivalents as having a history of coronary heart disease, other clinical atherosclerotic diseases, **(b)(4)**, or chronic kidney disease.

You failed to follow the investigational plan when Subject 1029 was randomized on September 12, 2014, without known **(b)(4)** equivalents (described in the protocol as a known history of coronary heart disease, other clinical atherosclerotic diseases, **(b)(4)**, or chronic kidney disease) and with the presence of only two of the listed risk factors. By definition of the protocol, this subject did not have a high or very high risk of incurring a CV event and should not have been enrolled.

In your November 19, 2015, written response to the Form FDA 483, you indicated that Subject 1029 had only two CV risk factors. You also noted that your study coordinator had received verbal confirmation from a study monitor to allow Subject 1029 to continue in the study. You indicated that as part of your corrective and preventive action plan, your study staff will complete continuing education training regarding NIH and GCP practices, which you will lead. You noted that study records will undergo a two-step verification process to monitor for completion, quality, and accuracy.

We are unable to undertake an informed evaluation of your written response because you did not provide a corrective action plan that, if properly carried out, would prevent this type of violation in the future. Specifically, you did not provide any details or descriptions of a corrective action plan to prevent similar violations in the future, nor did you provide sufficient details about your plan to implement additional measures and procedures to address the inspection findings regarding the enrollment of ineligible subjects.

The eligibility criteria for each clinical investigation are designed to optimize the interpretability of the 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 concerns about the validity and integrity of the data collected at your site. Particularly concerning to FDA is that you enrolled 9 of the 23 subjects randomized into Protocol **(b)(4)** at your site without having ensured their eligibility to be enrolled as subjects.

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

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Sincerely yours,
{See appended electronic signature page}
David Burrow, Pharm.D., J.D.
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/s/

DAVID C BURROW
03/10/2016

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