Jose Giron 5/19/16

Dear Dr. Giron:

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 September 1, 2015, and October 8, 2015. Ms. Brunilda Torres, representing FDA, reviewed your conduct of the following clinical investigations:

- Protocol (b)(4), “(b)(4),” of investigational drug (b)(4), performed for (b)(4)
- Protocol (b)(4), “(b)(4),” of 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. Torres presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your October 27, 2015, written response to the Form FDA 483, and of your second letter of the same date providing additional comments.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, your written response dated October 27, 2015, and your additional comments dated October 27, 2015, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations.
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) requires that you collect stool and blood samples from enrolled subjects for central laboratory assessment. In addition, the investigational plan for Protocol (b)(4) requires that subjects receive the correct dose of investigational drug. You failed to adhere to these requirements. Specifically:

1. Protocol (b)(4) required that, optimally before infusion but at least within 72 hours of infusion (Visit 1), a stool sample for anaerobic culture and other ancillary microbiological assessments (including microbial identification, toxigenic strain typing, and antibacterial susceptibility testing) be collected and sent to a central laboratory. Notably, Protocol (b)(4) specified that this stool sample was an absolute requirement.

For 13 out of 14 enrolled subjects (i.e., Subjects 106409, 106489, 106514, 106555, 106593, 106595, 106601, 106655, 106660, 106712, 106742, 106743, and 106801), you failed to send Visit 1 stool samples to the central laboratory for anaerobic culture assessment, as required.

Your failure to follow the protocol raises concerns about the reliability of the data collected at your site.

During the inspection, you indicated you were under the assumption that the Visit 1 stool sample was not required, since all participating subjects had a positive stool test for (b)(4) from a local laboratory. However, after reviewing the protocol with Ms. Torres, you agreed that the baseline stool sample was a protocol requirement. In your October 27, 2015, written response, you indicated you knew that at least some stool samples were collected, and that you did not suspect those samples would not be shipped. As a preventive action, you indicated you were implementing a system at your site to verify sample acquisition, storage, and shipment. In addition, you indicated you will have weekly meetings with site staff to go over any potential study issues, and “for any protocols in the future, we will be diligent to follow the procedures as outlined and, as a check, verify that indeed, such procedures are followed.”

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 sufficient details about your plan for implementing additional measures and procedures to address the inspection findings about your failure to follow protocol procedures. For example, you did not indicate whether you and your staff underwent retraining activities to prevent future protocol violations. In addition, your written response does not provide sufficient details about how you personally will ensure adequate oversight of study procedures, the activities of study coordinators, and protocol...
training for you and your study staff. Without these details, we are unable to determine whether your corrective action plan is adequate to prevent similar violations in the future.

2. Protocol (b)(4) required that the following blood samples be collected and sent to designated central laboratories:

- An assessment of (b)(4) levels to (b)(4), performed at Day 1 (Visit 1), Week 4 (Visit 4), Week 12 (Visit 6), and at any unscheduled visits
- A pharmacokinetic (PK) assessment of (b)(4) ((b)(4)) and (b)(4) ((b)(4)), performed at Day 1 (Visit 1) (pre- and post-infusion), Week 1 (Visit 2), Week 2 (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), and Week 12 (Visit 6)
- A test for anti-drug antibody (ADA) (including neutralizing antibody) levels performed at Day 1 (Visit 1), Week 2 (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), and Week 12 (Visit 6)

You failed to adhere to these requirements. Specifically, you failed to assess endogenous (b)(4) and (b)(4) antibodies; PKs for (b)(4), or both; and ADA levels for the following subjects and study visits:

a. For Subject 106408, you failed to provide the central laboratory blood samples for (b)(4) antibody testing (Visit 4); for PK assessments of (b)(4) (Visit 1 pre- and post-infusion, 2, 3, 4, and 6) and of (b)(4) (Visit 1 pre- and post-infusion, 2, 3, 4, 5, and 6); and for ADA levels [Visit 1 ((b)(4) only), 3, 4, 5, and 6 (both)]. Subject 106408 was randomized on February 21, 2012.

b. For Subject 106409, you failed to provide the central laboratory blood samples for (b)(4) and (b)(4) antibodies testing (Visit 4); for PK assessments of (b)(4) (Visit 1 pre-infusion, 4, and 5) and of (b)(4) (Visit 1 pre- and post-infusion, 3, 4, and 5); and for ADA levels [Visit 3 ((b)(4) only), 4, and 5 (both)]. Subject 106409 was randomized on February 27, 2012.

c. For Subject 106489, you failed to provide the central laboratory blood samples for (b)(4) and (b)(4) antibodies testing (Visit 4); for PK assessments of (b)(4) (Visit 1 post-infusion, 4, and 6) and of (b)(4) (Visit 1 pre-infusion, 2, 3, and 5); and for ADA levels (Visit 1, 3, 4, and 6). Subject 106489 was randomized on March 7, 2012.

d. For Subject 106514, you failed to provide the central laboratory blood samples for (b)(4) and (b)(4) antibodies testing (Visit 1 and 4); for PK assessments of (b)(4) (Visit 3 and 4) and (b)(4) (Visit 1 pre- and post-infusion, 2, 3, 4, and 5); and for ADA levels (Visit 1, 4, and 5). Subject 106514 was randomized on May 16, 2012.

e. For Subject 106555, you failed to provide the central laboratory blood samples for (b)(4) and (b)(4) antibodies testing (Visit 1); for PK assessments of (b)(4) (Visit 1 post-infusion and 3) and (b)(4) (Visit 1 pre-infusion, 2, 3, and 5); and for ADA levels (Visit 1 and 5). Subject 106555 was randomized on May 19, 2012.
f. For Subject 106593, you failed to provide the central laboratory blood samples for (b)(4) antibody testing (Visit 1) and (b)(4) antibody testing (Visit 1 and 4); for PK assessments of (b)(4) (Visit 1 pre- and post-infusion, 2, 3, and 4); and for ADA levels (Visit 1 and 4). Subject 106593 was randomized on May 23, 2102.

g. For Subject 106595, you failed to provide the central laboratory blood samples for (b)(4) and (b)(4) antibodies testing (Visit 1 and 4); for PK assessment of (b)(4) (Visit 3 and 4) and (b)(4) (Visit 1 pre- and post-infusion, 2, 3, 4, and 5); and for ADA levels (Visit 1, 4, and 5). Subject 106595 was randomized on May 30, 2102.

h. For Subject 106601, you failed to provide the central laboratory blood samples for (b)(4) and (b)(4) antibodies testing (Visit 1 and 4); for PK assessments of (b)(4) (Visit 3 and 4) and (b)(4) (Visit 1 pre- and post-infusion, 2, 3, 4, and 5); and for ADA levels [Visit 1 ((b)(4) only), 4, and 5 (both)]. Subject 106601 was randomized on June 16, 2012.

i. For Subject 106655, you failed to provide the central laboratory blood samples for (b)(4) antibody testing (Visit 4) and (b)(4) antibody testing (Visit 1, 4, and 6); for PK assessments of (b)(4) (Visit 2, 3, and 5) and (b)(4) (Visit 1 pre- and post-infusion, 4, 5, and 6); and for ADA levels [Visit 1 (both) and Visit 4, 5, and 6 ((b)(4) only)]. Subject 106655 was randomized on July 8, 2012.

j. For Subject 106660, you failed to provide the central laboratory blood samples for (b)(4) antibody testing (Visit 1 and 4) and (b)(4) antibody testing (Visit 1 and 6); for PK assessments of (b)(4) (Visit 4 and 5) and (b)(4) (Visit 1 pre- and post-infusion, 2, 3, 4, 5, and 6); and for ADA levels [Visit 1 (both), 4 ((b)(4) only), 5, and 6 (both)]. Subject 106660 was randomized on July 22, 2012.

k. For Subject 106712, you failed to provide the central laboratory blood samples for (b)(4) antibody testing (Visit 1); for PK assessments of (b)(4) (Visit 4) and (b)(4) (Visit 1 pre- and post-infusion, 2, 3, and 4); and for ADA levels (Visit 1 and 4). Subject 106712 was randomized on September 4, 2012.

l. For Subject 106742, you failed to provide the central laboratory blood samples for (b)(4) antibody testing (Visit 1 and 4); for PK assessments of (b)(4) (Visit 1 pre-infusion) and (b)(4) (Visit 1 pre- and post-infusion, 2, 3, and 4); and for ADA levels [Visit 1 ((b)(4) only) and 4 (both)]. Subject 106742 was randomized on August 21, 2012.

m. For Subject 106743, you failed to provide the central laboratory blood samples for (b)(4) antibody testing (Visit 1) and (b)(4) antibody testing (Visit 1 and 4); for PK assessments of (b)(4) (Visit 3) and (b)(4) (Visit 1 pre- and post-infusion, 2, 3, 4, and 5); and for ADA levels [Visit 1, 4, and 5 ((b)(4) only)]. Subject 106743 was randomized on August 27, 2012.
n. For Subject 106801, you failed to provide the central laboratory blood samples for (b)(4) antibody testing (Visit 4); for PK assessments of (b)(4) (Visit 3 and 5) and (b)(4) (Visit 1 pre- and post-infusion, 2, 4, and 5); and for ADA levels [Visit 1, 4, and 5 (b)(4) only]. Subject 106801 was randomized on October 2, 2012.

In your October 27, 2015, written response to the Form FDA 483, you acknowledged the missing blood samples, but you also indicated that you saw subjects at every visit, and that you observed the collection of blood samples. You noted that you learned of the missing samples much later in the course of the study. As a preventive action, you indicated that you were implementing a system at your site to verify sample acquisition, storage, and shipment. In addition, you indicated you will have weekly meetings with site staff to go over any potential study issues, and “for any protocols in the future, we will be diligent to follow the procedures as outlined and, as a check, verify that indeed, such procedures are followed.”

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 sufficient details about your plan for implementing additional measures and procedures to address the inspection findings about your failure to follow protocol procedures.

For example, you did not indicate whether you and your staff underwent retraining activities (such as sample collection, handling, and shipment) to prevent future protocol violations. In addition, your written response does not provide sufficient details on how you personally will ensure adequate oversight of study procedures, the activities of study coordinators, and protocol training for you and your study staff. As a result, we are unable to determine whether your corrective action plan is adequate to prevent similar violations in the future.

3. Protocol (b)(4) requires that subjects take (b)(4) 400 mg (2 tablets) in the morning and 400 mg (2 tablets) in the evening, for a total of 800 mg of (b)(4) per day. You failed to adhere to these protocol requirements. Specifically, starting on February 28, 2013 (first dose), Subject 557 was dosed with 600 mg of (b)(4) (3 tablets) in the morning and the evening, for a total of 1200 mg of (b)(4) per day. Study records indicate that this overdose event occurred on February 28, 2013, and was resolved on March 31, 2013.

Your failure to ensure that subjects received the correct doses of investigational drug raises significant concerns about the reliability of the data from your site.

In your October 27, 2015, written response, you indicated that this violation was corrected and reported to the sponsor, and “to the best of my knowledge, no harm has come to” the subject.

Your response is inadequate because you did not provide any corrective actions to prevent similar violations in the future.

Failure to follow the protocol requirements jeopardizes subject safety and welfare,
and raises concerns about the reliability of the data collected 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 comply 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 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:

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Sincerely yours,

David C. Burrow, Pharm.D., J.D.
Acting Office Director
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
DAVID C BURROW
05/19/2016