Kang Zhang, M.D., Ph.D. 1/5/17

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hapshire Avenue
Silver Spring, MD 20993

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Kang Zhang, M.D., Ph.D.
HFD-45-01-01
9415 Campus Point Drive, Room E214
La Jolla, CA 92093-0946

Ref.: 17-

Dear Dr. Zhang:

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 July 14, 2016, and August 1, 2016. Ms. Natalie J. Ayoub, representing FDA, reviewed your conduct of a clinical investigation (Protocol **(b)(4)**, "**(b)(4)** of the investigational drug **(b)(4)** for which you were both the sponsor and a clinical investigator.

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. Ayoub presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your August 18, 2016, 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 August 18, 2016, 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:

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 for Protocol **(b)(4)** required you to ensure that subjects met the protocol inclusion criteria before their enrollment. In addition, Protocol **(b)(4)** required you to perform certain study procedures, such as ophthalmologic evaluations, at specific times. You failed to adhere to these requirements. Specifically:

a. The investigational plan for the above-mentioned protocol required subjects to have lost more than five letters from baseline best vision to be eligible for enrollment. For Protocol **(b)(4)**, best vision was measured by assessing the Best Corrected Visual Acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) method or, in certain circumstances, the Snellen test. You enrolled five subjects who did not meet this requirement. Specifically, you or a subinvestigator allowed the enrollment of the following subjects even though they did not have a loss of more than five letters from baseline best vision:

- Subject C-001, enrolled on August 15, 2011
- Subject C-006, enrolled on August 13, 2012
- Subject C-007, enrolled on August 31, 2012
- Subject C-008, enrolled on September 18, 2012
- Subject C-009, enrolled on September 25, 2012

In your August 18, 2016, written response to the Form FDA 483, you indicated that you determined that enrollment of subjects who had lost five or fewer letters from baseline was acceptable for the course of the study. You noted that the rationale for this inclusion criterion was to better assess the primary objective of determining if subjects treated early after diagnosis could return to or maintain their baseline pre-disease visual acuity. You also noted that with inclusion of these subjects, there was no increased risk/benefit ratio.

b. The investigational plan required an assessment of BCVA using the ETDRS method at a distance of 4 meters on Day 0. Day 0 procedures may be carried out over the course of two separate visits within a two-week time period. You were required to assess BCVA on Day 0 to determine whether subjects met the inclusion criterion requiring a loss of more than five letters from baseline best vision.

You failed to perform a BCVA using ETDRS on Day 0 for Subject C-003 on October 6, 2011. However, Subject C-003 was enrolled into the study and received study

drug on Day 0. Therefore, you failed to fully evaluate this subject's eligibility before enrolling the subject into this study.

In your August 18, 2016, written response to the Form FDA 483, you indicated that you had baseline records for the required study procedures, and you marked in a table that ETDRS BCVA was performed for Subject C-003. In particular, you submitted a progress note dated June 27, 2011, showing that an ETDRS BCVA was performed on that date. We note that Day 0 for this subject was October 6, 2011, over three months after this June 27, 2011, progress note. We are thus unable to determine whether an ETDRS BCVA was performed on or within 2 weeks of the subject's Day 0 study visit on October 6, 2011.

In addition, you indicated that you understand that stringent adherence to the inclusion and exclusion criteria should be used to assess eligibility, and that any amendment to the inclusion and exclusion criteria should first be approved by the Institutional Review Board (IRB). You also indicated that for all current and future studies, a "Secondary Reviewer Screening Process" will be implemented to review inclusion and exclusion criteria for each newly enrolled subject within at least a 24-hour screening period after informed consent has been obtained.

We are unable to undertake an informed evaluation of your written response to Items 1.a. and 1.b. above 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 concerning your failure to ensure that only eligible subjects were enrolled.

We emphasize that 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 concerns about the validity and integrity of the data collected at your site. FDA is particularly concerned that you enrolled six of the twelve subjects enrolled into this study without ensuring their subject eligibility.

c. The investigational plan provided that subjects who withdraw from the study before completion should return for an early termination evaluation 30 days (± 7 days) following the last injection or study visit, for monitoring of all adverse events (serious and nonserious). Under the investigational plan, you were to perform the following study procedures at the early termination visit: an ophthalmological exam, ETDRS BCVA, spectral domain optical coherence tomography (SD-OCT), and serious adverse event (SAE) monitoring. Subject C-011 withdrew from the study on August 13, 2013, one day after being enrolled and receiving study drug on Day 0. However, you failed to conduct an early termination visit for Subject C-011.

In your August 18, 2016, written response to the Form FDA 483, you acknowledged that an early termination visit was not completed for this subject. You noted that this subject withdrew for personal reasons and remained under your care as a standard-of-care patient.

In addition, you indicated that study staff has been retrained on the importance of monitoring for adverse events during the early termination assessments. Specifically, you indicated that study staff will receive one-on-one retraining in IRB regulations, reporting timelines, and other regulations, documentation of which you noted should be provided to the FDA in 30 days.

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 concerning your failure to follow protocol procedures.

Failure to perform protocol-required study procedures, including ophthalmological evaluations and adverse event monitoring, jeopardizes subject safety and welfare and raises concerns about the validity and integrity of the data collected at your site.

2. 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. For Protocol **(b)(4)**, drug disposition records include study drug accountability logs and records documenting the destruction of unused supplies of study drug. You did not maintain adequate records with respect to these documents. Specifically, your study drug accountability logs failed to document the disposition of 25 units of unused supplies of study drug. Further, you were unable to produce the unused supplies of study drug, and there were no other records indicating the use or disposal of these missing unused supplies of study drug.

In your August 18, 2016, written response to the Form FDA 483, you agreed that the investigational drug records were inadequately maintained. You noted that the drug supply had been destroyed, and that the destruction of unused supplies of study drug was not documented adequately. You stated that the study drug was used solely for the purposes of this study.

In addition, you indicated that study staff will be retrained on the importance of maintaining accurate and complete records of the investigational drug. You indicated that you have written a detailed plan for monitoring accurate and complete drug accountability records in a standard operating procedure (SOP), which you intended to provide to FDA within 30 days of the transmittal of your response to the Form FDA 483. You also indicated that you planned to conduct a study closure visit to reconcile drug accountability, ensure destruction of expired supplies of the drug, and ensure completion and retention of all study records.

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 concerning your failure to maintain adequate drug accountability records.

Your inability to account for the disposition of 25 units of unused supplies of study drug raises significant concerns regarding the adequacy of your oversight and control of investigational drug. In addition, your failure to maintain adequate and accurate drug accountability records raises concerns about the validity and integrity 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 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 Adam Donat, M.S., at 301-796-5316; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Adam Donat, M.S.
Branch Chief
Compliance Enforcement Branch
Division of Enforcement and Postmarketing Safety
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5352
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,
{See appended electronic signature page}
David Burrow, Pharm.D., J.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

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
01/05/2017

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