Dear Dr. Doft:

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 17, 2012, and September 28, 2012. Ms. Erica Nicoll, representing the FDA, reviewed your conduct of a clinical investigation (Protocol FVF4579), titled “A Phase III, Double-Masked, Multicenter, Randomized, Active Treatment-Controlled Study of the Efficacy and Safety of 0.5 mg and 2.0 mg Ranibizumab Administered Monthly or on an As-Needed Basis (PRN) in Patients with Subfoveal Neovascular Age-Related Macular Degeneration”, of the investigational drug, ranibizumab (Lucentis®), performed for Genentech, Inc.

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. Nicoll presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your October 8, 2012 written response to the Form FDA 483.

From our review of the FDA’s Establishment Inspection Report, the documents submitted with that report, and your October 8, 2012 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 you ensure adherence to protocol (e.g., enrolling only subjects who meet the eligibility criteria, using certified personnel for visual acuity (VA) testing, and ensuring that VA testing was performed by personnel properly masked to the study eye). You failed to adhere to these requirements. Specifically:

a. Protocol Section 4.1.2 “Inclusion Criteria” requires the subject to have a Best Corrected Visual Acuity (BCVA), using Early Treatment Diabetic Retinopathy Study (EDTRS) charts, of 20/40–20/320 (Snellen equivalent). Two subjects who did not meet this inclusion criterion were included in the study. Subject #704201 had a BCVA of 20/32 at Day 0 and Subject #704220 had a BCVA of 20/400 at screening.

b. Protocol Appendix G states that the "Best corrected visual acuity (BCVA) will be measured by trained and certified personnel at the study sites". BCVA was measured by uncertified personnel in 5 subjects (Subjects 704201, 704202, 704203, 704204 and 704205) in 14 instances. Specifically, this occurred for Subject# 704201 on 3 visits; Subject# 704202 on 3 visits; Subject# 704203 on 2 visits; Subject# 704204 on 3 visits; and Subject# 704205 on 3 visits.

c. Protocol Section 4.2.2 states "the VA examiner will be masked to the patients' study eye and will conduct refraction, VA assessments, and low luminance testing . . . No other direct patient care tasks can be performed by the VA examiner". Your VA examiners measured the intraocular pressure (IOP), without being masked to the study eye, in nine subjects (Subject# 704201, 704202, 704203, 704204, 704205, 704206, 704207, 704208, and 704209) for a total of 35 documented protocol violations.

We acknowledge that, in your October 8, 2012 written response to the Form FDA 483, you stated that you have implemented Standard Operating Procedure (SOP) # 14 "Prescreening, Screening, and Randomization Procedures," SOP # 23 "Certification of Research Personnel," SOP # 24 "Screen Failure Patients," and SOP # 25 "Subject Visit Procedure." If properly implemented and executed, these SOPs appear adequate to prevent recurrence of similar violations in the future. However, it was your responsibility as the clinical investigator to ensure that Protocol FVF4579 was conducted in accordance with the investigational plan, including ensuring that only subjects that met eligibility criteria were enrolled, that subjects had BCVA measurements performed by certified personnel, and that VA measurements were made by personnel properly masked to the study eye.

Enrollment of subjects who do not meet eligibility criteria and failure to ensure that certified and properly masked evaluators measured VA raise concern 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 FVF4579, case histories include the Genentech Visual Acuity Worksheets. You have failed to maintain adequate and accurate case histories by failing to ensure that Genentech Visual Acuity Worksheets accurately listed the person who conducted exams as documented in subjects’ medical charts.
Our inspection revealed 10 examples in which the VA Examiner listed in the Genentech Visual Acuity (VA) Worksheets was not the person conducting the exams as documented in the subjects’ medical charts. These violations occurred in 5 of the 23 total subjects (22%) at this site. Specifically:

- Subject # 704201: 2 Genentech VA Worksheets did not accurately identify who conducted the VA exams.
- Subject # 704202: 2 Genentech VA Worksheets did not accurately identify who conducted the VA exams.
- Subject # 704203: 1 Genentech VA Worksheet did not accurately identify who conducted the VA exams.
- Subject # 704204: 3 Genentech VA Worksheets did not accurately identify who conducted the VA exams.
- Subject # 704205: 2 Genentech VA Worksheets did not accurately identify who conducted the VA exams.

We acknowledge that, in your October 8, 2012 written response, you stated that you have implemented SOP # 26 “Preparation of Source Documents.” If properly implemented and executed, this SOP appears adequate to prevent recurrence of similar violations in the future. However, as the clinical investigator, it was your responsibility 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.

Your failure to maintain adequate and accurate case histories, including the failure to ensure that the names and signatures of study personnel were accurately recorded on the Genentech VA Worksheets, raises concerns about the validity, reliability, and integrity of data captured at your site.

3. You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60, 21 CFR 50.20].

As a clinical investigator, it is your responsibility to obtain informed consent in accordance with 21 CFR Part 50. FDA regulations at 21 CFR 50.20 state that except as provided in 21 CFR 50.23 and 21 CFR 50.24, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject’s legally authorized representative. You failed to obtain legally effective informed consent.

Specifically, two subjects (Subject #10461 and #10620) underwent study procedures (i.e., BCVA, IOP, ocular imaging, fluorescein angiograms, optical coherence tomography, eye dilation, or the collection of laboratory examples) prior to signing the informed consent form. Subject #10461 signed the informed consent form on 03/18/2010, but underwent screening procedures (BCVA, IOP, fluorescein angiograms, optical coherence tomography and dilation of the eyes) in December 2009.

Subject #10620 signed the informed consent form on 01/28/2010, but underwent screening procedures, including BCVA and dilation of the eyes, prior to signing the consent form on the same day. Additionally, we note that it appears as if subject #10620 could not read the informed consent form, because the form was provided to the subject after the subject’s eyes were dilated.

We acknowledge that, in your October 8, 2012 written response, you stated that you have implemented several procedures including SOP # 8 “Informed Consent” and SOP # 27 “Oral Informed Consent” as well as a consent form alert system. If properly implemented and executed, these procedures appear adequate to prevent recurrence of similar violations in the future. However, as the clinical investigator, it was your responsibility to obtain informed consent in accordance with 21 CFR Part 50. Your failure to obtain informed consent in accordance with 21 CFR Part 50 prior to involving subjects in research raises concerns about your protection of study subjects enrolled at
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 that your written response to the Form FDA 483 dated October 8, 2012, fully explains the actions you have taken to prevent similar violations in the future, please communicate that to us in writing within fifteen (15) business days. You may reference the written response dated October 8, 2012, in your response to this letter.

If you have any questions, please contact Susan Thompson, M.D., at 301-796-0823; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5350
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,

{See appended electronic signature page}

Thomas N. Moreno, M.S.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

KASSA AYALEW
06/11/2013

THOMAS N MORENO
06/12/2013

Page Last Updated: 07/11/2013
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