DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN (NIDPOE)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Anil Kumar, M.D.
44215 15th Street, Suite 215
Lancaster, CA 93534

Dear Dr. Kumar:

Between October 11, 2011, and November 2, 2011, Uttaniti Limchumroon, representing the U.S. Food and Drug Administration (FDA), conducted an inspection to review your conduct of the following clinical investigations:

- Protocol 1160.26 (RE-LY), "Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) Comparing the Efficacy and Safety of Two Blinded Doses of Dabigatran Etexilate With Open Label Warfarin for the Prevention of Stroke and Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation: Prospective, Multi-Center Parallel-Group Non-Inferiority Trial (RE-LY study)," of the investigational drug dabigatran, performed for Boehringer Ingelheim Pharmaceuticals, Inc.;

- Protocol 1160.71 (RELY-ABLE), "RELY-ABLE Long Term Multi-Center Extension of Dabigatran Treatment in Patients With Atrial Fibrillation Who Completed the RE-LY Trial and a Cluster Randomized Trial to Assess the Effect of a Knowledge Translation Intervention on Patient Outcomes," of the investigational drug dabigatran, performed for Boehringer Ingelheim Pharmaceuticals, Inc.; and

- Protocol H7T-MC-TABY, "A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome (ACS) Subjects with Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) Who are Medically Managed--The Trilogy ACS Study," of the investigational drug prasugrel, performed for Eli Lilly and Company.

This inspection is a part of the 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, Uttaniti Limchumroon presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We acknowledge receipt of your November 21, 2011, written response to the Form FDA 483.

We have reviewed the FDA inspection report, the documents submitted with that report, and your November 21, 2011, written response to the Form FDA 483. We do not find your response to be acceptable in addressing the matters under complaint, which are described below.

Based on our evaluation of information obtained by the Agency, we believe that you have repeatedly or deliberately submitted false information to the sponsor or FDA in required reports, and repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products, as published under Title 21, Code of Federal Regulations (CFR), part 312.70 (copy enclosed).

This letter provides you with written notice of the matters complained of and initiates an administrative proceeding, described below, to determine whether you should be disqualified from eligibility to receive test articles as set forth under 21 CFR 312.70, and disqualified from eligibility to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.

A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. **You repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report [21 CFR 312.70(a)].**

   As a clinical investigator for Protocol 1160.71 (RELY-ABLE), you were required to perform laboratory tests at Visit 3. FDA has concluded that as the clinical investigator for Protocol 1160.71, you submitted false information to the sponsor by the submission of these required Visit-3 laboratory test results.

   a. In your written response to the Form FDA 483, you acknowledge that the laboratory results with identical values for different dates were falsified. Specifically:

      i. Subject 0246-021 had laboratory results with identical values on January 4, 2010, and October 4, 2010. The October 4, 2010, laboratory results also contain your initials (dated October 13, 2009) and were submitted as October 4, 2009 (Visit 3) laboratory results.

ii. Subject 0246-017 had laboratory results with identical values on February 22, 2007, and October 9, 2009 (Visit 3).

b. In your written response to the Form FDA 483, you acknowledge that the laboratory results contained in your study records were falsified because they could not be corroborated by the laboratories that purportedly analyzed the blood samples. Specifically:

i. December 30, 2009, laboratory results for Subject 0246-005 – (b) (4) had no record of these laboratory results.

ii. October 1, 2009, laboratory results for Subject 0246-010 – Antelope Valley Hospital had no record of these laboratory results.

iii. October 23, 2009, laboratory results for Subject 0246-015 – Antelope Valley Hospital had no record of these laboratory results.

iv. December 3, 2009, laboratory results for Subject 0246-020 – Antelope Valley Hospital had no record of these laboratory results.

v. October 22, 2009, laboratory results for Subject 0246-023 – Antelope Valley Hospital had no record of these laboratory results.

vi. October 20, 2009, laboratory results for Subject 0246-024 – (b) (4) had no record of these laboratory results.

vii. October 9, 2009, laboratory results for Subject 0246-030 – (b) (4) had no record of these laboratory results.

viii. October 27, 2009, laboratory results for Subject 0246-033 – (b) (4) had no record of these laboratory results.

ix. November 25, 2009, laboratory results for Subject 0246-042 – Antelope Valley Hospital had no record of these laboratory results.

In your written response to the Form FDA 483, you stated that the study coordinator falsified documents. We acknowledge your statements that you removed this study coordinator from responsibility for the RELY and RELY-ABLE trials on May 17, 2010, and that she was terminated due to concerns about her performance on May 28, 2010. We further acknowledge your statements that you brought all enrolled subjects in for an unscheduled visit to have repeat laboratory tests done, and that no gross abnormalities were found.

While your acts assured FDA that these specific subjects were evaluated for any safety issues, your response is inadequate because, after being made aware of the

falsified laboratory results in August 2010, you failed to investigate for additional acts of falsification within the same clinical investigation, or in other clinical investigations in which the study coordinator may have been involved. During the inspection, you indicated that this coordinator had worked for you for approximately four years as your clinical research coordinator. This coordinator's curriculum vitae also indicates that she worked for you for approximately four years as a clinical research coordinator. Therefore, without an investigation into the studies conducted during the years this coordinator worked for you, we cannot be assured that additional falsification did not occur in additional studies. Moreover, regardless of your corrective actions, as the clinical investigator you were ultimately responsible for the conduct of this study, including the fact that false information was submitted to the sponsor.

As the clinical investigator, it is your responsibility to ensure that the data collected from study subjects are accurate and can be relied upon in any analyses of the study endpoints. When you signed the Statement of the Investigator, Form FDA 1572, you agreed to provide accurate information to the sponsor, and to ensure that you will comply with FDA regulations related to the conduct of the clinical investigations of the investigational drugs. You also agreed to ensure that all associates, colleagues, and employees assisting in the conduct of the study were informed about their obligations in meeting their commitments. Furthermore, your signature constitutes your affirmation that you are qualified to conduct the clinical investigation, and also constitutes your written commitment to abide by FDA regulations in the conduct of the clinical investigations. The use of false information significantly compromises the study integrity, as well as the reliability and validity of the data.

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 1160.71 (RELY-ABLE), case histories include laboratory results. You have failed to maintain adequate and accurate case histories that reflect accurate laboratory values. Specifically:

   For Subject 0246-021, the October 6, 2006, and October 6, 2009, laboratory test results have the following identical values, and therefore represent inaccurate case histories:

   a. White blood cell count (WBC)
   b. Red blood cell count (RBC)
   c. Hemoglobin

d. Hematocrit
e. Mean corpuscular volume (MCV)
f. Mean corpuscular hemoglobin (MCH)
g. Mean corpuscular hemoglobin concentration (MCHC)
h. Red blood cell distribution width (RDW)
i. Platelets
j. % Neutrophils
k. % Lymphocytes (Lymphs)
l. % Monocytes
m. % Eosinophils (Eos)
n. % Basophils (Basos)
o. Absolute neutrophil count [Neutrophils (Absolute)]
p. Absolute lymphocyte count [Lymphs (Absolute)]
q. Absolute monocyte count [Monocytes (Absolute)]
r. Absolute eosinophil count [Eos (Absolute)]
s. Absolute basophil count [Basos (Absolute)]
t. Hematology comments
u. Serum glucose
v. Blood urea nitrogen (BUN)
w. Serum creatinine
x. BUN/Creatinine Ratio

We note that Item 2 above was not listed on the Form FDA 483 that was issued to you, and therefore your written response to the Form FDA 483 was not targeted to this violation. However, your written response is relevant, because in your response you admitted that your study coordinator had falsified laboratory results. Specifically, you stated that the study coordinator retrieved laboratory results from the past and "manufactured" new laboratory results by changing the dates of the laboratory tests. The existence of laboratory results with 24 identical values for the same subject on two different test dates, combined with the admitted submission of false data elsewhere, indicates that the data noted in Item 2 above were also manufactured. Your response to all violations involving falsification of data is inadequate because you failed to investigate for additional acts of falsification within the same clinical investigation, or in other clinical investigations in which the study coordinator may have been involved, in order to verify the accuracy of your case histories. Moreover, regardless of your corrective actions, as the clinical investigator you were ultimately responsible for the conduct of this study, including the fact that case histories were falsified.

As the clinical investigator, it is your responsibility to maintain adequate and accurate case histories. Your failure to maintain adequate and accurate case histories, including the failure to maintain accurate laboratory values, 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 studies of investigational products. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above-listed violations, FDA asserts that you have failed to protect the rights, safety, and welfare of subjects under your care; repeatedly or deliberately submitted false information to the sponsor; and repeatedly or deliberately failed to comply with the cited regulations, which placed unnecessary risks to human subjects and jeopardized the integrity of data, and the FDA proposes that you be disqualified as a clinical investigator. You may reply to the above-stated findings, including an explanation of why you should not be disqualified as a clinical investigator, either in a written response or at an informal conference in my office. This procedure is provided for by regulation 21 CFR 312.70.

Within fifteen (15) days of receipt of this letter, write to me at the address below or call me at 301-796-3865 to arrange a conference time or to indicate your intent to respond in writing.

Should you choose to respond in writing, your written response should be forwarded within thirty (30) days of receipt of this letter.

Your reply should be sent to:

Sean Y. Kassim, Ph.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5346
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above-listed violations. You should bring with you all pertinent documents, and a representative of your choice may accompany you. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

The FDA's Center for Drug Evaluation and Research (the Center) will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR 16 (enclosed) and 21 CFR 312.70. Before such a hearing, FDA will provide you with notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer who has not participated in this matter will conduct the hearing. After such hearing, the Commissioner will determine whether you will remain entitled to receive test articles and to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.

You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

To enter into the enclosed consent agreement with FDA, thereby terminating this disqualification process, you must:

(1) Initial and date each page of this Agreement;
(2) Sign and date the last page of this Agreement; and
(3) Return this Agreement, initialed, signed, and dated, to the signer below.

A copy of the fully executed Agreement will be mailed to you.

Sincerely yours,

{See appended electronic signature page}

Sean Y. Kassim, Ph.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosures:
#1 - Consent Agreement
#2 - 21 CFR 16
#3 - 21 CFR 312.70

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SEAN Y KASSIM
05/02/2014