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

Farid Marquez, M.D.
3700 West 12th Avenue
Suite 300
Hialeah, Florida 33012

Dear Dr. Marquez:

Between September 8 and October 6, 2014, Ms. Brunilda Torres and Mr. Craig Garmendia, representing the U.S. Food and Drug Administration (FDA) (hereafter referred to as the "agency"), conducted an inspection to review your conduct of the following clinical investigation of the investigational drug Empagliflozin and Linagliptin (Glyxambi), performed for Boehringer Ingelheim:

> Protocol 1275.1, "A Phase III Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Once Daily Oral Administration of BI 10773 25 mg/Linagliptin 5 mg and BI 10773 10 mg/Linagliptin 5 mg Fixed Dose Combination Tablets Compared with the Individual Components (BI 10773 25 mg, BI 10773 10 mg, and Linagliptin 5 mg) for 52 Weeks in Treatment Naïve and Metformin Treated Patients with Type 2 Diabetes Mellitus with Insufficient Glycemic Control"

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, Ms. Torres and Mr. Garmendia presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We acknowledge receipt of your October 23, 2014, and January 26, 2015, written responses to the Form FDA 483.

We have reviewed the FDA inspection report, the documents submitted with that report, and your October 23, 2014, and January 26, 2015, written responses to the Form

FDA 483. We do not find your responses 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.

This letter provides you with written notice of the matters under complaint and offers you an opportunity to explain the matter in writing or in an informal conference. This letter also initiates an administrative disqualification 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, including drugs, biologics, devices, new animal drugs, food, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.

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

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

   As a clinical investigator for Protocol 1275.1, you were required to obtain records (including records to confirm subjects' type-2 diabetes mellitus (T2DM) diagnosis and treatment status prior to informed consent) to ensure that enrolled subjects met study protocol-specified inclusion criteria. In the study protocol and in memos dated November 4, 2011, and January 10, 2012, the sponsor indicated that subjects should not be consented to participate in Protocol 1275.1 without written confirmation of T2DM diagnosis. This source documentation was needed before consenting either treatment-naïve or metformin-treated subjects. Acceptable forms of documentation to confirm T2DM diagnosis specified by the sponsor in the Protocol included:

   - Copies of medical records indicating T2DM diagnosis, or
   - A letter from the subject's physician stating date of T2DM diagnosis.

   Additionally, the Protocol required you to maintain source documents at your site, and to provide direct access to source data and documents for trial-related monitoring, audits, and regulatory inspections. As described in the Protocol, the source documents were needed to provide evidence of the existence of the subjects and to substantiate the integrity of the data collected.

FDA has concluded that you repeatedly or deliberately submitted false information to the sponsor in the form of falsified study records used to confirm T2DM diagnosis for study enrollment.

Specifically, the FDA investigation found that both on study records documenting T2DM diagnosis and on records identifying facilities where subjects were patients, signatures of primary care physicians were falsified and submitted to the sponsor for the following enrolled subjects:

a. For Subject 92462, study records (dated November 23, 2011) indicate that the subject's primary care physician confirmed T2DM diagnosis and metformin treatment. However, FDA has obtained evidence that the signature on the study record dated November 23, 2011, is not the signature of the identified physician, and that this subject was not a patient of the physician shown on that record. In addition, the location (H & L Medical Center Inc.) listed on the medical history records dated February 24, 2012, is not a location in which the identified physician has ever worked. Furthermore, the subject indicated that she did not bring a study record dated November 23, 2011, to your site.

b. For Subject 92451, study records (dated September 2, 2011) indicate that the subject's primary care physician confirmed T2DM diagnosis and metformin treatment. However, FDA has obtained evidence that the signature on the study record dated September 2, 2011, is not the signature of the identified physician, and that this subject was not a patient of the physician shown on that record. In addition, the study record dated September 2, 2011, is on letterhead that the identified physician has explained he does not use in his practice, and the location of the office indicated on the letterhead is one that he has not held since 2009.

c. For Subject 92452, study records (dated February 1, 2011) indicated that the subject's primary care physician confirmed T2DM diagnosis and metformin treatment. However, FDA has obtained evidence that the signature on the study record dated February 1, 2011, is not the signature of the identified physician, and that this subject was not a patient of the physician shown on that record. In addition, the study record dated February 1, 2011, is on letterhead that the identified physician does not use in his practice.

d. For Subject 92455, study records (dated January 3, 2011) indicated that the subject's primary care physician confirmed T2DM diagnosis and metformin treatment. However, FDA has obtained evidence that the signature on the study record dated January 3, 2011, is not the signature of the identified physician; and although Subject 92455 is a patient of physician CI, there is no corresponding information dated January 3, 2011, for Subject 92455 in the identified physician's records. In addition, the study record dated January 3, 2011, is on letterhead that the identified physician does not use in his practice.

e. For Subject 92468, study records (dated December 12, 2011) indicated that the subject's primary care physician confirmed T2DM diagnosis and metformin treatment. However, FDA has obtained evidence that the signature on the study record dated December 12, 2011, is not the signature of the identified physician, and that this subject was not a patient of the physician shown on that record. In addition, FDA has obtained evidence that the study record dated December 12, 2011, is on letterhead that the identified physician does not use in his practice.

Throughout the investigation, there have been inconsistencies in your communications with FDA regarding these source documents. In your October 23, 2014, written response to the Form FDA 483, you acknowledged that you did not have any prior medical history for the six subjects listed in the Form FDA 483. In a contradictory statement, you indicated that the study records in question were brought in by study subjects for medical history purposes. Additionally, you claimed that these records were not generated by your site; however, during the inspection, the Site Director indicated that your site provided the subjects with a medical note template to obtain written documentation from their primary care physicians to confirm T2DM diagnosis and treatment.

We acknowledge your implemented corrective actions, including site training and new standard operating procedures to prevent future violations. However, your response is inadequate because you failed to ensure that the records used to confirm diagnosis of T2DM and treatment were true and accurate. These source documents served as the basis for the data recorded in the Case Report Forms (CRFs) that were submitted to the sponsor, and ultimately to FDA in a New Drug Application. As a result of your failure to confirm the accuracy of subjects' records, false information was ultimately submitted to the sponsor in the CRFs.

2. 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 enroll subjects based on the inclusion criteria. Specifically, Protocol 1275.1 required:

- Diagnosis of type 2 diabetes mellitus prior to informed consent
- Male and female patients on diet and exercise regimen who are drug-naïve (defined as absence of any oral antidiabetic therapy, GLP-1 analog or insulin for 12 weeks prior to randomization) or pre-treated with metformin (>1500 mg/day or on the maximum tolerated dose or the maximum dose according to local label) unchanged for 12 weeks prior to randomization.

Additionally, the Protocol required you to exclude subjects treated with any antidiabetic drug other than metformin within 12 weeks prior to randomization. Furthermore, you were required to document a subject's diagnosis of T2DM, either by the subject's medical records or by a letter from the subject's primary care physician.

You failed to adhere to these requirements. FDA determined that subjects were enrolled and randomized in the study without the medical records necessary to document whether the subjects were diagnosed with T2DM and were drug-naïve, pre-treated with metformin, or treated with any antidiabetic drug within 12 weeks prior to randomization. The FDA investigation found that either no medical records were available or medical records were available post-enrollment for the following subjects:

a. For Subject 92455, based on the discrepancies in the primary care physician's letter noted in Item 1.d. above, historical medical records were needed to document the subject's eligibility prior to study enrollment. Subject 92455 was enrolled on November 14, 2011, and randomized to investigational drug on December 5, 2011. However, you failed to obtain medical records to confirm Subject 92455's eligibility prior to randomization with investigational drug.

b. For Subject 92462, based on the discrepancies in the primary care physician's letter noted in Item 1.a. above, historical medical records were needed to document the subject's eligibility prior to study enrollment. Subject 92462 was enrolled on November 30, 2011, and randomized to investigational drug on December 28, 2011. However, your site did not obtain medical records until February 24, 2012, approximately two months after Subject 92462 was randomized to investigational drug.

c. For Subject 92464, because no primary care physician's letter was obtained, historical medical records were needed to document the subject's eligibility prior to study enrollment. Subject 92464 was enrolled on December 2, 2011, and randomized to investigational drug on December 27, 2011. However, your site did not obtain medical records until January 23, 2012, twenty-seven days after Subject 93464 was randomized to investigational drug.

We recognize that the Form FDA 483 issued to you does not list this violation, so that your written response did not directly address this violation.

Your failure to collect past medical records to ensure that subjects met the eligibility criteria prior to study enrollment, jeopardized subject's safety and welfare, and raises concerns about the validity and integrity of data collected at your site.

When you signed the Statement of the Investigator, Form FDA 1572, you agreed to maintain adequate and accurate records and to 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(ies) are

informed about their obligations in meeting their commitments. Furthermore, your signature constitutes both your affirmation that you are qualified to conduct the clinical investigation and your written commitment to abide by FDA regulations in the conduct of the clinical investigations. The use of false information compromises the study integrity significantly, as well as the reliability and validity of the data.

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 violations listed above, FDA asserts that you have 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) working days of your receipt of this letter, respond in writing 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) working days of your receipt of this letter.

Your reply should be sent to:

Sean Y. Kassim, Ph.D.
Director, Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51,
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 violations listed above. 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.

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 if we cannot come to terms on a consent agreement, or if you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR 16 (copy enclosed) and 21 CFR 312.70 (copy enclosed). 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.
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
06/26/2015