



WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Francisco Hernandez, M.D.
777 E. 25th Street, Suite 118
Hialeah, FL 33013-3850

Ref: 09-HFD-45-04-02

Dear Dr. Hernandez:

Between February 19, 2008 and March 13, 2008, Ms. Dianiris Ayala, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of the following clinical investigations of the investigational drug insulin glulisine (Apidra), performed for Sanofi-Aventis U.S.:

- Protocol (b) (4) : One versus two versus three daily rapid-acting insulin injections of Apidra® (insulin glulisine) as add-on to Lantus® and oral sensitizer basal therapy in type 2 diabetes: a multi-center, randomized, parallel, open-label clinical study; and
- Protocol (b) (4) : Apidra® (insulin glulisine administered premeal versus postmeal in adult subjects with type 2 diabetes mellitus receiving Lantus® (insulin glargine) as basal insulin: a multi-center, randomized, parallel, open-label clinical study.

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects participating in those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, your April 16, 2008 written response to Form FDA 483, your June 14, 2008 written response, and your October 6, 2008 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 are aware that

at the conclusion of the inspection, Ms. Ayala presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You failed to ensure that the investigations were conducted according to the signed investigator statement and investigational plans [21 CFR 312.60].

Regarding Protocol (b) (4) [REDACTED] :

- a. Of fifteen subjects randomized in Protocol (b) (4) [REDACTED], twelve subjects were enrolled in violation of protocol inclusion and exclusion criteria. The details for these subjects are described below.
 - i. The protocol excluded subjects that had received insulin within the prior year. The following subjects reportedly received insulin at their first visit to the clinical site, but were enrolled in the study in violation of protocol exclusion criteria:
 - (1) Subject # 3511-001 was consented and screened on August 7, 2006, even though he received 6 units of Humalog® subcutaneously on June 5, 2006.
 - (2) Subject # 3511-005 received 5 units of Novolog® subcutaneously on August 14, 2006, the same day she was consented and screened in the study.
 - (3) Subject # 3511-011 received Novolog® subcutaneously on October 17, 2006, the same day she was consented and screened in the study.
 - (4) Subject # 3511-012 received 5 units of Humalog® subcutaneously on October 18, 2006, the same day he was consented and screened in the study.
 - (5) Subject # 3511-013 received 5 units of insulin subcutaneously on November 2, 2006, the same day he was consented and screened in the study.
 - (6) Subject # 3511-015 received 8 units of Novolog® subcutaneously on November 22, 2006, the same day he was consented and screened in the study.
 - (7) Subject # 3511-016 was consented and screened on December 15, 2006, even though he received 7 units of Humalog® subcutaneously on November 15, 2006.
 - (8) Subject # 3511-019 received 4 units of insulin on January 22, 2007, the same day he was consented and screened in the study.

In your April 16, 2008 response letter, you noted that standard office procedures dictated that subjects receive an isolated dose of insulin when they presented with a defined level of hyperglycemia. Additionally, you stated that subjects were regular clinic patients who enrolled in research as subjects, and that this was an attempt to avoid the enrollment of "professional patients". Your responses are acknowledged. Nonetheless, the administration of insulin within the year prior to enrollment remains a violation of protocol exclusion criteria, and had the potential to influence study results. In your response letter, you proposed corrective measures to avoid future violations pertaining

to inclusion and exclusion criteria. Specifically, you outlined plans to present inclusion and exclusion criteria, thoroughly review past medical histories, and discuss borderline candidates in detail with your staff and the sponsor prior to enrollment decision-making. Additionally, you proposed measures to provide a clear separation of study procedures and clinical practice visits. These corrective measures are acceptable if implemented as proposed.

- ii. The protocol required subjects to be on a stable dose of two or three of the following oral agents for at least three months before the screening visit: Sulfonylureas, Biguanides, or Thiazolidinediones. The following subjects were enrolled in the study in violation of this criterion:

- (1) Subject # 3511-007 was not on a stable dose of the protocol-required classes of oral agents, but was reportedly using Glyset® (miglitol), an oral agent that was not approved for the study, up to the time of consent and screening.

In your April 16, 2008 response letter, you noted that Glyset® (miglitol) was not listed as an exclusionary medication in the protocol. While this is true, it is irrelevant to the protocol violation noted above, namely that the subject was not on a stable dose of two or three of the following classes of oral agents: sulfonylureas, biguanides, and thiazolidinediones. Glyset® is an alpha glucosidase inhibitor, and is not a sulfonylurea, biguanide, or thiazolidinedione. As noted in 1. a. i. above, your plan for corrective measures regarding violations pertaining to inclusion and exclusion criteria is acceptable if implemented as proposed.

- (2) Subject #3511-012 was similarly not on a stable dose of the protocol-required classes of oral agents, but was reportedly using Glyset® (miglitol), an oral agent that was not approved for the study, up to the time of consent and screening.

As noted in 1. a. ii. (1) above, your statement that Glyset® was not listed as an exclusionary medication is irrelevant to the protocol violation of the subject not having been on a stable dose of two or three of the protocol-required classes of oral agents (sulfonylureas, biguanides, and thiazolidinediones). Again, your plan for corrective measures to avoid future violations pertaining to inclusion and exclusion criteria is acknowledged.

- b. Illnesses detected during the study, concomitant illnesses that worsened during the study, and concomitant medications were not reported as required by the protocol. Specifically:

- i. Subject # 3511-008 was hospitalized in December 2006 due to complications of a viral infection (pneumonia), but this serious adverse event was not reported to the sponsor until July 13, 2007. Per the protocol, an adverse event that required in-subject hospitalization or prolongation of existing

hospitalization was considered a serious adverse event (SAE). As such, the protocol required this SAE to be recorded on the "Serious Adverse Event/Expedited Report from a Clinical Trial" form, and faxed to the sponsor's Pharmacovigilance department within 24 hours, with a copy faxed to the study monitor. The "Serious Adverse Event/Expedited Report from a Clinical Trial" form documents that the subject's adverse event of pneumonia started on (b) (6), and ended on (b) (6). However, the form is dated July 13, 2007, approximately six and a half months following the onset of the adverse event.

In your April 16, 2008 response letter, you noted that elucidating details pertaining to hospital visits and associated diagnoses were erratic, and obtaining verification took longer than expected. You also stated that it was not clear to your clinical research coordinator that there was a need to report these events immediately upon discovery even if only a general statement could be made. However, as clinical investigator, it was your responsibility to ensure the investigation was conducted according to the approved protocol. This SAE was not reported as required by the protocol. In your response letter, you proposed a corrective measure to avoid future occurrences of this nature, namely to use available information to immediately report any adverse event, regardless of significance or relation to the study drug, with updates to follow. This corrective measure is acceptable if implemented as proposed.

- ii. Subject # 3511-019's case report form (CRF) lacks information on the reported use of Cymbalta® and the clinical condition corresponding to the use of this medication. Per the protocol, all treatments taken by subjects on entry to the study, or at any time during the study, in addition to the investigational product, are regarded as concomitant treatments and must be documented on the appropriate pages of the CRF.

In your April 16, 2008 response letter, you indicated that some chronic medications were discovered late in the course of the study (including psychiatric medications, i.e., antidepressants), and that they had been in use for non-psychiatric reasons such as neuropathic pain. Your response is acknowledged. However, Subject #3511-019's use of Cymbalta® was not documented on the CRF as required by the protocol, regardless of when its use was discovered and its specific indication in this case. You have proposed a plan to clarify your staff members' handling of records, as well as a policy to make revisions and ensure that materials are returned properly to subjects' charts at the conclusion of monitoring visits. Additionally, you proposed measures to record times of any revisions and submissions to queries. Your corrective measures are acknowledged and acceptable.

Regarding Protocol (b) (4):

- c. Of seven subjects randomized in Protocol (b) (4), three subjects were enrolled in violation of protocol inclusion and exclusion criteria. The details for these subjects are described below.

- i. The protocol excluded subjects who were treated with sulfonylureas, thiazolidinediones, or any other oral antidiabetic drugs, except for insulin analogues with or without metformin, within the three months before study entry. The following subjects reportedly were treated with exclusionary oral antidiabetic agents and were screened and enrolled in the study, in violation of this exclusion criterion:

- (1) Subject # 3503-0005 was treated with Avandia® (rosiglitazone maleate, a thiazolidinedione) until April 10, 2006, and was later consented and screened for the study on June 5, 2006.
- (2) Subject # 3503-0007 was treated with Avandamet® (rosiglitazone maleate, a thiazolidinedione, and metformin hydrochloride) until May 22, 2006, and was later consented and screened on June 8, 2006.
- (3) Subject # 3503-0009 was treated with Avandia (rosiglitazone maleate, a thiazolidinedione) until June 12, 2006, the same day he was consented and screened.

In your April 16, 2008 response letter, you indicated that based on your review, subjects were probably off treatment with these exclusionary medications for over three months, but that the dates were not clearly documented. Your response is acknowledged. However, the dates of use noted above were documented in study records, and indicate that these three subjects' use of the exclusionary medications was within three months prior to study entry, in violation of the protocol. As noted above, you proposed corrective measures to avoid future violations pertaining to inclusion and exclusion criteria in your response letter. Namely, you outlined plans to present inclusion and exclusion criteria, thoroughly review past medical histories, and discuss borderline candidates in detail with your staff and the sponsor prior to enrollment decision-making. These corrective measures are acceptable if implemented as proposed.

- d. Illnesses detected during the study, concomitant illnesses that worsened during the study, and concomitant medications were not reported as required by the protocol. Specifically:
 - i. Subject # 3503-0010's SAE of heart failure related to a pacemaker site infection was not reported to the sponsor in the 24-hour timeframe required by the protocol. Per the protocol, the "Serious Adverse Event/Expedited Report from a Clinical Trial" form was to be completed and faxed to the sponsor's Pharmacovigilance department within 24 hours, with a copy faxed to the study monitor. The form completed at the clinical site documents that the adverse event was life-threatening, and therefore, met the protocol-specified definition of an SAE. The start date of the adverse event is documented as (b) (6); however, the form is dated July 2, 2007, approximately two months after the onset of the adverse event.

In your April 16, 2008 response letter, you noted that hospital records and details sometimes took months to obtain despite efforts to secure them promptly. Your response is acknowledged. Nonetheless, general reporting of this SAE was not carried out within the protocol-specified 24-hour timeframe, regardless of whether hospital records and details were available. In your response letter, you proposed a corrective measure to avoid any such future occurrences. Specifically, you outlined a plan to use available information to immediately report any adverse event, regardless of significance or relation to the study drug, with updates to follow. This corrective measure is acceptable if implemented as proposed.

2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual [21 CFR 312.62(b)].

- a. There are discrepancies in the dates the source records were reviewed and signed and the dates when the study activities actually occurred. For example:

Regarding Protocol (b) (4) [REDACTED] :

- i. Subject # 3511-018 came to the clinical site on April 23, 2007 for visit # 6; however the source document was signed by the study coordinator on April 11, 2007.

In your April 16, 2008 response letter, you noted that it appeared that the clinical research coordinator occasionally dated and signed forms at the time study activities occurred, but printed forms on other dates, and that no initialing was done to explain any discrepancies. You acknowledged that proper record keeping should have been carried out. Your response is acknowledged. However, it does not explain how Subject #3511-018's visit #6 occurred after the source document for that visit was signed. As clinical investigator, it is your responsibility to ensure that adequate and accurate records are maintained. As stated earlier, you proposed a plan to clarify your staff members' handling of records, as well as a policy to make revisions and ensure that materials are returned properly to subjects' charts at the conclusion of monitoring visits. Additionally, you proposed measures to record times of any revisions and submissions to queries. Your corrective measures are acknowledged and acceptable.

- ii. Subject # 3511-002's visit # 1 physical exam source documents dated August 8, 2006 were amended six months later, on February 8, 2007, to add information regarding the presence of a systolic ejection murmur. The murmur was noted on the November 21, 2006 physical exam source documents for visit # 5. A memo-to-file dated October 11, 2007 notes that the principal investigator inadvertently forgot to add the abnormal heart condition to the subject's visit # 1 physical exam source documents, and that the records were changed during visit # 5 when the error was realized. However, given that the amendment to the

visit #1 physical exam source document is dated February 8, 2007, the amendment does not comport with the October, 11, 2007 memo stating that the change was made on November 21, 2006.

In your April 16, 2008 response letter, you acknowledged this observation, stating that the murmur was observed during the original physical examination, but that the exam records failed to document it, and a later explanation was documented in such a way that it was difficult to assess the specific time of findings. Your response is acknowledged, and your responsibility to maintain adequate and accurate records is reiterated. As stated in 2. a. i. above, your plan for corrective actions to prevent future record keeping discrepancies is acceptable if implemented as proposed.

Regarding Protocol (b) (4) [REDACTED] :

- iii. Subject # 3503-0001's visit # 1 physical exam was conducted on April 26, 2006. The physical exam source document was amended on May 10, 2006 to include information that the thyroid was palpable. However, no source documentation was included to explain the reason for the change after the actual evaluation was conducted. We note that you did not specifically address this observation in your response letters.
- iv. Subject # 3503-0001's adverse event of a thyroid cyst was documented in a patient note dated September 21, 2006. However, the CRF records the start date of this adverse event as August 22, 2007.

In your April 16, 2008 response letter, you indicated that subjects were followed for conditions that were in the process of being worked up, such as thyroid conditions, and that diagnoses were sometimes made during the course of the study for pre-existing conditions. You noted that these conditions should have been reported at the time your site was aware of them, but that hospital records and details sometimes took months to obtain despite efforts to secure them promptly. Your response is acknowledged. However, it does not explain the discrepancy in the documentation noted above. Specifically, it does not adequately explain how the thyroid cyst was documented in a patient note on September 21, 2006, but that the CRF recorded the start date as August 22, 2007, almost one year later.

- b. The electronic diary information for Subject #3511-007 was not retrieved in a timely manner, such that the information was not available for review during the FDA inspection. A Note to File, dated March 1, 2007, indicates that missing data from November 1, 2006 to December 4, 2006 was not available due to the failure of the study coordinator to print the diary readings from the website, which was later rendered inaccessible. Nonetheless, as clinical investigator, you are required to maintain adequate and accurate study records. We note that you did not specifically address this observation in your response letters.

3. You failed to report promptly to the Institutional Review Board (IRB) all unanticipated problems involving risk to human subjects or others. [21 CFR 312.66].

The IRB required serious adverse events to be reported within three business days of your site becoming aware of the event. Your site failed to report the following SAEs to the IRB within the requisite three-day period:

Regarding Protocol (b) (4) [REDACTED] :

- a. Subject # 3511-018 was hospitalized in December 2006 due to a viral infection (pneumonia). This SAE was not reported to the IRB.

Regarding Protocol (b) (4) [REDACTED] :

- b. Subject # 3503-0010 was hospitalized for implantation of a pacemaker on (b) [REDACTED] and suffered a subsequent infection of the implant pocket on (b) (6) [REDACTED]. These SAEs were not reported to the IRB until July 31, 2007, approximately three months after the start of the first reportable serious adverse event.

In your April 16, 2008 response letter, you indicated that your site had difficulty in obtaining details pertaining to hospital visits and associated documentation despite conscious efforts to obtain them, and that this process often took longer than expected. While we acknowledge this, it remains your responsibility as clinical investigator to report SAEs to the IRB in a timely manner. Your proposed corrective actions to prevent future violations through the clarification of site personnel's record handling are acknowledged. You indicated that these measures include a policy to make revisions and ensure that materials are returned properly to subjects' charts at the conclusion of monitoring visits. Additionally, you proposed measures to record times of any revisions and submissions to queries such that third parties, such as the IRB, receive data in a timely manner. Your corrective measures are acceptable.

We acknowledge your April 16, June 14, and October 6, 2008 responses, and your explanations of the events that may have led to the violations noted herein. Specifically, we acknowledge your statement that your clinical research coordinator had personal problems, and that there were also problems with an interim clinical research coordinator. Additionally, we note your response that your site had six different monitors in a period of eight months. We also acknowledge corrective actions you have undertaken or are in the process of undertaking. Specifically, we acknowledge that among these actions, you halted new trials to address violations once you became aware, removed a clinical research coordinator from working with protocols, assigned new personnel to complete pending tasks, and made a sub-investigator aware of supervising flaws found in the course of study conduct. Additionally, we also note that you have instituted plans for the separation of study procedures and clinical practice visits as well as the implementation of formal training of study personnel. These corrective measures, in addition to those addressed specifically above, are acceptable.

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 on-going 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 or will be taking to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Lewin, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

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Sincerely yours,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
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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/

LESLIE K BALL
04/20/2009