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Inspections, Compliance, Enforcement, and Criminal Investigations

Dimitri Sirakoff 9/12/13



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

CERTIFIED MAIL RETURN RECEIPT REQUESTED

Dimitri Sirakoff, D.O.
1206 E. 17th Street, Suite 204
Santa Ana, CA 92701

Ref: 13-HFD-45-08-03

Dear Dr. Sirakoff:

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 January 9 and February 6, 2013. Ms. Yvette M. LaCour-Davis, representing the FDA, reviewed your conduct of the following clinical investigations:

- Protocol 1VIT09031, titled "A Multicenter, Randomized, Active Controlled Study to Investigate the Efficacy and Safety of Intravenous Ferric Carboxymaltose (FCM) in Patients with Iron Deficiency Anemia (IDA)," of the investigational drug ferric carboxymaltose, performed for Luitpold Pharmaceuticals, Inc.
- Protocol **(b)(4)**, titled "**(b)(4)**," of the investigational drug **(b)(4)**, performed for **(b)(4)**.

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. LaCour-Davis presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your April 10, 2013, written response to the Form FDA 483.

From our review of the FDA establishment inspection report, the documents submitted with that report, and your April 10, 2013, written response, 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:

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 plans for Protocols 1VIT09031 and **(b)(4)** required you to ensure that subjects met all inclusion and exclusion criteria prior to randomization. In addition, Protocol 1VIT09031 required you to ensure that subjects who were randomized to Cohort 2, Group D, received intravenous (IV) iron standard of care. You failed to adhere to these protocol requirements. Specifically:

1. For Protocols 1VIT09031 and **(b)(4)**, you failed to ensure that study subjects met the protocol inclusion and exclusion criteria prior to subject randomization.

a. Protocol **(b)(4)**, Inclusion Criterion # 3, specifies that subjects "must have a diagnosis of OA [osteoarthritis] of the hip based on American College of Rheumatology criteria (Appendix 1 with x-ray confirmation (a Kellgren-Lawrence x-ray grade of ≥ 2)" taken within the last 12 months. Appendix 1 of the protocol notes that the "protocol-defined requirement for diagnosis of OA of the Hip [*sic*] will be the presence of hip pain, presence of osteophytes on x-ray and either an ESR [erythrocyte sedimentation rate] < 20 mm/hour OR joint space narrowing on x-ray." Appendix 1 further notes that the presence of osteophytes on X ray is a protocol requirement, defined by a Kellgren-Lawrence X-ray grade of ≥ 2 .

i. Subject 1107-1057 was enrolled into Protocol **(b)(4)** even though the subject did not meet Inclusion Criterion # 3. The October 7, 2009, radiology report for this subject's right hip X rays, taken September 29, 2009, states the radiologist's impressions: "Mild superior loss of joint space. No evidence of osteophyte formation." Based on this radiology report, Subject 1107-1057 was not eligible for enrollment into Protocol **(b)(4)**. Nevertheless, this subject was randomized into this protocol on October 26, 2009.

On July 22, 2010, approximately nine months after Subject 1107-1057's randomization, you added a late entry note both on this subject's radiology report and on the Screening Visit study record, indicating that joint narrowing and osteophytes had been observed prior to randomization, thus making the subject appear to have been eligible for the study. However, you failed to provide explanatory documentation to support your late entries' conclusion that Subject 1107-1057 was eligible prior to randomization.

ii. Subject 1107-1062 was enrolled into Protocol **(b)(4)** even though the subject did not meet Inclusion Criterion # 3. The September 22, 2009, radiology report for this subject's right hip x-rays, which were taken on September 18, 2009, states the radiologist's impressions: "Evidence of mild axial joint space loss at the hip. No osteophyte formation." Based on this radiology report, Subject 1107-1062 was not eligible for enrollment into Protocol **(b)(4)**. Nevertheless, this subject was randomized into this protocol on October 30, 2009.

On July 22, 2010, approximately nine months after Subject 1107-1062's randomization, you added a late entry note on this subject's Screening Visit study record, indicating that joint space narrowing and osteophytes had been noted prior to randomization, thus making the subject appear to have been eligible for the study. However, you failed to provide explanatory documentation to support your late entry's conclusion that Subject 1107-1062 was eligible prior to the randomization.

iii. Subject 1107-1060 was enrolled into Protocol **(b)(4)** even though the subject did not meet Inclusion Criterion # 3. The October 7, 2009, radiology report for this subject's

left hip X rays, which were taken on October 1, 2009, states the radiologist's impressions: "Minimal superior femoral joint space loss. No evidence of osteophyte formation." Based on this radiology report, Subject 1107-1060 was not eligible for enrollment into Protocol **(b)(4)**. Nevertheless, this subject was randomized into this protocol on October 29, 2009.

iv. Subject 1107-1045 was enrolled into Protocol **(b)(4)** even though the subject did not meet Inclusion Criterion # 3. The September 10, 2009, radiology report for this subject's left hip X rays, which were taken on September 4, 2009, states the radiologist's impressions: "Minimal medial joint space loss. No hip osteophytes." Based on this radiology report, Subject 1107-1045 was not eligible for enrollment into Protocol **(b)(4)**. Nevertheless, this subject was randomized into this protocol on October 1, 2009.

On July 22, 2010, approximately nine months after Subject 1107-1045's randomization, you added a late entry note on this subject's Screening Visit source record and radiology report. These late entries indicated that you re-examined Subject 1107-1045's X ray prior to randomization and noted joint narrowing and osteophytes, thus making the subject appear to have been eligible for the study. However, you failed to provide explanatory documentation to support your late entries' conclusion that Subject 1107- 1045 was eligible prior to the randomization.

In your April 10, 2013, written response to the violations noted in Item 1.a. above, you indicated that for all four subjects listed above, you initially evaluated the X rays prior to referring them to the radiologist for review, and that joint space narrowing was present in all subjects. You also indicated that you understood a Kellgren-Lawrence Grade of 2 to be either observation of a definite osteophyte or possible narrowing of joint space that was less than 50% loss of joint space width. However, we note that the Kellgren-Lawrence Grading Scale Grade 2 classification required both definite osteophytes and definite narrowing of joint space. We further note that the protocol-defined criteria for the diagnosis of OA of the hip required the presence of osteophytes on X ray, in addition to the presence of hip pain and either an erythrocyte sedimentation rate < 20 mm/hour or joint space narrowing on X ray.

In your written response, you further noted that in your "24 years of clinical practice and reading radiographs" you have "never received radiology results with the Kellgren-Lawrence radiological assessment grades." We emphasize that the use of the Kellgren-Lawrence grading system was a protocol requirement for determination of subject eligibility, and that you failed to follow this requirement.

Your response is inadequate because you have not provided explanatory documentation to support your late entries' conclusions that these four subjects (1107-1045, 1107-1057, 1107-1060, and 1107-1062) were eligible for the study prior to randomization. Your response is also inadequate because you have not submitted a corrective action plan that, if properly carried out, would prevent the recurrence of this type of violation in the future.

b. Protocol **(b)(4)**, Inclusion Criterion # 6, required that subjects have a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale Numeric Rating Scale (NRS) score ≥ 5 in the index hip at the Baseline Visit. In addition, Protocol **(b)(4)**, Section 9.2., Efficacy Analysis, specifies that change from Baseline to Week 16 in the WOMAC pain subscale is one of three co-primary endpoints of the protocol.

i. Subject 1107-1045 was randomized on October 1, 2009, one day prior to evaluation of eligibility criteria pertinent to the Baseline Visit (Day 1) on October 2, 2009. As a result, Subject 1107-1045 was enrolled into Protocol **(b)(4)** when the subject did not meet Inclusion Criterion # 6. At the Baseline Visit (Day 1) on October 2, 2009, Subject 1107-1045's WOMAC pain score was 4.0. This subject was randomized even though the

subject was not eligible for the study.

In your April 10, 2013, written response to the violation noted in Item 1.b.i. above, you attributed the violation to your study coordinator's miscalculation of the WOMAC pain subscale you also acknowledged that you overlooked this error. In addition, you indicated that your study coordinator and other study staff members were retrained on both the WOMAC pain subscale and the study protocol.

Your response is inadequate because, although you stated that the study coordinator and your team were retrained on the WOMAC, you have submitted no documentation of that training. As a result, we are unable to evaluate whether the training was adequate to prevent occurrence of this and similar violations in the future.

ii. Subject 1107-1053 was enrolled into Protocol **(b)(4)** even though the subject did not meet Inclusion Criterion # 6. At the Baseline Visit (Day 1) on October 1, 2009, Subject 1107-1053's WOMAC pain score was 2.2. Inclusion Criterion # 6 requires a WOMAC pain score ≥ 5 . You randomized this subject on October 1, 2009, despite the fact that the subject was not eligible for the study.

We acknowledge that this violation, as written, was not included on the Form FDA 483 that you received.

c. Protocol **(b)(4)**, Inclusion Criterion # 9, required the Patient Global Assessment of Osteoarthritis for each subject to be "fair," "poor," or "very poor" at Baseline. In addition, Section 9.2. (Efficacy Analysis) of the protocol indicates that a change from Baseline to Week 16 in the Patient Global Assessment of Osteoarthritis is one of the three co-primary efficacy endpoints of the study.

Subject 1107-1053 was enrolled into Protocol **(b)(4)** even though the subject did not meet Inclusion Criterion # 9. At the Baseline Visit (Day 1) on October 1, 2009, Subject 1107-1053 checked the Patient Global Assessment of Osteoarthritis as "Good," thereby making the subject ineligible for the study. This subject was randomized on October 1, 2009, despite the fact that the subject was not eligible for the study.

In your April 10, 2013, written response to the violation noted in Item 1.c. above, you appear to have acknowledged that Subject 1107-1053 did not meet Inclusion Criterion # 9. (We note that in your response to this violation, you incorrectly noted the subject number as 1107-1055, but you associated that number with the same subject initials as those for Subject 1107-1053.)

Your written response to this violation is inadequate because, although you noted that you and your study coordinator were retrained on the WOMAC, you failed to address the violation of enrolling a subject who did not meet the eligibility requirement of a "fair," "poor," or "very poor" score on the Patient Global Assessment of Osteoarthritis scale at Baseline.

d. Protocol 1VIT09031, Inclusion Criterion # 3, required that subjects have "Screen 1 ferritin ≤ 100 ng/ml or ≤ 300 when TSAT [transferrin saturation] is $\leq 30\%$."

Subject 21903 was randomized into Protocol 1VIT09031 on July 31, 2010, even though the subject failed to meet Inclusion Criterion # 3. Subject 21903's blood sample was collected during the screening visit on July 16, 2010. The laboratory report dated July 18, 2010, indicates that this subject had a screening TSAT of 33% and a screening ferritin value of 881.4 ng/ml, which is significantly higher than the protocol-allowed maximum value of 100 ng/ml. Therefore, Subject 21903 was not eligible for Protocol 1VIT09031.

In your April 10, 2013, written response to the violation noted in Item 1.d. above, you indicated that no deviation occurred with reference to randomizing this subject because the subject was

randomized per protocol prior to receiving central lab results; and that, when you received the central lab results, you felt that the subject was stable enough to continue with the study. You further noted that you monitored the subject closely and felt that your clinical judgment was correct. Further, you indicated that the sponsor reviewed this subject's records and allowed the subject to enroll and to continue in the study.

Your response is inadequate in that Protocol 1VIT09031 does not allow enrollment of subjects based solely on the clinical investigator's judgment when the subject does not meet required inclusion criteria, including Inclusion Criterion #3. In addition, you did not provide us with documentation of sponsor and IRB approval to enroll this subject prior to your doing so.

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 concern about the validity and integrity of the data collected at your site. Particularly concerning to us is the fact that five of the thirteen subjects enrolled into Protocol **(b)(4)** at your site were ineligible for enrollment into the protocol.

2. For Protocol 1VIT09031, you failed to adhere to the requirement that subjects randomized to Cohort 2, Group D, receive "IV standard of care (other IV iron) as determined by the study site physician" and that all study medication and IV iron standard of care (including iron sucrose injection USP and iron dextran injection USP) be provided by the sponsor.

Study records show that Subject 21639 was assigned to Cohort 2, Group D, and therefore should have received IV iron standard of care, but instead received study drug, FCM, on Day 0 (June 8, 2010) and Day 7 (June 15, 2010).

In your April 10, 2013, written response to the violation noted in Item 2 above, you indicated that administering study drug, FCM, to subjects in Cohort 2, Group D, was not a protocol deviation because treatment assignment was at the discretion of the clinical investigator. In addition, you stated, "Therefore, per my clinical judgment, I chose to randomize the patient on the study medications Group D, medication FCM (Ferris [sic] Carboxymaltose)." Further, you noted correctly that subjects in Group D may receive additional IV iron at the discretion of the investigator.

Your response is inadequate because for subjects in Cohort 2, Group D, the protocol allows you to assign subjects only to an "IV standard of care (other IV iron)." Although the protocol does allow you to provide additional IV iron to subjects in Group D, the protocol does not allow you to give the investigational drug, FCM, to a subject assigned to Group D.

Failure to follow the protocol-specified treatment assignment and regimen has the potential to affect data integrity negatively.

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

Constance Cullity, M.D., M.P.H.

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Sincerely yours,

{See appended electronic signature page}

Thomas N. Moreno, M.S.
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/s/

THOMAS N MORENO
09/12/2013

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