Excel Diagnostic Imaging Clinics

May 17, 2015

Reynaldo R. Rodriguez, Director
Food and Drug Administration
Dallas District Office
4040 North Central Expressway, Suite 300
Dallas, TX 75204

Re: Response to Inspectional Observations
IND 78256

Dear Director Rodriguez:

Between April 16 and May 4, 2015, FDA Investigator Zerita White performed an inspection of records relating to an expanded access clinical trial titled, "177 Lutetium DOTA-Octreotate Therapy in Somatostatin Receptor-Expressing Neuroendocrine Neoplasms." The study is being conducted under Investigational New Drug (IND) exemption 78256 at the Excel Diagnostics research facility at 9701 Richmond Avenue, Houston, Texas. Upon completion of the inspection, Ms. White issued a Form FDA 483, with three observations. As the sponsor and principal investigator for the study, I am writing to respond to each observation. As I hope this response demonstrates, my colleagues and I understand the importance of complying with applicable regulatory requirements and good clinical practice generally, which safeguard patients and data integrity. For that reason, we are committed to taking appropriate action to enhance those aspects of compliance raised by the inspectional observations.

Partial Clinical Hold

The first observation (noted on Page 1 of the 483, but not numbered) describes six study subjects who were enrolled in the study and treated after the study had been placed on partial clinical hold. The identified subjects were enrolled between March 18 and April 7, 2015, after a March 17, 2015 teleconference that my colleague, Dr. Hamidi, and I had with the Division of Oncology Products 2 (the Division) within the Office of Hematology and Oncology Products at the Center for Drug Evaluation and Research (CDER). The teleconference took place in response to my request for permission to increase the trial enrollment ceiling from 150 to 250 subjects. That request was denied during the call, and we were told that the Division would send a letter confirming the discussion within 30 days.

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After the call, Dr. Hamidi and I both thought that, although we had not obtained the permission we had sought to enroll the additional 100 subjects, we were allowed to continue enrolling patients up to the existing limit of 150 subjects. This was consistent with the expressed purpose of the teleconference, which was to discuss our request to increase the enrollment maximum.[1] With that understanding, because we had not yet reached 150 subjects, we continued enrolling patients. It was only when the promised written confirmation was received via email on April 14, 2015 that we realized we had been mistaken, and it had been FDA's intention for us to stop enrolling patients as of March 17, the day of the teleconference. We immediately stopped enrolling patients (with the most recent six, we had enrolled a total of 144 subjects), and notified the Division of our error. With the agency's express permission, we completed treatment of the last six enrollees.[2]

We regret the misunderstanding. Obviously, we will not resume enrolling any patients into this study unless and until the partial clinical hold is lifted.

Observation 1: Failure to ensure that FDA is promptly informed of significant new adverse effects or risks.

This involves the timeliness of our reporting to FDA three adverse events – two deaths (Subject GF LU 22; Subject KF LU 101), and one cardiac arrest/pulmonary embolism after a long flight) (Subject RB LU 51). In each case, we submitted an IND Safety Report within 15 days of our being informed of the event, which is the deadline imposed by 21 CFR 312.32(c)(1) for reporting a "serious and unexpected suspected adverse reaction." Ms. White's inspectional observation is with regard to the requirement under 21 CFR 312.32(c)(2) for submitting "unexpected fatal or life-threatening suspected adverse reaction reports" within seven days of first receiving the information.

We recognize the importance of providing FDA with timely notice of adverse event information, both as a matter of public safety and regulatory compliance, and particularly in the context of an expanded access trial. Although each of the three adverse events cited by Ms. White was fatal or life-threatening, we did not consider the 7-day deadline applicable, because it is for an "unexpected fatal or life-threatening ***suspected adverse reaction***", and none of the events was a "suspected adverse

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[1] Attached is a March 12, 2015 email from Meredith Libeg, the Regulatory Project Manager within the Division, which states, "Our clinical team would like to have a brief call with you to discuss your protocol amendment submission." The protocol amendment to which she refers is our February 19, 2015 request to increase enrollment.

[2] Attached is an April 29, 2015 email from Ms. Libeg stating that we were permitted to "continue the planned treatment course" for these patients.

reaction," as FDA regulations define that term. Under 21 CFR 312.32(a), a "suspected adverse reaction" is:

> any adverse event for which there is a reasonable possibility that the drug caused the caused event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

There was nothing to suggest that any of the three adverse events was caused by the investigational drug. [In fact, given the patient population in this study *whom are terminal cancer patients*, there was every reason to believe that the events were related to the subject's underlying condition.] That is why we did not think the 7-day deadline of 21 CFR 312.32(c)(2) applied. Actually, it was not clear that the 15-day reporting required by 21 CFR 312.32(c)(1)(i) – which also applies to suspected adverse reactions, not all adverse events – applied, but we erred on the side of caution and reported the events.

Continuing our conservative approach, going forward we will report within seven days ***all*** fatal or life-threatening adverse events – even those where there is no evidence to suggest a causal relationship between the study drug and the adverse event. To that end, we have retrained our research staff of the specific reporting requirements under 21 CFR 312.32, and will provide training on this topic for each new employee. We also have adopted a form for internal reporting that requires study personnel to classify the adverse reaction and to note whether a 7-day or 15-day report is required.

Observation 2: Failure to conduct an investigation in accordance with the signed statement of the investigator.

This involves two events: The pretreatment labs for Subject NR LU 03 were drawn six days past the two weeks before therapy required by the protocol, and the IV infusion for Subject JD LU 01 lasted 18 minutes longer than the 30 minutes (due to the patient's sickness during the infusion) provided for in the protocol. Our research team understands the importance of adherence to the protocol in conducting a clinical trial, both as a matter of patient safety and for purposes of data integrity. We regret these inadvertent lapses, and to prevent their recurrence, we have retrained our staff on the need to strictly follow the protocol, and revised our case report forms to note the protocol-required timeframes.[3]

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[3] Without meaning to minimize the importance of adherence to protocol, we would note that these two deviations from protocol occurred in the course of treating 144 patients and giving more than 420 infusions of drug.

I hope this response adequately addresses the inspectional observations and conveys to you the importance we place on compliance with the applicable regulatory requirements and good clinical practice more generally. Please contact me at 713-781-6200 if you need additional information or have any questions.

Sincerely,

Ebrahim S. Delpassand, M.D.

Attachments

cc: Dr. Patricia Keegan, Director, Division of Oncology Products 2