



[Home](#) > [Inspections, Compliance, Enforcement, and Criminal Investigations](#) > [Enforcement Actions](#) > [Warning Letters](#)

Inspections, Compliance, Enforcement, and Criminal Investigations

Zaiac, Martin N. 3/21/11



Department of Health and Human Services

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

WARNING LETTER

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

11-HFD-45-03-01

Dr. Martin Zaiac
Greater Miami Skin and Laser Center
4308 Alton Road, Suite 750
Miami Beach, FL 33140

Dear Dr. Zaiac:

Between April 22 and July 14, 2010, Ms. Dianiris Ayala, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol **(b)(4)**, Version 4.0, dated August 13, 2009, entitled "**(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 research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, 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 acknowledge receipt of your August 5, 2010, response to Form FDA-483, but note that this response was received past the 15 working days from close of the inspection. Thus, while we have reviewed the response, we have not included a discussion of the response in this letter, as per the Commissioner's Enforcement Initiative announced on August 11, 2009. We wish to emphasize the following:

1. You failed to personally conduct or supervise the clinical investigation [21 CFR 312.60].

When you signed the Statement of Investigator (Form FDA 1572) for the above-referenced clinical trial, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities as a clinical investigator include ensuring that the clinical trial is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the

rights, safety, and welfare of subjects under your care; and ensuring control of drugs under investigation [21 CFR 312.60]. By signing Form FDA 1572, you specifically agreed to personally conduct the clinical trial or to supervise those aspects of the trial that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as a clinical investigator you may not delegate your general responsibilities. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trial was conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and that these trials were conducted in a manner that protects the rights, safety, and welfare of human subjects.

We note that your failure to adequately supervise this study led to significant problems with the conduct of the study as mentioned below, which included enrollment of subjects who did not meet eligibility criteria, and failure to follow safety monitoring procedures with respect to abnormal laboratory values and QTcF intervals, among other violations.

2. You failed to conduct the studies or ensure they were conducted according to the investigational plan, and failed to protect the rights, safety, and welfare of subjects under the investigator's care [21 CFR 312.60].

Section 7.5.3 of the protocol states:

The following monitoring procedures should be followed for any subject who develops a QTc prolongation (Fridericia's correction will be used):

- If an ECG from an enrolled subject records a QTcF exceeding 450 ms, an ECG should be repeated within 30 to 60 minutes. If the repeat ECG also records a QTcF greater than 450 ms, concomitant medication should be verified and a cardiologist should be consulted to confirm the read out and consider to determine [sic] subsequent monitoring activities.
- If an ECG from an enrolled subject records a QTcF exceeding 480 ms, or if an increase in QTcF versus baseline exceeding 60 ms is observed, an ECG should be repeated within 30 to 60 minutes. If the repeat ECG also records a QTcF greater than 480 ms or a change versus baseline > 60 ms, levels of electrolytes (these must include potassium and magnesium) should be assessed from a blood sample. Any abnormalities should be corrected, concomitant medication should be verified, and a clinical cardiologist should be consulted to confirm the read out and determine proper subsequent monitoring activities. If the abnormalities are confirmed by the cardiologist, subjects will be discontinued from treatment and procedures in Section 7.5.1 should be followed. The sponsor must be notified and the case discussed with the Project Physician.
- If an ECG from an enrolled subject records a QTcF interval exceeding 500 ms, subjects should be admitted to a telemetry unit or an emergency unit with continuous ECG recording capabilities until normalization of the QTcF interval. During the subject's monitoring at the emergency or telemetry unit, standard practices for the unit will be followed including, at a minimum, electrolyte monitoring, serial 12-lead ECGs, and consultation with a clinical cardiologist. If the abnormalities are confirmed by the emergency or telemetry unit, subjects will be discontinued from treatment and procedures in Section 7.5.1 should be followed. The sponsor must be notified and the case discussed with the Project Physician.

a. As discussed in Item 2.i. below, Subject 0270309 had a Week 36 ECG conducted on July 16, 2009, that resulted in a QTcF value of 526 ms, according to the ECG machine readout. You failed to follow the protocol because you did not admit the subject to a telemetry unit or an emergency unit with continuous ECG recording capabilities until normalization of the QTcF interval, nor did you perform electrolyte monitoring or serial 12-lead ECGs, or obtain consultation with a clinical cardiologist.

b. Subject 0270393 had a Week 36 ECG conducted on April 27, 2009, that resulted in a QTcF value of 458 ms, according to the ECG machine readout. You failed to follow the protocol because you did not perform a repeat ECG within 30 to 60 minutes. Furthermore, when the confirmed ECG report of the Week 36 ECG was received by your office and signed by you on May 8, 2009, it stated that the QTcF was 509 ms. You

failed to follow the protocol because you did not admit the subject to a telemetry unit or an emergency unit with continuous ECG recording capabilities until normalization of the QTcF interval, nor did you perform electrolyte monitoring or serial 12-lead ECGs, or obtain consultation with a clinical cardiologist.

c. Subject 02700419 had a Week 4 ECG conducted on December 8, 2008, that resulted in a QTcF value of 470 ms; a Week 8 ECG conducted on January 9, 2009, that resulted in a QTcF value of 460 ms; and a Week 12 ECG conducted on February 2, 2009, that resulted in a QTcF value of 464 ms, according to the ECG machine readouts. You failed to follow the protocol because you did not perform a repeat ECG within 30 to 60 minutes at each of these visits.

d. Section 7.3 of the protocol, eligibility criterion number 7, states: "Subjects will not be enrolled if they have alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin values greater than 1.5 times the upper normal limit at screening..."

Subject 0270249 had screening labs performed on September 22, 2008, that reported an AST of 63 U/L and an ALT of 87 U/L. These values are greater than 1.5 times the upper normal limit values of AST (41 x 1.5) 61.5 U/L and ALT (45 x 1.5) 67.5 U/L, and therefore render the subject ineligible to enroll in the clinical investigation. Additionally, the subject continued to have elevated AST and ALT values throughout the clinical investigation, as evidenced by laboratory results from the baseline visit on November 24, 2008; the Week 4 visit on December 22, 2008; the Week 8 visit on January 20, 2009; the Week 12 visit on February 16, 2009; the Week 16 visit on March 16, 2009; the Week 20 visit on April 13, 2009; the Week 24 visit on May 11, 2009; the Week 30 visit on June 22, 2009; the Week 36 visit on August 4, 2009; and finally, the Week 52 visit on December 10, 2009.

You failed to follow the protocol by enrolling this subject in the clinical investigation. Furthermore, you failed to protect the rights, safety, and welfare of this subject and placed this subject at risk by maintaining this subject in the clinical investigation for the entire 52-week investigative period.

e. Section 7.5.4 of the protocol, Clinical Laboratory Test Values, states: "Subjects with ALT and/or alkaline phosphates and/or total bilirubin exceeding twice the upper normal limit should be closely monitored and not receive additional study drug until values are back in the normal range. Concomitant medication should be verified and possible causes of liver function abnormalities evaluated..."

As illustrated by the table below, Subject 0270436 had elevated laboratory test values exceeding twice the upper normal limit ($45 \times 2 = 90$) on January 5, 2009 (Week 4), with an ALT of 370 U/L; and on February 2, 2009 (Week 8), with an ALT of 144 U/L. You did not follow the protocol and placed the subject at risk because the subject's record does not reflect that you closely monitored the situation, nor does the record indicate that you stopped study drug until the values were back in the normal range. The subject's ALT remained elevated throughout the study and never returned to the normal range.

Furthermore, this subject should not have been enrolled in the clinical investigation due to the elevated ALT at the baseline visit (> 67.5 U/L). Section 9.1.2 of the protocol states: "The following assessments and procedures will be performed at the baseline visit: inclusion/exclusion criteria..." If one refers to the inclusion criterion mentioned above, the subject would have been excluded because the ALT was > 1.5 times the upper normal limit of 67.5 U/L.

Week	Date	ALT Value	Medication Kit #
Screening	10/16/08	42	None
Baseline	12/8/08	80	20354
4	1/5/09	370	20697
8	2/2/09	144	20714
12	3/2/09	No record available	20783
16	3/30/09	82	22128
Early Withdrawal	4/27/09	74	None

f. Section 7.3 of the protocol, Inclusion Criteria, number 2.d., states that subjects must have “[a] positive dermatophyte culture.”

Subject 0270532 did not have a positive dermatophyte culture at the time of randomization and administration of study drug. You failed to follow the protocol by enrolling this subject, who did not meet eligibility criteria.

g. Section 9.1.1 of the protocol, Screening, states that “[i]f subject is not randomized within 60 days of screening, all screening assessments must be repeated.”

Subjects 0270249, 0270253, and 0270281 were not randomized within the 60 days of screening, yet the screening assessments were not repeated.

i. Subject 0270249 was screened September 22, 2008. Subject was randomized outside the 60-day screening period and underwent the baseline visit on November 24, 2008.

ii. Subject 0270253 was screened September 23, 2008. Subject was randomized outside the 60-day screening period and underwent the baseline visit on January 8, 2009.

iii. Subject 0270281 was screened September 25, 2008. Subject was randomized outside the 60-day screening period and underwent the baseline visit on December 4, 2008.

h. Section 11.5 of the protocol, Safety Laboratory Determinations, states: “All safety laboratory tests with values that become abnormal to a clinically important degree after study product administration should be repeated until the values stabilize. If laboratory values do not return to normal or baseline within a reasonable period, the etiology should be identified and the sponsor notified.”

In addition, Section 7.4 of the protocol, Exclusion Criteria, states:

Subjects with any of the following conditions or characteristics will be excluded from study enrollment:

10. Subject is currently suffering from any disease or condition, that could include abnormal laboratory tests, and/or who are currently using medication which in the opinion of the investigator may affect the evaluation of the study product or place the subject at undue risk.

12. Subject has a history of any condition that could possibly affect absorption of drug (e.g., gastrectomy), uncontrolled diabetes, clinically significant peripheral vascular disease or peripheral circulatory impairment, or has had any major illness within 30 days prior to screening examination.

We note that multiple subjects had uncontrolled diabetes at the time of screening and/or at one or more study visits. You did not follow the protocol because you did not exclude any of the subjects from enrollment; nor is there any evidence in the subjects’ records that you repeated the abnormal values until stabilized, according to Section 11.5 of the protocol.

i. Subject 0270292 had elevated blood glucose values and urine glucose values at screening and throughout his participation in the study.

ii. Subject 0270360 had elevated blood glucose values and urine glucose values at screening and throughout his participation in the study.

iii. Subject 0270281 had elevated blood glucose values and urine glucose values at screening and throughout his participation in the study.

i. Section 7.3 of the protocol, Inclusion Criteria numbers 5 and 6, state:

5. Sexually active non-lactating females of childbearing potential participating in the study must agree to use a medically acceptable method of contraception while receiving protocol-assigned product and up to the first menses 60 days following the last dose of study product. A woman of childbearing potential is defined as one who is biologically capable of becoming pregnant; including perimenopausal women who are less than 2 years from their last menses. Contraceptive methods include:

- Hormonal contraception, including oral, injectable, or implantable methods started at least 2 months prior to screening. If hormonal contraception was started less than 2 months prior to screening, then a form of non-hormonal contraception should be added until the third continuous month of hormonal contraception has been completed.
- Two forms of non-hormonal contraception, including intrauterine devices or properly used barrier methods (eg, male or female condoms, diaphragm, or cervical cap). Subjects with surgical sterilization, including tubal ligation or partner's vasectomy, must use a form of nonhormonal contraception. A barrier method or sterilization plus spermicide are acceptable.

Women who are not currently sexually active or lactating must agree to use a medically accepted method of contraception should she [*sic*] become sexually active while participating in the study.

6. Women of childbearing potential must have a negative pregnancy test at enrollment.

Additionally, Section 9.1 of the protocol, Study Visit Assessments, outlines that pregnancy tests are to be obtained at Screening (urine), Baseline (serum and urine), Week 12 (urine), Week 24 (urine), Week 36 (urine), and at Week 52 (urine).

Furthermore, Section 11.6 of the protocol, Pregnancy Testing, states: "A pregnancy test will be conducted on urine from female subjects of childbearing potential at screening, baseline, weeks 12, 24, 26, and 52 visits. In addition a serum pregnancy test will be performed on all female subjects at baseline. A negative urine pregnancy test result must be received before either randomization or administration of study product." This information is also graphically expressed in Section 3 of the protocol, Study Flowcharts, Table 1, labeled "Schedule of Assessments – General."

We note that during the 36 weeks that Subject 0270309 participated in the study, you did not document the presence of a pregnancy and its progression to term. We acknowledge that you performed the pregnancy tests as required by the protocol at screening, baseline, Week 12, Week 24, and Week 36 visits, and that those tests were negative. However, you did not document the subject's weight gain or the presence of a gravid abdomen at the time of her physical exams, which you reported as normal during study visits at screening, Week 12, Week 24, and Week 36, thereby exposing the developing fetus to harm from the investigational drug. The subject died on **(b)(6)**. We note that in the autopsy, the subject was reported as weighing 316 pounds; however, in the subject's study records for multiple study visits, including her final visit (Week 36, dated July 16, 2009), she was reported as weighing 265 pounds. Additionally, the autopsy reported the presence of an intrauterine, normally developed, male fetus that was consistent with an average full-term fetus, based on weight and measurements. The autopsy reported the subject's cause of death as peripartum cardiomyopathy, with contributory causes of pneumonia, morbid obesity, and substance abuse (evidence of a cocaine metabolite).

We note that your failure to adequately supervise pregnancy tests, physical examinations, and QTcF monitoring procedures during the clinical investigation, contributed to the inappropriate continued participation of Subject 0270309 and her full-term fetus in the clinical investigation.

Enrollment of subjects who do not meet eligibility criteria and failure to perform study-related procedures jeopardize subject safety and welfare and compromise the interpretation and validity of the investigational endpoints.

3. 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)].

Section 15.1 of the protocol, Case Report Forms, states: "The investigator is required to maintain adequate and accurate CRFs [Case Report Forms] and to record all observations and other data relevant to the clinical investigation. These forms are to be completed in a neat, legible manner with permanent ink to ensure accurate interpretation of data."

a. We note that study records were signed as having been reviewed on a date prior to the date they were faxed to the clinical site, or prior to the submission of the report. For example:

i. For Subject 0270281: The subject's baseline ECG report was signed as having been reviewed on December 7, 2008, when the record itself was dated December 8, 2008.

ii. For Subject 0270532: The subject's screening ECG was signed as having been reviewed on February 2, 2009, when the record itself was dated February 3, 2009.

iii. For Subject 0270576: The subject's mycology results were signed as having been reviewed on February 9, 2009, when the records were not received by facsimile until February 10, 2009.

b. We note that the following study records were signed as having been reviewed on a date prior to the date they were brought to Dr. Zaiac's attention during a study monitor's visit:

i. For Subject 0270145: On April 21, 2009, the study monitor pointed out that Dr. Zaiac had not reviewed and signed the Week 12 ECG and had not evaluated the Week 12 abnormal laboratory results. A subsequent review of these records disclosed that they had been signed using the date they were received at the site, instead of using a date after April 21, 2009, when the monitor had brought them to Dr. Zaiac's attention.

ii. For Subject 0270174: On November 19, 2008, the study monitor pointed out that Dr. Zaiac had not signed the screening ECG. A subsequent review of the screening ECG disclosed that it had been signed using the date it was conducted, instead of using a date after November 19, 2008, when the monitor had brought it to Dr. Zaiac's attention.

Failure to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation compromises the interpretation and validity of the investigational endpoints.

4. You failed to obtain informed consent of each subject in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60].

Except as provided in 21 CFR 50.23 and 50.24, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative [21 CFR 50.20].

As an investigator, it is your responsibility to obtain informed consent in accordance with 21 CFR part 50. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative.

You failed to obtain legally effective informed consent from Subjects 0270354 and 0270174, to whom you prescribed the investigational new drug, **(b)(4)**. Specifically, the informed consent forms for Subject 0270354 that were dated August 7, 2008, and the informed consent forms for Subject 0270174 that were dated October 13, 2009, for Protocol **(b)(4)** were written in English, unlike the other consent forms signed by these subjects, which were written in Spanish.

Failure to obtain adequate informed consent and to minimize the possibility of coercion or undue influence jeopardizes the safety and welfare of enrolled subjects by denying them an opportunity to assess the risks and benefits of their participation in the clinical investigation.

5. You failed to assure that an Institutional Review Board (IRB) that complies with the requirements set forth in part 56 was responsible for the initial and continuing review and approval of Protocol (b)(4) [21 CFR 312.66].

FDA regulations require that clinical investigations conducted under an IND (i.e., those subject to 21 CFR part 312) not be initiated unless that investigation has been reviewed and approved by an IRB meeting the requirements of 21 CFR Part 56. Clinical investigators are responsible for ensuring that an appropriate IRB conducts initial and continuing reviews of clinical investigations [21 CFR 312.66]. The investigator shall also ensure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects. You violated these requirements as described below:

a. You failed to report to the IRB that the clinical investigation was terminated at your site by the study sponsor. The sponsor terminated your site in December 2009, yet you did not notify the IRB of site closure until April 30, 2010, after the initiation of this FDA inspection. We note that at the time of the inspection, you admitted to the FDA investigator that you thought the sponsor was responsible for submitting the report to the IRB.

b. You failed to report all unanticipated problems involving risk for Subjects 0270436 and 0270532. Specifically, you were aware that Subject 0270436 was positive for HIV and hepatitis in April 2009, yet you did not report that information to the IRB until September 2009. You also failed to report to the IRB that Subject 0270532 did not have a positive dermatophyte culture at the time of randomization and administration of study drug.

Your failure to ensure that the IRB was notified of the termination of your site by the sponsor, and your failure to report unanticipated problems involving risk to subjects, impeded the IRB's ability to review your application to conduct Protocol **(b)(4)**, and to make a determination regarding the continued adequacy of that application. Therefore, you failed to ensure continuing IRB review of Protocol **(b)(4)**, as required under 21 CFR 312.66.

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 adequately and promptly explain the violations noted above may result in regulatory action without further notice. If you believe that your written response to the Form FDA 483 dated August 5, 2010, fully explains the actions you have taken to prevent similar violations in the future, please communicate that to us in writing within fifteen (15) business days. You may reference the written response dated August 5, 2010, in your response to this letter.

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 (formerly Lewin), M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5354

10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,
{See appended electronic signature page}
Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

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
03/21/2011

Links on this page: