



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Dr. Lynette Stewart
Georgia Center for Female Health
4775 Jimmy Carter Blvd., Suite 101
Norcross, GA 30093 USA

Ref: 09-HFD-45-01-01

Dear Dr. Stewart:

Between April 26 and May 18, 2007, Ms. Myla Chapman, 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

(b) (4), performed for (b) (4)

- Protocol No. (b) (4) : A Phase 3, 12-Month, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Two Doses of (b) (4) Versus Placebo in Subjects with (b) (4)
- Protocol No. (b) (4) : A Phase 3, 12-Month, Extension Study to Evaluate the Safety of (b) (4) in Subjects with (b) (4)

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 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. Chapman presented and discussed with you Form FDA 483, Inspectional Observations.

We wish to emphasize the following:

1. You failed to protect the rights, safety and welfare of subjects under your care [21 CFR 312.60].

As required in this protocol evaluating a potentially therapeutic (b) (4) agent, subjects were to have (b) (4) and (b) (4) biopsies performed to evaluate for potential proliferative effects of the test agent. In addition, the protocol required conducting safety and follow up evaluations and excluding subjects who met certain criteria. By omitting these safety evaluations, delaying follow up evaluations or continuing subjects in the study despite the presence of exclusion criteria, you placed the study subjects at risk. Specifically,

a.i) Subject (b) (6) had an (b) (4) biopsy on 12/2/03 which was required for the Month 12 visit for protocol # (b) (4) and the Day -1 visit for protocol # (b) (4) 1. The biopsy yielded inadequate tissue for analysis. Both protocols required a repeat of the procedure within one month. The repeat biopsy was not performed.

a.ii) Subsequently, subject (b) (6) had a biopsy at the Month 6 visit for protocol # (b) (4) on 6/16/04 which yielded adequate tissue for analysis. The result indicated a (b) (4), which according to the protocol should have resulted in discontinuation of the subject from the study and should have been recorded as an adverse event. However, you allowed the subject to remain in the study, did not record this an adverse event, and continued to provide randomized medication that may have placed the subject at risk for injury.

b.i) Subject (b) (6) had a (b) (4) on 4/20/04 that was part of the Month 12 visit for protocol (b) (4) and the Day -1 visit for protocol (b) (4). The results of the (b) (4) ear were reported (b) (4) as exclusionary. The records indicate that you reviewed the (b) (4) test results on 6/4/04. The protocol allows for the subject to continue in the study pending a (b) (4) result that is negative for (b) (4) /cancer. Based on the documents in the file, it does not appear as if the subject had the required (b) (4) test until 7/30/04.

b.ii) In addition, it appears that the protocol specified laboratory did not receive the tissue for this test until 9/3/04. There is no explanation in the files for these delays. Despite these potential exclusionary results, the subject remained in the study until January 2005 when she was lost to follow up.

2. You failed to conduct the studies or ensure they were conducted according to the investigational plan [21 CFR 312.60]. In addition to items 1a.-b. above, we note the following:

a. The protocol inclusion criteria required an (b) (4) level of (b) (4). The following subjects were enrolled in protocol # (b) (4) with exclusionary (b) (4) levels:

- i) Subject (b) (6) had a Day -1 5/4/04 (b) (4) level of 1.7.
This subject was allowed to enroll in the study and there is no documentation indicating that you ever requested a wavier.
- ii) Subject (b) (6) had a Day -1 6/28/04 (b) (4) level of 0.7.
This subject was allowed to enroll in the study. You did not request a waiver for this enrollment until 9/30/04; the sponsor allowed for the subject to stay on the study pending the Month 3 results. An (b) (4) result of 1.0 was reported for the labs drawn at the Month 3 visit on 9/29/04 and reported on 10/11/04 as exclusionary. An (b) (4) sample collected on 10/26/04 was also reported as exclusionary at .08. Your review of the Month 3 results did not occur until 11/9/04 and categorized the exclusionary result as not clinically significant. The subject was ultimately withdrawn December 2004.
- b. You performed a (b) (4) on Subject (b) (6) on 3/2/04 at the Month 3 visit for protocol # (b) (4). This procedure was not required by the protocol for that visit and there is no mention in the clinic notes as to why this (b) (4) was done. In addition, the site did not make the Month 2 phone call to this subject.
- c. Subject (b) (6) had a biopsy for the Month 6 treatment visit for protocol # (b) (4) on 11/19/04 that did not yield enough tissue for an analysis. The biopsy should have been repeated within one month, but it was not. There is no documentation regarding performance of a repeat biopsy.
- d. Subject (b) (6) missed her scheduled post-treatment follow-up for protocol # (b) (4) on March 14, 2005. The records do not indicate that the site tried to contact the subject until May 2005 regarding the missed visit.
- e. The Quality of Life Questionnaire and the (b) (4) Function Index were not completed by Subject (b) (6) at the Month 12 visit for protocol # (b) (4) on 12/2/03.
- f. The Month 5 phone call was not made to Subject (b) (6) during the extension study.

3. You failed to prepare and 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. Source documents show phone calls for Month 7 (dated 1/17/05) and Month 8 (dated 2/17/05) for Subject (b) (6) for # (b) (4). Based on the subject's early termination date in 12/04, the information should have been reported as Month 1 and Month 2 *post* treatment follow-up phone calls.
- b. Month 6 records conflict for Subject (b) (6) enrolled in protocol # (b) (4). For the Month 6 visit, the subject apparently visited the office on two different days, 10/6/03 and 10/7/03. A note to file dated 6/8/04 states that page 2 of the source document for the visit done on 10/7/03 is missing and indicates that the physical exam was not done because you were not at the office. The note also states that a brief physical exam was conducted at the Month 8 visit which took place 12/15/04 and 12/23/04. By contrast, a note written on 10/6/03 by a different

study coordinator states that all appropriate procedures were done except for a biopsy because the physician had to leave the office.

- c. There were two subjects screened for # (b) with the initials (b); both were screen fails. The records for these two subjects were mixed in the different folders and because of the way that the records are identified, it is difficult to discern which documents belong to which subject.

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:

Constance 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
Bldg 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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CYNTHIA A WELSH

01/21/2009

would not upload file
would not add Todd-Murrell, Dawn

CONSTANCE LEWIN

01/21/2009

LESLIE K BALL

01/23/2009