Dear Dr. Dallas:

Between March 16 and April 8, 2009, Ms. Donna Gallien, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations:

- Protocol (b)(4) entitled (b)(4) of the investigational drug (b)(4) performed for (b)(4), and
- Protocol (b)(4) entitled (b)(4) of the investigational drug (b)(4) performed for (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, the documents submitted with that report, and your written response dated May 7, 2009, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Ms. Gallien presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

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

When you signed the investigator statements (Form FDA 1572) for the above referenced clinical investigations, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities (21 CFR 312.60) include ensuring that the investigation 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. You specifically agreed to personally conduct the clinical studies or to supervise those aspects of the studies that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as 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 clinical trials were conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protected the rights, safety, and welfare of human subjects.

Specifically, multiple blank source document worksheets for Protocol (b)(4) were signed by you for subjects #0011, #008, and #003. Your signature on a document indicates that you have reviewed the data within; thus, source documents should not be signed until relevant data has been added and reviewed.

We note your acknowledgment in your written response that you relied on the study coordinator to follow the investigational plan as well as that the correspondence regarding the various studies was sent to the study coordinator without an appropriate flow of information. We also acknowledge that you have described corrective actions such as having all study correspondence sent directly to you to prevent recurrence of the findings noted above in the future. However, these corrective procedures do not address how you will assure that you personally conduct or supervise investigational studies in the future as well as ensure the integrity of the investigational procedures in the other clinical investigations in which the study coordinator may have been involved.

2. You failed to conduct the studies or ensure they were conducted according to the signed investigator statement and the investigational plan [21 CFR 312.60].

a. Protocol (b)(4) specifically stated that subjects with current use of
postmenopausal oral hormone replacement therapy were to be excluded from the clinical investigation. Furthermore, Appendix I of the protocol, Disallowed Concomitant Medications, lists "oral hormone replacement therapy" and specifies "estrogens and progestins". Subject #0011 was randomized on 8/16/05 and allowed to continue in the clinical investigation despite clinic records dated 8/8/06 and 1/24/07 documenting the use of the disallowed concomitant medication, Prempro, an oral hormone replacement therapy.

b. Protocol (b)(4) states that newly diagnosed (b)(4) subjects or subjects currently untreated for greater than 4 weeks may combine visits 1 and 2. The protocol also states that subjects on current (b)(4) medication must undergo a washout period and must be completely off their previous (b)(4) medication for at least one week before entering visit 2.

i. The clinic chart dated 10/12/06 documents subject #0001 as currently taking the medication, yet he did not undergo a washout period prior to visit 2, as required in the protocol.  
ii. Visits 1 and 2, which occurred on 10/13/06, were combined for subject #0001, who was currently treated with (b)(4) against protocol guidelines that state combined visits 1 and 2 are only for subjects who are newly diagnosed as (b)(4) or are currently untreated for at least 4 weeks. There is no evidence that subject #0001 met these criteria, and therefore he should not have combined visits 1 and 2.

We note your acknowledgment that the investigation was not conducted in accordance with the signed statement and investigational plan. We also acknowledge that you have described adequate corrective actions in your written response to prevent recurrence of the findings noted above in the future.

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 administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

Deficiencies were noted in the accuracy of the case histories of multiple subjects participating in Protocol (b)(4):

a. Subject #0008: Clinic chart on 11/22/04 documented excision of basal cell carcinoma yet screen visit 2 Case Report Form (CRF) on 6/8/05 fails to document this as past medical history. There is no written documentation to explain this inconsistency.

b. Subject #0003:
i. The documentation in the records for the early termination of subject #003 contradicts an affidavit signed by subject #003. For example, the source document for visit 7 dated 10/18/06 written by the study coordinator states that the subject was out of town and declined to schedule the final study visit. Additionally, source document for visit 8.1 dated 7/19/07 written by the study coordinator states that subject #003 was no longer taking the study medication due to discontinuation from the study because the subject withdrew consent. However, the affidavit of subject #003 contradicts the above mentioned source documents regarding the subject’s discontinuation from the study due to withdrawal of consent. The affidavit of subject #003 states that the subject never saw the study coordinator after the third visit. Furthermore, the affidavit states that the subject did not decline the final study visit, did not withdraw consent, and that the subject had attempted to continue participation in the study but that the telephone messages were not returned.

ii. Multiple concomitant therapy case report forms documenting medications used by subject #0003 contain conflicting information with respect to start and stop dates. There is no written documentation to explain these inconsistencies.

c. Subject #0011:

i. For Visit 7 (2/20/07), the source document fails to document any adverse events after Visit 6 (9/7/06), yet the CRF documents numerous adverse events.

ii. Visit 8 was conducted on 9/19/07. Source documents from that visit are inconsistent in that some records document that the subject underwent medication changes and sinus surgery on (b)(6), but other records state there were no changes in medication or health.

iii. CRF fails to include documentation of visit 6.1 and the accompanying memo-to-file does not explain this lack of documentation.

There is no written documentation to explain these inconsistencies for Subject #0011.

Deficiencies were noted in the accuracy of the case histories of multiple subjects participating in Protocol (b)(4):

d. Subject #003:

i. The adverse event log fails to document adverse events listed in the clinic chart between 1/23/07 through 6/13/07.

ii. Visit 1 screening form CRF was changed from smoker to non-smoker on 12/5/06, yet clinic records dated 6/27/07 document that subject stated she stopped smoking “about 1 month ago”. There is no explanation for the different dates recorded in the subject’s records.
e. Subject #005: Adverse event log fails to document numerous adverse events listed in the clinic chart between visit 2 (10/31/06) and visit 6 (1/3/07).

f. Subject #001: failure to document use of (b)(4) in the six months prior to visit 1 (10/12/06) on Prior (b)(4) Medication case report form, yet clinic notes from same date list the use of (b)(4) and state that the purpose of the subject’s visit was for a (b)(4) refill.

g. Subject #004: The Mean Sitting Systolic Blood Pressure using the right arm was miscalculated as 150 mmHg and MSDBP as 84 mmHg for Visit 1 on 10/23/06 instead of the correct values of 147 and 86, respectively.

h. Subject #0006: Section 7.5.2 of the protocol states that a complete physical examination be performed by the investigator at Visit 11. Furthermore, information about the physical examination must be present in the source documentation at the study site. The Visit 11 complete physical examination was not documented in source documents at your site.

We note your acknowledgment that you failed to maintain adequate and accurate records. We also acknowledge the corrective actions, described in your written response, that you have taken to improve recordkeeping in the future.

4. You failed to maintain adequate records of the disposition of the drug, including dates, quantity and use by subjects [21 CFR 312.62(a)].

a. For subject #0011 enrolled in Protocol (b)(4)

i. Visit 4: The study medication section of the source document worksheet documents medication dispensed for visit 4 on 11/14/05, yet the study medication compliance check for visit 4 documents kit number 5097765 was dispensed on 11/15/05. The medication bottle label for kit number 5097765 also documents that it was dispensed on 11/15/05. There is no written documentation to explain this discrepancy.

ii. Visit 7: The study medication case report form for visit 7 documents 200 tablets returned on 2/20/07, yet the study medication compliance check for visit 7 documents 38 tablets returned on 2/20/07.

b. For subject #00002 enrolled in Protocol (b)(4): Visit 5 CRF Drug Labels form documents that kit number 513548 was dispensed on 11/21/06, yet the Drug Accountability Log fails to document this kit.

c. For subject #00004 enrolled in Protocol (b)(4), Visit 8 on 3/5/07:
i. Medication Re-Supply Call Worksheet dated 3/5/07 documents kit numbers 515201, 519282, and 519101 as being dispensed but ClinPhone Re-Supply Confirmation form dated 3/18/07 does not list kit number 515201 as being dispensed. There is no written documentation to explain this discrepancy.

ii. Drug Accountability Log documents kit numbers 519282 and 519101 as being dispensed 3/19/07 but the Drug Summary Log dated 4/29/08 documents kit number 519101 as not dispensed. Additionally, Drug Labels forms fail to document the label for kit number 519101 and the study subject number for kit number 519282.

We note your acknowledgment that you failed to maintain adequate and accurate drug accountability records. We also acknowledge the adequate corrective actions, described in your written response, that you have taken to prevent drug accountability discrepancies in the future.

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 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.
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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
11/09/2009