



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**WARNING LETTER**

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Nicola Spirtos, M.D.  
Women's Cancer Center of Nevada  
3131 La Canada St., Ste 110  
Las Vegas, NV 89169

Ref: 09-HFD-45-12-01

Dear Dr. Spirtos:

Between November 12 and December 1, 2007, CAPT Anthony Keller, representing the U.S. Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of a clinical investigation (Protocol (b) (4) ) entitled "A Pilot Phase II Study Evaluating the Combination of (b) (4) with (b) (4) as First Line Therapy in Patients with (b) (4) of the investigational drugs (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 participating in those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your undated letter provided to FDA investigator Keller at the end of the inspection, 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, FDA investigator Keller presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

**1. You failed to ensure that the investigation was conducted according to the signed investigator statement and investigational plan [21 CFR 312.60].**

A. Both the original protocol and Protocol Amendment #1 specified that the study treatment was to be administered in the following concentration and schedule:

(b) (4) IV over 30-90 minutes, followed by  
(b) (4) IV as a 1-hour infusion, followed immediately by  
(b) (4) IV over 2 hours.

In addition, both the original protocol and Protocol Amendment #1 specified that all study medications were to be infused on Day 1 every 21 days for 6 Cycles (1 Cycle = 21 days) or until disease progression, and after Cycle 6, (b) (4) as a single agent would continue as an infusion every 3 weeks for a total of 12 months from initiation of therapy. The protocols further stated that the dosing of (b) (4) should be adjusted depending upon individual patient tolerance and the dose of (b) (4) was to remain fixed at 100% of recommended dose. In addition the protocols stated that if a patient's weight changed by  $\geq 10\%$  from screening weight during the study, the study drug dosages were to be recalculated. Examples of protocol violations include but were not limited to the following:

- i. For Cycle 2, Subject #2 received the investigational drugs in the following incorrect order: (b) (4).
- ii. With respect to Subject #7,
  - 1. For Cycles 1 through 5, your site appears to have reported the values for the weight and height measurements on the chemotherapy order forms based on information from the subject's driver's license (i.e. 190 lbs, 5 foot 3 inches, respectively). We note however, that source documents showed that the subject's weight for these cycles was less than the weight noted on the driver's license:

Cycle	Weight per visit worksheet	Equivalent weight
1	67.3 kg	148.1 lbs
2	67 kg	147.4 lbs
3	61.4 kg	135.1 lbs
4	61.4 kg	135.1 lbs
5	58 kg	127.6 lbs

As the investigational pharmacy prepared the study drugs based on the weight and height values noted per the chemotherapy order forms generated by your site, Subject #7 apparently was overdosed with investigational drugs at all of these visits.

2. Between the baseline visit (i.e. June 19, 2006) and the Cycle 5 Day 1 visit the subject’s weight had decreased by greater than 10%. However, based on the chemotherapy order forms, you did not adjust the subject’s weight, which resulted in a failure to recalculate the dosages.
  
- iii. With respect to Subject #10, for Cycles 1 through 6, your site reported the values for the weight and height measurements on the chemotherapy order forms based on the subject’s driver’s license (i.e. 120 lbs, 4 foot 10 inches, respectively). We note, however, that source documents showed that the subject’s weight for these visits was less than the weight noted on the driver’s license:

Cycle	Weight per source	Equivalent weight
1	45 kg	99 lbs
2	45 kg	99 lbs
3	45 kg	99 lbs
4	45 kg per progress note 49 kg per (b) (4) visit worksheet	99 lbs 107.8 lbs
5	45 kg per progress note 48 kg per (b) (4) visit worksheet	99 lbs 105.6 lbs
6	44.5 kg	97.9 lbs

As the investigational pharmacy prepared the study drugs based on the weight and height values noted per the chemotherapy order forms generated by your site, Subject #10 apparently was overdosed with investigational drugs at all of these visits.

- B. The original protocol and Protocol Amendment #1 specified that subjects should be carefully monitored for toxicity and that the dosing of (b) (4) were to be adjusted depending on the individual patient tolerance. In addition, the protocols stated that the recommended dose modifications on Day 1 of a new cycle were based on the most severe toxicity observed in the previous cycle and/or upon laboratory values on the scheduled day of treatment in the new cycle. With respect to (b) (4), the protocols explicitly detailed the dose modifications needed for Day 1 of the new cycle based on the worst type of toxicity observed in the prior cycle. Specifically, a subject who experiences a Grade 4 neutropenia was to have a delay in the dose, and then a decrease in one dose level when resolved to at least  $\geq$  Absolute Neutrophil Count (ANC) 1200 for neutropenia.

Source documents showed that Subject #2 experienced what was identified by your site as a Grade 4 neutropenia on June 8, 2006 at the Cycle 3 Day 8 visit. On June 13, 2006 the ANC rose to  $0.6 \times 10^3/\text{uL}$ . Labs showing that the subject’s ANC rose above the 1200 mark (i.e.  $1.2 \times 10^3/\text{uL}$ ) were taken on June

17, 2006. Source records showed that Subject #2 had her Cycle 4 Day 1 visit on June 19, and the subject received the standard dosage of investigational drugs on June 20, 2006, without a decrease in dose level as specified in the protocol. We note that the labs showing recovery from the Grade 4 neutropenia were not taken within the 24 hr window specified by the protocol for the hematology tests to be taken on Day 1 of each Cycle (i.e. June 20, 2006). Thus the hematology lab result on June 17, 2006 for the Cycle 4 Day 1 visit is not taken in accordance with the protocol.

- C. The original protocol and Protocol Amendment #1 specified that within one working day after a Serious Adverse Event, the investigator was to fill out and submit the SAE notification form. The information on the form was to include an evaluation of the relationship to the study drugs, and the form was also to be signed and dated. Per the written consultation report by Dr. (b) (6) dated July 27, 2006, your sub-investigator was aware that Subject #10 had been admitted to the hospital with chest pains. During the hospital stay, a left heart catheterization, bilateral selective coronary angiogram and angioplasty were subsequently performed on the subject. You did not submit the initial report of the SAE to the sponsor (signed and dated by you) until December 5, 2006.
- D. The original protocol and Protocol Amendment #1 specified that while informed consent could be taken prior to 14 days before study treatment, the baseline study procedures which included but were not limited to a (b) (4) performance status evaluation, physical exam, neurosensory assessment, and ECG were to be done within 14 days of study treatment. The following were examples of deviations from protocol requirements:
  - i. With respect to Subject #2, source documents showed that the baseline study procedures including but not limited to the physical exam, neurological assessment, and (b) (4) performance status evaluation were performed on March 23, 2006. The subject did not receive the first dose of investigational drugs until either April 15 or April 17, 2006, which was greater than the 14 days allotted by the protocol.
  - ii. With respect to Subject #10, source documents showed that the baseline study procedures including the physical exam, neurological assessment, vital signs, and (b) (4) performance standards were performed on June 16, 2006 and the ECG was performed on June 22, 2006. The subject did not receive the first dose of study treatment until July 21, 2006, which was greater than the 14 days allotted by the protocol.
- E. The original protocol and Protocol Amendment #1 specified that at the baseline visit, a urinalysis and urine protein/creatinine (UPC) ratio was to be performed. Source records showed that this was not performed for Subject #2 at the baseline visit.

F. The original protocol and Protocol Amendment #1 specified that all study medication will be infused on Day 1 every 21 days for 6 cycles (1 cycle = 21 days) or until disease progression. Thereafter, only (b) (4) as a single agent will continue as an infusion every 3 weeks for a total of 12 months from initiation of therapy. With respect to study procedures that were to be performed on the Day 1 visit, the original protocol specified that on Day 1 of each Cycle, specific study procedures including but not limited to a physical exam, vital signs and neurosensory assessment, (b) (4) exam, and Peripheral Neurotoxicity Questionnaire were to be administered prior to study drug therapy. Protocol Amendment #1 only changed the requirement that a (b) (4) exam was to be performed at least every other cycle. The following protocol deviations included but were not limited to:

i. With respect to Subject #2:

1. A neurosensory assessment was not performed at the Cycle 1 Day 1 visit.
2. The Cycle 1 Day 1 Peripheral Neurotoxicity Questionnaire was administered on April 11, 2006, which was 6 days prior to the date the subject was dosed with study medication (i.e. April 17, 2006.).

ii. With respect to Subject #7:

1. For several cycles where study procedures, including but not limited to the physical exam and neurosensory assessment were performed on Day 1 of the cycle, the investigational drugs were not administered on Day 1 of the cycle as specified in the protocol:

Cycle	Date of Day 1 visit per visit worksheet and/or CRF	Date of administration of investigational drugs for that cycle
1	June 19, 2006	June 26, 2006
2	July 12, 2006	July 17, 2006
3	August 2, 2006	August 7, 2006
4	August 23, 2006	August 28, 2006
5	September 11, 2006	September 18, 2006
6	October 4, 2006	October 9, 2006

2. The Peripheral Neurotoxicity Questionnaire was not administered at the Day 1 visit of each cycle when the subject was to receive study medication per the protocol requirement. Specifically, source records showed that no questionnaire was administered at the Cycle 1 Day 1 visit. Also, at the Day 1 visit for Cycle 2 and Cycle 5, the questionnaires were done 5 and 7 days, respectively, prior to the date the subject was administered study medication.

iii. With respect to Subject #10, we note that:

1. For several cycles where study procedures, including but not limited to the physical exam and neurosensory assessment were performed on Day 1 of the cycle, the investigational drugs were not administered on Day 1 of the cycle as specified in the protocol. Examples include:

Cycle	Date of Day 1 visit per visit worksheet and/or CRF	Date of administration of investigational drugs for that cycle
2	August 1, 2006	August 11, 2006
3	August 29, 2006	September 1, 2008
4	September 19, 2006	September 22, 2006
6	October 31, 2006	November 3, 2006

2. The Peripheral Neurotoxicity Questionnaire was not administered at the Day 1 visit of each cycle when the subject was to receive study medication per the protocol requirement. Specifically, a neurotoxicity questionnaire was not completed for the Cycle 6, Day 1 visit. Additionally, for the Day 1 visit for Cycle 2, the questionnaire was completed 10 days prior to the date the subject was administered study medication.

G. The original protocol specified that prior to study medication administration on Day 1 and Day 8 during the cytotoxic chemotherapy and (b) (4) treatment, specific laboratory studies were to be performed including hematology (every cycle within a 24 hr window prior to Day 1; except Cycle 1 Day 1 which has a 72 hr window), serum chemistries (every cycle within a 72 hr window, prior to Day 1), coagulation (every cycle within a 72 hr window prior to Day 1), urinalysis and urine protein/creatinine (UPC) determination (every cycle within a 72 hr window) and a (b) (4) test (Day 1 each cycle). Protocol Amendment #1, amended some of the requirements for the laboratory studies during the cytotoxic chemotherapy and (b) (4) treatment: hematology (72 hr window; required on both Day 1 and Day 8 of each cycle), serum chemistries (72 hr window; not required on Day 8), coagulation (72 hr window; not required on Day 8), urinalysis and urine protein/creatinine (UPC) determination (72 hr window; at baseline, Day 1 and every cycle prior to chemotherapy treatment; not required on Day 8) and (b) (4) test (Day 1 each cycle). In our comparison of the case histories found at your site with the protocol in effect during the time of each visit, protocol deviations were identified. Examples include but are not limited to:

i. With respect to Subject #2:

1. Although laboratory samples were taken for certain tests, including the hematology, biochemistry, coagulation and/or the (b) (4) test,

these laboratory samples were not performed within the protocol specified time periods prior to study drug administration for the Day 1 visits of Cycles 1, 2, 3, 4, 5 and/or 6.

2. Serum chemistries were not performed for the Cycle 1 Day 8 visit or the Cycle 6 Day 8 visit.
  3. A urinalysis sample and UPC determination was not performed for the Cycle 1 Day 8, Cycle 2 Day 1, Cycle 3 Day 8, and Cycle 5 Day 1 visits.
  4. The partial thromboplastin time (PTT) test was not performed at the Cycle 2 Day 8, Cycle 3 Day 1, Cycle 3 Day 8, Cycle 4 Day 1, and Cycle 6 Day 1 visits.
- ii. With respect to Subject #7, we note that:
1. The UPC was not performed for the Cycle 4 Day 1 visits.
  2. The hematology sample was not performed at the Cycle 2 Day 8 visit.

H. Both the original protocol and Protocol Amendment #1 specified that (b) (4) vials were to be refrigerated at (b) (4) and should remain refrigerated until just prior to use. Our inspection found that there were no records found prior to January 2007 to confirm that the study medication was stored appropriately per the protocol requirements.

I. The protocol specified that (b) (4) was to be stored at temperatures between (b) (4) and (b) (4) at (b) (4) with excursions permitted to (b) (4). Our inspection found that there were no records prior to April 2007 to show that the investigational drugs were stored appropriately per the protocol requirements.

J. Both the original protocol and Protocol Amendment #1 specified that the Investigator was required to ensure compliance with the visit schedule and all procedures required by the protocol and was to provide all information required in the Case Report Form (CRF) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents to Sponsor Representatives. Both protocols further noted that it was the responsibility of the Investigator to maintain adequate and accurate CRFs designed by the sponsor, to record all observations and other data pertinent to the clinical investigation. All CRFs were to be completed in their entirety in a neat, legible manner to ensure accurate interpretation of the data. In addition, the protocols noted that should a correction be made, the information to be modified must not be overwritten, that the corrected information was to be transcribed by the authorized person next to the previous value, initialed and

dated, and that the use of white-out and/or correction fluids was not allowed under any circumstances.

Based on FDA investigator Keller's observations, your site utilized correction fluid and write over corrections in multiple places throughout the source documents that were reviewed during the FDA inspection. Furthermore, these corrections were made without explanation. Examples include but were not limited to:

- i. The dose of (b) (4) given to the Subject #2 as noted on the CRF.
- ii. The weight information on the (b) (4) visit worksheet for Subject #7 at the Day 1 visits of Cycle 2, 3, and 4.
- iii. The weight and/or height information on the (b) (4) visit worksheet for Subject #10 at the Day 1 visit of Cycle 1, 2, 3, 5 and 6.
- iv. The investigational agent accountability records.

Your use of these documentation practices leads to the inability to verify the information within the records at your site. The rationale and the source for the corrections could not be determined.

**2. You failed to 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. Examples of inaccurate case histories with respect to FDA's review of the records for Subject #2 include but were not limited to the following:
  - i. The Cycle 13 Day 1 visit CRF for Subject #2 listed the UPC ratio as 0.21. The corresponding lab report however, showed the UPC ratio as 0.109.
  - ii. The clinic note for the baseline visit on March 23, 2006 had late entries inputted on June 21, 2006 noting information including but not limited to the subject's (b) (4) test, (b) (4) performance status and consent process used to enroll the subject into the study. The source for the late entries could not be verified.
  - iii. The chemotherapy order for the Cycle 1 visit noted in the "date given section" that the investigational drugs were given on April 15, 2006. However, a hand written note written on the top of the order form stated "Chemo Given April 17<sup>th</sup> In-patient."
- B. Examples of inaccurate case histories with respect to FDA's review of the records for Subject #7 include but were not limited to the following:

- i. The case histories for the Baseline and Day 1 Cycle 1 visits are discrepant and we were unable to determine where information provided in the CRF for these visits was derived. Specifically, the (b) (4) visit source document for the Cycle 1 Day 1 visit appears to show that the date the physical exam, neurological assessment and vital signs were taken was on June 19, 2006. The Cycle 1 Day 1 visit CRF, however, notes that the physical exam and neurological assessment were not done and that the vitals signs were taken on June 26, 2006. In addition, the Baseline CRF notes that the physical exam, neurological assessment, and vital signs were done on June 19, 2006, but the vital signs information placed into the CRF does not match the information listed in the (b) (4) visit worksheet for the Cycle 1 Day 1 visit.
  - ii. The Cycle 5 Day 1 CRF listed the subject's weight as 61.4 kg on September 15, 2006. FDA investigator Keller noted that he was unable to find a record to substantiate this weight. The progress note dated September 11, 2006 noted the subject's weight as 127 lbs and the (b) (4) visit worksheet noted the subject's weight as 58 kg.
  - iii. The CRF for the Cycle 8 Day 1 visit noted that the study drug was administered on November 11, 2006. Source records however indicated that the study drug was administered on November 20, 2006.
- C. Examples of inaccurate case histories with respect to FDA's review of the records for Subject #10 include but were not limited to the following:
- i. There were two chemotherapy order forms found for the Cycle 6 Day 1 visit. The chemotherapy order form found in the research file was not similar to the one that was found in the investigational pharmacy. Specifically, the one found in the research file was not signed and noted that the subject weighed 48 kg. The chemotherapy order form found in the investigational pharmacy and used by the pharmacy to prepare the investigational agents, was signed and listed the subject's weight as 120 lbs (approximately 54 kg).
  - ii. There were discrepancies identified with respect to the source records found for the Cycle 7 Day 1 visit. Specifically, two chemotherapy order forms were found for this visit. The chemotherapy order form found in the research file listed the subject's weight as 45 kg. The chemotherapy order form found in the investigational pharmacy and used by the pharmacy to prepare the investigational agents, listed the subject's weight as 55 kg. The (b) (4) visit worksheet for the Cycle 7 Day 1 visit, however, did not note any value for the subject's weight.
  - iii. During FDA's inspection of your site, no documentation could be found to verify that your site submitted an SAE report to the IRB for Subject #10's hospitalization which occurred on (b) (6).

- D. Your site utilized the sponsor's (b) (4) worksheet as a source document. At the bottom of this document, there was a place for the individual who filled out the form to sign and date the form. In our review of this document, we found many instances where the individual who filled out the form either did not sign and date the form or the form was signed and date at a later time. Examples include but were not limited to the following:
- i. For the Cycle 8 Day 1 and Cycle 12 Day 1 visits for Subject #2, the individual(s) who completed the form did not sign and date when the form was completed. The (b) (4) visit worksheet documenting Patient #2's neurological assessment, vital signs, (b) (4) performance state, physical exam and (b) (4) exam performed on May 4, 2006 was signed and dated August 16, 2006.
  - ii. For the Cycle 1 Day 1, Cycle 2 Day 1, Cycle 5 Day 1 and Cycle 6 Day 1 visits for Subject #7, the individual(s) who completed the form did not sign and date when the form was completed.
  - iii. For the Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, and Cycle 7 Day 1 visits for Subject #10, the individual(s) who completed the form did not sign and date when the form was completed.

Your site's lack of signature and date on the forms and/or delayed signature and date of the forms lead to concerns about the accuracy of these source documents during the course of the study.

Per your undated response provided to FDA investigator Keller at the conclusion of the inspection, you noted that your site was responsive to the deficiencies that were identified by the monitors during the course of the study, which led to the termination of the data coordinators and replacement of your entire research staff. You further noted that had FDA investigator Keller had the time to examine and perform a comprehensive review of the records, you believe that he would have found an ever decreasing number of deviations as your site responded to previously noted deficiencies and made changes to the data management team.

We note that this response is inadequate. Specifically, we note that as the clinical investigator, it was your responsibility to ensure that the study was conducted in accordance with the investigational plan and that adequate and accurate case histories were maintained as specified in applicable FDA regulations. In addition, we note that your sole corrective action appears to be the termination and replacement of your staff with no information provided as to corrective actions your site will take to ensure that these violations will not take place in any ongoing or future studies.

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 Tejashri Purohit-Sheth, M.D., at 301-796-3402; 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.  
Director  
Division of Scientific Investigations  
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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.**  
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/s/  
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LESLIE K BALL  
01/03/2009