



WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Virendra Desai, M.D.
Physician Alliance Research Center
21520 S. Pioneer Blvd., Suite 203
Hawaiian Gardens, California 90716

Ref: 09-HFD-45-02-03

Dear Dr. Desai:

Between March 17, 2008 and April 17, 2008, Mrs. Yvette LaCour-Davis and Ms. Yvonne LaCour, 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) entitled "A Phase III, Randomized, Double-Blind Study of (b) (4) versus (b) (4) in the Treatment of Complicated (b) (4) of the investigational drug (b) (4) (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, the Form FDA 483, Inspection Observations, and your written response to the Form FDA 483 dated June 9, 2008, 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 personnel presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You failed to conduct the study according to the investigational plan [21 CFR 312.60].

- a. Our investigation found that all 18 subjects randomized into the study received study drug prior to your review and assessment of their baseline laboratory results, thereby potentially compromising the safety of subjects in the study. Specifically, the laboratory results from (b) (4) were received and reviewed by you up to 3 days after the study subjects were infused intravenously with study drug and in some instances, results from (b) (4) were not received and reviewed by you up to 20 days after the study subjects were infused intravenously with study drug, as summarized in the following table.

Informed Consent Document (ICD) Signed	Date/Time Pre-Screen Labs drawn	Date/Time Randomized into study	Date/Time 1 st dose of study drug received by subject	Date Baseline labs rec'd from central lab (b) (4)	Date Baseline labs reported by local lab (b)	Date P.I. signed off on baseline lab results from (b) (4)
#141051 7/27/06	27 Jul 2006 @ 13:10 hrs	27 Jul 2006 @ 13:17 hrs	07/27/06 @ 1655 hrs	08/04/06 (by fax)	08/03/06	(b) = 8/4/06 (b) = 7/28/06
#141052 7/27/06	27 Jul 2006 @ 15:38 hrs	27 Jul 2006 @ 14:56 hrs	7/27/06 @ 1704 hrs	09 Aug 06 reprint/fax	08/03/06	(b) = 8/9/06 (b) = 8/7/06
#141059 8/1/06	1 Aug 2006 @ 14:50 hrs	1 Aug 2006 @ 15:08 hrs	08/01/06 @ 1705 hrs	08/03/06 (by fax)	08/25/06	(b) = 8/3/06 (b) = 8/25/06
#141060 8/1/06	01 Aug 2006 @ 15:10 hrs	01 Aug 2006 @ 15:09 hrs	8/1/06 @ 1710 hrs	08/03/06 (by fax)	08/25/06	(b) = 8/3/06 (b) = 8/25/06
#141061 8/2/06	02 Aug 2006 @ 11:30 hrs	02 Aug 2006 @ 14:10 hrs	8/2/06 @ 1622 hrs	08/09/06 reprint/fax	08/07/06	(b) = 8/9/06 (b) = 8/3/06
#141062 8/3/06	03 Aug 2006 @ 11:00 hrs	03 Aug 2006 @ 11:14 hrs	8/3/06 @ 1655 hrs	08/04/06 (by fax)	08/09/06	(b) = 8/4/06 (b) = 8/10/06
#141066 8/7/06	07 Aug 2006 @ 16:30 hrs	07 Aug 2006 (no fax conf found on file)	8/7/06 @ 1645 hrs	08/09/06 (by fax)	08/16/06 C&S only	(b) = 8/9/06 (b) = 8/16/06
#141067 8/8/06	08 Aug 2006 @ 1402 hrs	08 Aug 2006 (no fax conf found on file)	8/8/06 @ 1638 hrs	08/11/06 (by fax)	08/25/06	(b) = 8/11/06 (b) = 8/25/06
#141068 8/9/06	09 Aug 2006 @ 13:23 hrs	09 Aug 2006 @ 12:41 hrs	8/9/06 @ 1644 hrs	08/11/06 (by fax)	08/16/06	(b) = 8/10/06 (b) = 8/18/06
#141069 8/10/06	10 Aug 2006 @ 11:23 hrs	10 Aug 06 @ 11:28 hrs	8/10/06 @ 1656 hrs	08/15/06 (by fax)	08/17/06	(b) = 8/15/06 (b) = 8/18/06
# 141079 8/14/06	14 Aug 2006 @ 14:10 hrs	14 Aug 2006 @ 13:46 hrs	8/14/06 @ 1647 hrs	8/17/06 (by fax)	8/30/06	(b) = 8/17/06 (b) = 8/30/06
#141080 8/14/06	14 Aug 2006 @ 14:26 hrs	14 Aug 2006 @ 13:48 hrs	8/14/06 @ 1652 hrs	8/16/06 (by fax)	8/30/06	(b) = 8/16/06 (b) = 8/30/06
#140051 8/16/06	16 Aug 2006 @ 12:45 hrs	16 Aug 2006 @ 12:18 hrs	8/16/06 @ 1644 hrs	08/20/06 (by fax)	08/28/06	(b) = 8/20/06 (b) = 8/28/06
#140063 8/16/06	16 Aug 2006 @ 15:00 hrs	16 Aug 2006 @ 13:52 hrs	8/16/06 @ 1650 hrs	08/18/06 (by fax)	08/25/06	(b) = 8/18/06 (b) = 8/25/06
#140040 8/18/06	18 Aug 2006 @ 14:10 hrs	18 Aug 2006 @ 13:13 hrs	8/18/06 @ 1655 hrs	8/21/06	8/28/06	(b) = 8/22/06 (b) = 8/28/06
#140076 8/18/06	18 Aug 2006 @ 1535 hrs	18 Aug 2006 @ 14:09 hrs	8/18/06 @ 1658 hrs	08/20/06 (by fax)	08/30/06	(b) = 8/20/06 (b) = 8/30/06
#141050 8/21/06	21 Aug 2006 @ 11:10 hrs	21 Aug 2006 @ 11:00 hrs	8/21/06 @ 1644 hrs	08/23/06 (by fax)	08/21/06	(b) = 8/23/06 (b) = 8/30/06
# 141074 8/21/06	21 Aug 2006 @ 12:50 hrs	21 Aug 2006 @ 13:35 hrs	8/21/06 @ 1650 hrs	8/23/06 (by fax)	08/30/06	(b) = 8/23/06 (b) = 8/30/06

Your explanation provided in your written response to the Form FDA 483 is unacceptable. You stated in your response that, “section 5.2.2 of the protocol only indicates that central laboratory testing needs to be obtained. In addition, section 5.1.7.4 of the protocol only mentions that the pregnancy tests need to be reviewed prior to first dosing of study medication.” While these statements are true, page 58 of the protocol clearly states that “all screening/predose assessments will be considered as baseline and must be performed and reviewed before randomization and dosing on Day 1...” When you signed the Statement of Investigator, Form FDA 1572, you agreed to the responsibilities of a clinical investigator that included ensuring that the study is conducted according to the investigational plan and the signed Investigator Statement, to protect the safety, rights or welfare of the subjects and to comply with all the obligations of a clinical investigator and all other pertinent requirements in 21 CFR 312. We remind you that as a clinical investigator, you retain responsibility for the conduct of the study.

- b. The protocol required that subjects with known or suspected hepatic dysfunction (total bilirubin ≥ 2 x upper limit of the normal range [ULN], or alanine aminotransferase [ALT] ≥ 3 x ULN, or aspartate aminotransferase [AST] ≥ 3 x ULN) be excluded from study enrollment.

Our investigation found that Subject 140063 was enrolled into the study on 8/16/06 despite having a baseline AST of 110 U/L (which was greater than 3 x ULN) as reported by (b) (4). In addition, (b) (4), your local laboratory, reported the subject’s baseline ALT as 120 U/L, which was also greater than 3 x ULN. You stated during our inspection that the subject did not have known or suspected hepatic dysfunction and was not known to have elevated liver tests. However, in your written response dated 6/9/08, you admitted that “if the laboratory results had been obtained and reviewed prior to the randomization on August 16, 2007, that this subject would not have meet the inclusion/exclusion criteria.” In addition, the Nurse’s Notes dated 8/17/06 @ 1500 state that, “subject discontinued from participation in the study due to elevated liver function test. Subject with history of alcohol abuse.” According to the subject’s Medication Administration Record (“MAR”), the subject was infused with five (5) doses of study medication from 08/16/06 @ 1650 hours through 08/17/06 @ 1021 hours prior to being withdrawn from the study on 8/17/06. The inclusion of this subject into the study was a clear violation of study protocol.

- c. The protocol required that all women of childbearing potential have a negative pregnancy test performed at baseline prior to receiving the first dose of study medication. However, Subject 141066 was randomized and received study medication without having the pregnancy test completed. In your response to the Form FDA 483, you acknowledged that this subject should have completed a pregnancy test before she received the study drug.

- d. The protocol required “physical exam,” “wound assessment,” and “overall clinical assessment since baseline” at the Day 8 Visit. These were not conducted for Subject 14150. In your response to the Form FDA 483, you acknowledged that the Day 8 information was not obtained.

2. 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)].

- a. Our investigation found that the Screening Laboratory Report for Subject 141068 documented that the sample was received by (b) (4) on 8/10/06, and reported by the laboratory on 8/11/06. At the top of the report, there is the date of 8/12/06 with a time stamp of 12:28 am and the words, (b) (4) ” and “PAGE 4 of 5” which appears to be the date the report was faxed to you. Your signature is dated 8/10/06, two days prior to when the report was sent to you.
- b. Our investigation found that for 5 of 18 subjects enrolled in the study, there were numerous instances where subject data on the MAR and/or “Nurse’s Notes” were changed without dates or the initials of the person making the change. It appears that these “write-overs” were done to match the times on the CRFs. As such, it is difficult to accurately determine when the drug was administered. For example, for Subject 141051, the following times for the “Change of Start Time of Infusion” and “Stop Time of Infusion were all “write-overs.”

Date & length of infusion	Change of Start Time of Infusion	Stop Time of Infusion
7/28/06 – 2 hour infusion	1703 hours	1906 hours
7/29/06 – 2 hour infusion	1710 hours	1916 hours
7/30/06 – 2 hour infusion	1720 hours	1922 hours
7/31/06 – 2 hour infusion	1722 hours	1927 hours
7/31/06 – 1 hour infusion	2238 hours	2320 hours
8/1/06 – 2 hour infusion	1725 hours	1925 hours
8/2/06 – 2 hour infusion	1700 hours	1903 hours
8/2/06 – 1 hour infusion	2230 hours	2333 hours

- c. Our investigation found that Subjects’ 141051, 141061 and 41067 End-of-Therapy Visit (EOT) case report forms (CRFs) documented that TOC assessment was conducted and the “overall clinical assessment since baseline” was documented as “improved”; however, the subjects only received 33 doses of study medication instead of the protocol required 35 doses of study medication for the minimum 7 day treatment period.

We note that the protocol states that if at the “test of cure” (TOC) assessment, the clinical outcome was deemed “cured”, than no further (b) (4) l therapy was necessary in subjects who had received at least 5 days of treatment. This would equate to at least 25 doses of study medication.

In your response to the Form FDA 483, you stated that “in reviewing the subjects’ clinical condition I felt that the subject had improved sufficiently and did not require additional interventional therapy. This is in line with the definition of “cure” provided in the protocol”. However, you failed to adequately document this assessment. We acknowledge your explanation and remind you of the importance of adequate and accurate documentation of events.

3. You failed to maintain adequate and accurate records for disposition of drug [21 CFR 312.62(a)].

- a. Our investigation found numerous discrepancies between the (b) (4) dose#/kit #/vial # dispensing records kept by the unblinded pharmacy and what was recorded on the Drug Accountability Forms for five (5) of seven (7) subjects randomized into the (b) (4) treatment arm and for four (4) of the eleven (11) subjects randomized into the (b) (4) /Placebo treatment arm. Specifically, the same dispensing vials from the same kits were documented as being dispensed to one subject on the (b) (4) s Form and to a different subject on the drug accountability form. In addition, drug dispensing information was missing for several subjects on the Drug Accountability Forms. See the following table for examples.

Examples of the same kit dispensed to different subjects:

(b) (4) Dose # Name of drug, Kit # & Vial # Subject # date dispensed	“Drug Accountability Form” Name of drug, Kit # & Vial# Subject # date dispensed
Dose # 2 Kit # 21148 – 8 Dispensed to Subject # 141059 (b) (6) 01 Aug 06 (Subject #141059 randomized on 01 Aug 06)	Kit # 21148 – 8 Dispensed to Subject # 141052 (b) (6) 30 Jul 06 (Subject # 141052 randomized 27 Jul 06)
Dose # 4 Kit 21148 – 1 Dispensed to Subject # 141059 (b) (6) 01 Aug 06	Kit # 21148 – 1 Dispensed to Subject # 141052 (b) (6) 02 Aug 06 (documented as “unused”)
Dose # 7 Kit # 26609 – 2 Dispensed to subject # 141059 (b) (6) 2 Aug 06	Kit # 26609 – 2 Dispensed to Subject # 141052 (b) (6) 27 Jul 06
Dose # 9 (b) (4) - Kit # 22609 – 1 Dispensed to Subject # 141059 (b) (6) 02 Aug 06	(b) (4) - Kit # 26609 – 1 Dispensed to Subject # 141052 (b) (6) 27 Jul 06
Dose # 12 (b) (4) - Kit # 22609 – 4 Dispensed to Subject # 141059 (b) (6) 03 Aug 06	(b) (4) -Kit # 22609 – 4 Dispensed to Subject # 141059 (b) (6) 08 Aug 06
Dose # 14 (b) (4) - Kit # 22609 – 3 Dispensed to Subject # 141059 (b) (6) 03 Aug 06	(b) (4) - Kit # 22609 – 3 Dispensed to Subject # 141062 (b) (6) 09 Aug 06 (Subject # 141062 randomized on 03 Aug 06)

Examples of discrepant or missing information:

<p>(b) (4) Dose # Name of drug, Kit # & Vial # Subject # date dispensed</p>	<p>“Drug Accountability Form” Name of drug, Kit # & Vial# Subject # date dispensed</p>
<p>Dose # 17 (b) (4) - Kit # 23666 – 13 Dispensed to Subject # 141059 (b) (6), 4 Aug 06</p>	<p>(b) (4) - Kit # 23666 – 13 Dispensed to Subject # 141059 (b) (6) 05 Aug 06</p>
<p>Dose # 11 & Dose # 15 (b) (4) – Kit # 60936 – 13 (documented as being dispensed twice) Subject # 141052 (b) (6) 29 Jul 06 (Subject # 141052 randomized on 27 Jul 06)</p>	<p>(b) (4) – Kit # 60936 – 13 Dispensed to Subject # 141052 (b) (6) 29 Jul 06</p>
<p>No record of (b) (4), Kit # 60936 – 12 being dispensed on the (b) (4) Form</p>	<p>(b) (4) – Kit # 60936 – 12 Dispensed to Subject # 141052 (b) (6) 29 Jul 06</p>
<p>Dose #18 & Dose #20 (b) (4) – Kit # 60936 – 20 (documented as being dispensed twice) Subject # 141052 (b) (6) 30 Jul 06</p>	<p>(b) (4) – Kit # 60936 – 20 Dispensed to Subject # 141052 (b) (6) 30 Jul 06</p>
<p>Dose # 33 (b) (4) – Kit # 23110 – 4 Dispensed to Subject # 141066 (b) (6) 14 Aug 06</p>	<p>No record of (b) (4) Kit # 23110 – 4 as being dispensed</p>
<p>Dose # 26 (b) (4) – Kit # 23110 – 13 Dispensed to Subject # 141066 (b) (6) 15 Aug 06</p>	<p>No record of (b) (4) Kit # 23110 – 13 as being dispensed</p>
<p>Dose # 28 (b) (4) – Kit # 23110 – 14 Dispensed to Subject # 141066 (b) (6) 15 Aug 06</p>	<p>No record of (b) (4) Kit # 23110 – 14 as being dispensed</p>
<p>Dose # 30 (b) (4) – Kit # 23110 – 6 Dispensed to Subject # 141066 (b) (6) 15 Aug 06</p>	<p>No record of (b) (4) Kit # 23110 – 6 as being dispensed</p>
<p>Dose # 31 (b) (4) – Kit # 24107 – 13 Dispensed to Subject # 141066 (b) (6) 16 Aug 06</p>	<p>No record of (b) (4) Kit # 24107-13 as being dispensed</p>
<p>Dose # 33 (b) (4) – Kit # 24107 – 12 Dispensed to Subject # 141066 (b) (6) 16 Aug 06</p>	<p>No record of (b) (4) Kit # 24107-12 as being dispensed</p>

- b. Our investigation found numerous discrepancies between the “Nurses Notes” and what was recorded on the corresponding MAR regarding doses of study medication. Some of the doses are documented as being administered more than once, and some doses were not recorded in the “Nurses Notes.” For example,
- i. The “nurse’s notes” for Subject # 141059 documented that the subject was administered dose # 17, # 18, & #31 twice, and there is no documentation that doses #12, #13, & # 33 were administered.
 - ii. The “nurse’s notes” for Subject # 141050 documented that the subject was administered dose # 16, and 17 twice. There is no documentation in the nurses notes that dose 11 was administered.

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; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg 51, Room 5358
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
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/s/

Leslie Ball

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