DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
250 Marquette Ave, Ste. 600 Minneapolis, MN 55401 (612)334-4100 Fax:(612)334-4134	4/18/2016-4/22/2016
	FEI NUMBER 3010820545

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Dr. Brian Driver , Clinical Investigator

FIRM NAME	STREET ADDRESS
Brian E. Driver, MD, Sponsor/Investigator	701 Park Ave
CITY, STATE, ZIP CODE, COUNTRY Minneapolis, MN 55415-1623	TYPE ESTABLISHMENT INSPECTED Clinical Investigator

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Failure to ensure proper monitoring of the study.

Specifically,

No monitoring was performed for study titled "(b) (4)", no documented evidence of monitoring exists.

OBSERVATION 2

An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically, for the study titled, (b) (4)":

A. The protocol was not followed for enrollment of subjects. Two (2) subjects (143 and 165) were enrolled in the study that met exclusion criteria and should not have been enrolled. Furthermore, these issues were not identified as protocol deviations. No documentation addressing the protocol deviations exist and no deviations have been reported for the study.

B. The protocol was not followed for reporting Serious Adverse Events (SAEs):
   a. Three (3) subjects (127, 135 and 160) experienced an SAE resulting in death. These SAE's were not documented, reviewed or evaluated per study protocol and were also not reported to the IRB within the required 30 day time frame per IRB reporting

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requirements.

b. No Adverse Events (total of 13 AEs) that occurred for subjects enrolled after study enrollment resumed (on 9/18/15) were documented as reviewed and evaluated until after this inspection was announced (on 4/15/16).

C. The protocol was not followed for notification after enrollment. Five (5) subjects (142, 147, 151, 167 and 171) did not receive a face-to-face discussion of study enrollment and no documented evidence exists to show that the study protocol was followed for making a phone call to the subject or mailing the study information sheet to them.

D. The protocol was not followed for subject randomization. Subject randomization numbers 159 and 174 were skipped. No deviation documentation exists addressing these issues. Furthermore, no deviations have been reported for the study.

E. The protocol was not followed regarding the dose of (b) (4) administered to nine (9) of twenty-eight (28) subjects reviewed (32% of total subjects reviewed; subjects 126, 127, 138, 142, 144, 151, 154, 155, 161)

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a. Subject 126 weighed 80 kg, should have been administered (b) (4) mg of (b) (4) but was given (b) (4) mg.

b. Subject 127 weighed 112 kg, should have been administered (b) (4) mg (b) (4) but was administered (b) (4) mg.

c. Subject 138 weighed 96.1 kg, should have been administered (b) (4) mg (b) (4) but was administered (b) (4) mg.

d. Subject 142 weighed 121.1 kg, should have been administered (b) (4) mg (b) (4) but was given (b) (4) mg.

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e. Subject 144 weighed 81 kg, should have been administered (b) (4) mg (b) (4) but was given (b) (4) mg.

f. Subject 151 weighed 54.3 kg, should have been administered (b) (4) mg (b) (4) but was given (b) (4) mg.

g. Subject 154 weighed 78.9 kg, should have been administered (b) (4) mg (b) (4) but was given (b) (4) mg.

h. Subject 155 weighed 101.8 kg, should have been administered (b) (4) mg (b) (4) but was given (b) (4) mg.

i. Subject 161 weighed 89 kg, should have been administered (b) (4) mg (b) (4), but was given (b) (4) mg.

OBSERVATION 3

Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.

Specifically, for the study titled, (b) (4) ":

F. Discrepancies with determination of severity were observed for 8 out of 12 Adverse Events (AE's). For example subject 164 experienced a grade 4 increase in SBP, per safety assessment table (9-1) in the protocol a grade 4 severity is potentially life-threatening. However, also documented on the AE form is a determination of severity from the adverse event table (9-2) in the protocol, which was determined as moderate. The discrepancy between these severities

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(potentially life-threatening vs. moderate) was not addressed or resolved. As documented, it is unclear if any of the 8 AEs qualify as Serious Adverse Events (SAE's). None of the 8 AEs were handled as SAE's or reported to the IRB.

G. Data entered into the electronic database, (b) (4), were inaccurate for two (2) of eleven (11) subjects reviewed (18% of total reviewed; subjects 135 and 141). Subject 135 was randomized to (b) (4) according to the paper data collection form, but the electronic data reflect randomization to (b) (4) with doses (b) (4) administered. In addition, the paper data collection form failed to record the drug dose administered. For subject 141, the paper data collection form shows the highest heart rate experienced as 129, whereas the electronic data reflect 127 for this measure.

Unverified

X Nicole C Victoria

Nicole C Victoria
Ph.D., Investigator
Signed by: Nicole Victoria -S

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