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SUMMARY

This For-Cause inspection of Clinical Investigator, Shaker R. Dakhil, M.D., F.A.C.P (Cancer Center of Kansas) was conducted per FY2015 High Priority CDER For-Cause, (b) (5) and CP 7348.811. The FACTS work assignment ID for this inspection is 11551437.

The title of the study audited during this inspection is:

(b) (4)

Protocol (b) (4). The principal investigator is Dr. Dakhil.

The previous inspection of this Clinical Investigator was conducted March 6-26, 2012 and classified VAI; an Inspectional Observations (FDA form 483) was issued to Dr. Dakhil with the following objections:

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

- Pre-dose serum samples for the study drug pharmacokinetic levels were collected outside of study protocol
- Post-dose serum samples for the study drug pharmacokinetic levels were collected outside of the protocol
- Pre dose serum samples for pharmacokinetic levels were collected while having the study drug administered
- Post dose serum samples for pharmacokinetic levels were collected while subjects received (b) (4) chemotherapy drugs

- Serum samples for pharmacokinetic levels were not collected after the first faster infusion and/or during the last infusion cycle
- Hematology and/or Serum Chemistry tests were performed outside of the protocol
- Specific serum chemistry tests (b) (4)) were not performed
- Subjects received the study drug before a review of hematology and/or serum chemistry test results had been performed
- Subjects were not given an adverse event diary card during the Cycle 2 Day 1 visit
- Subjects did not have documentation in their file showing that the Cycle 2 follow-up visit documenting adverse event coverage occurred.
- Subjects did not have assessment forms documenting adverse events in their file
- Subjects were administered the study drug by a site staff not authorized

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

- Subjects had inconsistent pre or post serum sample collection times documented for pharmacokinetic serum samples when comparing forms
- Incomplete and/or obliterated data was observed on study documents

During the inspection there were four discussion items:

- Some study subjects were consented with a version of the informed consent document that was not current at the time of enrollment.
- The original source record diary cards were missing in several subject files,
- Several visits were conducted outside of the study window
- Some subjects were documented as having the study drug infused at a rate faster that the protocol stated.

This inspection covered all study related records including the following: study protocols, protocol agreement and investigator's agreement (FDA 1572), review of all IRB approvals and communication, review of sponsor monitoring activities (including site monitoring visits and sponsor monitor communication and training), review of investigator's financial disclosure, review of informed consents, review of the accuracy of documentation and reporting of subject demographics, drug storage and accountability records, adverse events (including serious adverse events) and protocol deviations. All study subject case histories were audited. No refusals were encountered and no samples were collected.

The initial closeout discussion occurred on September 14, 2015; a one item, three part Inspectional Observations (FDA form 483) was issued to Dr. Dakhil. After close-out and leaving the firm, it was determined that a subjects' identification in the original FDA 483 and the number of occurrences in which specific procedures not conducted per protocol were incorrect.

The final closeout discussion occurred on October 8, 2015; an amended one item Inspectional Observations (FDA form 483) was issued to Dr. Dakhil with the following three part objection:

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

1) A change in the study protocol, Amendment 8 dated July 25, 2014 reduced the study drug administration on all cycles and all days, from (b) (4) (b) (4)) unless (b) (4) (b) (4) per the Protocol.
Subject (b) (6) signed the informed consent version 9, dated August 7, 2014 on January 7, 2015; the subject was randomized on January 14, 2015 to the investigational therapy regimen. Subject (b) (6) first date of treatment, cycle 1/day1 (C1D1) occurred on January 15, 2015. Subject (b) (6) was administered the study drug at (b) (4) which is equivalent to (b) (4) of the study drug on January 15, 2015 (C1D1) and on January 22, 2015 (C1D8) instead of the (b) (4) dose per Protocol, Amendment 8. The correct dosage per Protocol should have been (b) (4) (subject documented (b) (4) (b) (4) as dosed per Protocol during the remainder of the study visits).

2) The current study protocol, Amendment 8 dated July 25, 2014 and placed in use at the study site was not signed by the study Investigator, Dr. Shaker R. Dakhil until September 1, 2015. Between July 25, 2014 and September 1, 2015; (b) (4) of the (b) (4) total study site subjects were enrolled in the study and either completed or discontinued treatment.

3) Of the (b) (4) subjects enrolled at this site, there were 13 occurrences in which specific procedures were not conducted per protocol.

Dr. Dakhil was advised of his opportunity to respond to observations and promised a written response to the FDA 483.

Dr. Dakhil was also warned of his responsibility to comply with the FD&C Act and penalties were explained.

ADMINISTRATIVE DATA

Inspected firm:	Dakhil, Dr Shaker
Location:	818 N Emporia St Ste 403, Cancer Center of Kansas Wichita, KS 67214-3728
Phone:	316-262-4467
FAX:	(316)262-0706
Mailing address:	818 N Emporia St Ste 403, Cancer Center of Kansas

	Wichita, KS 67214-3728
Dates of inspection:	9/1/2015-9/3/2015 , 9/14/2015, 10/8/2015
Days in the facility:	5
Participants:	**Michael S Kopf, Investigator**

I presented my credentials, and issued a Form FDA 482, Notice of Inspection, to Dr. Shaker R. Dakhil on September 1, 2015. Credentials were also presented to Patricia L. Stone, RN/ Study Coordinator and (b) (6) . Daily discussions of findings were offered.

Following issuance of the Form FDA 482, I asked whether Dr. Dakhil was familiar with the Guidance for Industry 85 document Good Clinical Practice VICH GL9; he stated he was familiar with it.

On September 14, 2015, I presented my credentials, and issued a second Form FDA 482, Notice of Inspection, to Dr. Shaker R. Dakhil as he left the Country on September 2, 2015 and returned to the office September 14, 2015. Credentials were also presented to Patricia L. Stone, RN/ Study Coordinator

During the close out discussion on September 14, 2015, Ms. Stone signed an FDA 463a describing labs not collected per study protocol.

Dr. Dakhil was issued the FDA 483, Inspectional Observations on September 14, 2015.

On October 8, 2015, I presented my credentials, and issued a third Form FDA 482, Notice of Inspection, to Dr. Shaker R. Dakhil in order to issue an amended form FDA 483. Credentials were also presented to Patricia L. Stone, RN/ Study Coordinator. Dr. Dakhil was also issued an amended FDA 483, Inspectional Observations on October 8, 2015.The amended 483 corrected Observation 1, part 1's subject identification as (b) (6), the 483 issued on September 14, 2015 incorrectly identified subject (b) (6) as being overdosed. Also corrected was Observation 1, part 2 to clarify the observation. Observation 1, part 3 in which the original 483 stated "***there were 15 occurrences in which protocol specific procedures were not conducted per protocol***", the correct number of occurrences was changed to 13.

HISTORY

See the previous inspection report dated March 6-26, 2012 for a detailed history for Dr. Dakhil.

The Cancer Center of Kansas (CCK) continues to maintain a website at http://cancercenterofkansas.com.

A list of studies performed by Dr. Dakhil (including protocol number, title, sponsor and study dates) conducted since the previous inspection in 2012 was collected and is attached to this report as **Exhibit 1**.

The current inspection is this Clinical Investigators fourth inspection in the last six years.

The firms initial inspection was conducted July 20-22, 2009 and was classified VAI.

Since the 2009 inspection, an inspection in 2010 was classified NAI and the previous inspection in 2012 was classified VAI.

Dr. Dakhil's regular office hours are Monday thru Friday, 8:30-5:00.

All official inspectional correspondence should be addressed to:

Shaker R. Dakhil, M.D.
Cancer Center of Kansas
818 North Emporia, Suite 403
Wichita, Kansas 67214

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Shaker R. Dakhil, M.D., F.A.C.P., is the principle Clinical Investigator for this study; he is also President of the Cancer Center of Kansas. As such, he is responsible for ensuring all staff involved in research studies conducted at the firm are qualified and trained according to the study protocol and all applicable regulations are followed. He is responsible for administrative decisions regarding the studies conducted, subject recruitment, enrollment, and obtaining informed consents from subjects and conducting exams as required by the protocol. He is also responsible for reviewing all adverse events and their relationship to the investigational drug and ensuring all serious adverse events are adequately reported to the sponsor, IRB and FDA in accordance with regulations. Dr. Dakhil reported that he has been involved in clinical trials for over 30 years. Dr. Dakhil was present at the inspection initiation, was presented credentials and issued the FDA Form 482; Dr. Dakhil was also issued an second form FDA 482 and FDA form 483, Inspectional Observations on the initial close-out day due to a lapse in on sight inspection time. Dr. Dakhil was also issued a third form FDA 482 and FDA amended form 483, Inspectional Observations on the final close-out day due to errors on the initial FDA Form 483.

Patricia L. Stone, RN/ Study Coordinator, was my principle contact, provided information on her responsibilities, answering questions concerning the study and assisted in provided copies of requested documents. Ms. Stone was responsible for subject enrollment and obtaining informed consent, informing subjects of all aspects of the study, overseeing the investigational drug, communicating with the sponsor/monitor and IRB, ensuring all protocol deviations and serious adverse events are reported to the sponsor, IRB and FDA in accordance with the regulations. Ms. Stone reports directly to Dr. Dakhil.

COMPLAINTS

(b) (7)(D)

Dr. Dakhil reported no additional complaints.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483

OBSERVATION 1

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

Specifically,

4) A change in the study protocol, Amendment 8 dated July 25, 2014 reduced the study drug administration on all cycles and all days, from (b) (4) (b) (4) Subject (b) (6) signed the informed consent version 9, dated August 7, 2014 on January 7, 2015; the subject was randomized on January 14, 2015 to the investigational therapy regimen. Subject (b) (6) first date of treatment, cycle 1/day1 (C1D1) occurred on January 15, 2015. Subject (b) (6) was administered the study drug at (b) (4) which is equivalent to (b) (4) of the study drug on January 15, 2015 (C1D1) and on January 22, 2015 (C1D8) instead of the (b) (4) dose per Protocol, Amendment 8. The correct dosage per Protocol should have been (b) (4) (subject (b) (6) documented (b) (4) (as dosed per Protocol during the remainder of the study visits).

5) The current study protocol, Amendment 8 dated July 25, 2014 and placed in use at the study site was not signed by the study Investigator, Dr. Shaker R. Dakhil until September 1, 2015. Between July 25, 2014 and September 1, 2015; (b) (4) of the (b) (4) total study site subjects were enrolled in the study and either completed or discontinued treatment.

6) Of the (b) (4) subjects enrolled at this site, there were 13 occurrences in which specific procedures were not conducted per protocol; see table below.

For example, in five instances, central labs were not collected while subjects were actively receiving either the study or control drugs; in two instances, subjects failed to have central labs collected in follow-up.

Safety, Cardiac and Disease Assessments that were not completed or conducted outside of Protocol Requirements

Subject ID	Local Lab Not Collected	Central Lab Not Collected	Visit Out of Window	(b) (4)			
(b) (6)		Cycle 1 Day 8 Cycle 3 Day 15		Cycle 3 Day 1	Cycle 1 Day 15		
		Cycle 2 Day15 Cycle 6 Day 15 Week 8 Follow-up Week 60 Follow-up	Week 8 Follow-up Week 60 Follow-up				
						First Follow-up on Treatment	
	Screening	Cycle 5 Day 1					
							End of Treatment

Reference: 21 CFR 312.60

Supporting Evidence and Relevance:
See:
Exhibit 27, Orders and Lab Documents for all treatment cycles of Subject (b) (6). During the Cycle 1 Day 1 and Cycle 1 Day 8 visits, Exhibit 27, pages one and six show dosage of the study drug at (b) (4) (b) (4) which is equivalent to (b) (4) when (b) (4) (b) (4) which is also documented on the same pages.

Protocol Amendment 8, see **Exhibit 17**, reduced the study drug dosage from (b) (4) on all cycles, all days (b) (4) per the Protocol.

Exhibit 17, section 3.4, page 37 describes how to obtain the (b) (4) are included at the top portion of each cycle/days Scheduled Orders document (**see Exhibit 27**). So, (b) (4) the correct dosage per Protocol should have been (b) (4).

Exhibit 27, page nine shows laboratory results for reduced absolute (b) (4) (b) (4) resulting in the treatment (b) (4) for the Cycle 1 Day 15 visit.

Exhibit 28, Dosage Documents for all treatment cycles of Subject (b) (6), shows date and times the study drug was administered, pages 15 and 16 document administration of the study drug on Cycle 1, Days 8 and 1 respectively.

Exhibit 29, Serious Adverse Event Documents for Subject (b) (6), describes the study drug overdose, reported as a Serious Adverse Event, communication with the IRB and corrective action taken by the Study Investigator.

Exhibit 30, Protocol Amendment 8, Clinical Investigator Signature Page, shows the Study Investigator signed the signature page the day this inspection started, 367 days after the Protocol Amendment was approved. (b) (4) of the (b) (4) study subjects received treatment during the lapse in implementing Protocol Amendment 8 and the Study Investigator signing the Signature page.

Exhibit 31, Screen Shot of Subject (b) (6) Chart, for Cycle 1, Day 15 showing temperature not taken per Protocol (b) (4).

Exhibit 32, Screen Shot of Subject (b) (4), (b) (6) Chart for Week 8 follow-up, showing date of September 19, 2013 visit is one day out of visit window per Protocol requirements of (b) (4) (b) (4) from last (b) (4) which occurred July 17, 2013.

Exhibit 33, Screen Shot of Subject (b) (4), (b) (6) Chart for Week 60 follow-up, showing date of September 26, 2014 visit is two days out of visit window per Protocol requirements of (b) (4) (b) (4) from last (b) (4) which occurred July 17, 2013.

Exhibit 34, Radiology Report for Subject (b) (6)), shows exam ordered March 3, 2015, requesting (b) (4) for Week 8 into study which coincides with Cycle 3 Day 8. The Study Protocol requires (b) (4).

Exhibit 35, (b) (4) documents for Subject (b) (6)), showing (b) (4) conducted August 4, 2015, approximately 56 days since last dosing date of June 9, 2015. This subject's (b) (4) was required between (b) (4) weeks since the last treatment per protocol or between approximately (b) (4).

FDA Form 463a, signed by Ms. Stone on September 14, 2015 documenting local and central lab samples not collected for subjects (b) (6)

Discussion with Management:
I discussed protocol requirements and compliance with Dr. Dakhil, Ms. Stone and Ms. (b) (6) .

Ms. Stone stated that all staff had been properly trained on Amendment 8 of the Study Protocol, and at the time of approval the site was currently treating Subject (b) (6) with the study drug. Dosage changes were made to Subject (b) (6) treatment which are documented in the subjects file. Ms. Stone further explained that a request to update the firm's electronic database with the dosage changes was submitted but the database was not updated. Subject (b) (6), was consented approximately two years later and was the first subject to be randomized to the study drug since Subject (b) (6). As the electronic database was not updated with current dosages and two years had passed, the nursing staff, under the Study Coordinator's oversight, dosed according to an outdated Visit Guidance Document developed per the Study Protocol; see **Exhibit 36,** Visit Guidance Document. No additional dosage errors have occurred to date.

During the Inspection close-out, Dr. Dakhil notified me that the Study Coordinator responsible for the dosing error no longer works at the site as a result of the dosing error which Dr. Dakhil stated was a patient safety concern, her last day was September 11, 2015

Regarding item two, Ms. Stone stated that a signature sheet was not provided to them when Amendment 8 was released and staff oversight was the reason a signature page was not requested. Ms. Stone provided training documentation on the Amendment 8 Protocol documenting the Clinical Investigators and staff knowledge of changes.

Regarding item three, Ms. Stone stated that oversights to protocol requirements were unacceptable and that they will review all instances to determine why these occurrences happened. Ms. Stone also presented a document developed during the current inspection titled "Protocol Amendment Checklist", attached as **Exhibit 37** and explained how this document would be incorporated in each study to be used as a tool in documenting Protocol changes in the firms electronic and paper records.

During the initial close out discussion, Dr. Dakhil stated that the sites problems were a combination of the length of the study with few study subjects enrolled and staff oversight.

At the initial close-out of the inspection, I met with Shaker R. Dakhil, M.D., F.A.C.P., Patricia L. Stone, RN/ Study Coordinator, and (b) (6). A one observation, three item FDA Form 483 was issued to Dr. Dakhil; following issuance, a review and discussion occurred.

At the final close-out of the inspection, I met with Shaker R. Dakhil, M.D., F.A.C.P., Patricia L. Stone, RN/ Study Coordinator, (b) (6). A one observation, three item, amended FDA Form 483 was issued to Dr. Dakhil; following issuance, a review and discussion occurred.

REFUSALS
No refusals were encountered.

GENERAL DISCUSSION WITH MANAGEMENT
The initial closeout discussion occurred on September 14, 2015 at approximately 3:30pm.

The following individuals were present for the closing meeting:
Shaker R. Dakhil, M.D., F.A.C.P., Clinical Investigator
Patricia L. Stone, RN/ Study Coordinator
(b) (6)
Michael S. Kopf, Investigator

Patricia L. Stone, RN/ Study Coordinator reviewed and signed the form FDA 463a Affidavit, explaining that labs were not collected during some of the study subjects visits.

Dr. Dakhil was issued the FDA form 483 Inspectional observations and it was discussed. Remarks are included in the Objectionable Conditions and Management's Response portion of this report.

Dr. Dakhil was read the following statement, “You have the opportunity to respond to my observations. Written response must be with-in 15 business days. Your response will be considered before and if a Warning Letter is issued.” Dr. Dakhil indicated that a written response would be submitted.

I instructed Dr. Dakhil to submit the written response to the Kansas City District Office listed on the FDA form 483 and provided him the fax and e-mail address.

Dr. Dakhil was warned of his responsibility to comply with the FD&C Act and penalties were explained.

I told Dr. Dakhil that the inspection report would be forwarded to headquarters for review and final classification. I thanked everyone for their cooperation and concluded the inspection.

The final closeout discussion occurred on October 8, 2015 at approximately 12:47 pm.

The following individuals were present for the closing meeting:
Shaker R. Dakhil, M.D., F.A.C.P., Clinical Investigator
Patricia L. Stone, RN/ Study Coordinator
Michael S. Kopf, Investigator

Dr. Dakhil was issued the amended FDA form 483 Inspectional observations and it was discussed.

Dr. Dakhil was read the following statement, "You have the opportunity to respond to my observations. Written response must be with-in 15 business days. Your response will be considered before and if a Warning Letter is issued." Dr. Dakhil indicated that a written response had been submitted.

Dr. Dakhil was warned of his responsibility to comply with the FD&C Act and penalties were explained.

I thanked everyone for their cooperation and concluded the inspection.

SAMPLES COLLECTED
No samples were collected during the investigation.

ATTACHMENTS
1 Issued 483
2 Amendment 1
3 Assignment Memo 11551437, 7 pages
4 FDA 482 issued to Dr. Shaker R. Dakhil on 9_1_2015, 3 pages
5 FDA 482 issued to Dr. Shaker R. Dakhil on 9_14_2015, 3 pages
6 FDA 482 10_8_2015, 3 pages
7 FDA 463a signed by Patricia L. Stone, Study Coordinator on 9_14_2015, 1 page

EXHIBITS COLLECTED

1 Dr. Dakhil List of Studies Since 2012, 17 pages
2 FDA 1572 3 15 11, 2 pages
3 FDA 1572 9 26 11, 3 pages
4 FDA 1572 11 16 11, 4 pages
5 FDA 1572 2 14 12, 5 pages
6 FDA 1572 5 16 12, 4 pages
7 FDA 1572 8 20 12, 6 pages
8 FDA 1572 10 8 12, 3 pages
9 FDA 1572 3 18 13, 4 pages
10 FDA 1572 10 31 13, 8 pages
11 FDA 1572 5 6 14, 8 pages
12 FDA 1572 3 26 15, 6 pages
13 FDA 1572 6 12 15, 8 pages
14 Protocol Amendment 4, 71 pages
15 Protocol Amendment 5, 73 pages
16 Protocol Amendment 6, 74 pages
17 Protocol Amendment 8, 84 pages
18 IRB Rooster, 3 pages
19 Informed Consent 11 17 11, 20 pages
20 Informed Consent Version 4, 20 pages
21 Informed Consent Version 6, 22 pages
22 Informed Consent Version 7, 21 pages
23 Informed Consent Version 8, 21 pages
24 Informed Consent Version 9, 21 pages
25 Study Subject Visit Log, 2 pages
26 Monitor Sign-in Log, 2 pages
27 (b) (6) Orders and Labs, 51 pages
28 (b) (6) Dosage Docs, 16 pages
29 Subject (b) (6) Significant Adverse Event Records, 22 pages
30 Protocol Amendment 9 Investigator Statement and Signature Page, 2 pages
31 Subject (b) (6) Visit Screen Shot, 1 page
32 Subject (b) (6) Week 8 Follow-up Visit Screen Shot, 81 pages
33 Subject (b) (6) Week 60 Follow-up Visit Screen Shot, 81 pages
34 Subject (b) (6) Radiology Report, 4 pages
35 Subject (b) (6) , 2 pages
36 Visit Guidance Tool, 2 pages
37 Protocol Amendment Checklist, 3 pages

10/8/2015

X Michael S Kopf

Michael S Kopf
Investigator
Signed by: Michael S. Kopf -S