

Khosla, Ranjan PH/US

From: Khosla, Ranjan PH/US
Date: Thursday, December 05, 2002 10:15 AM
To: Armas, Eileen PH/US
Cc: Hickey, Colleen M. PH/US; Marini, Gerard PH/US
Subject: FW: KETEK ADULT NDA 21-144: FDA CONTACT REPORT, OCTOBER 24, 2002 - FDA FORM 483 FOR KIRKMAN-CAMPBELL SITE

Importance: Low

Dear Eileen,

It was a pleasure speaking to you today. I am forwarding the email requested by you.

Thanks and regards

Ranjan Khosla, MBBS, MD, CQA
 Senior GCP QA Specialist
 GCP NA Operations Center
 Phone: 908 541 5476
 Fax 908 231 3725

-----Original Message-----

From: Khosla, Ranjan PH/US
Sent: Tuesday, October 29, 2002 11:25 AM
To: Nusrat, Roomi PH/US
Cc: Grethe, Nadine I. PH/US; Shoemaker, Mike PH/US; Grethe, Nadine I. PH/US; Marini, Gerard PH/US; Leroy, Bruno PH/US; Deshpande, Sanjay PH/US/EXT
Subject: RE: KETEK ADULT NDA 21-144: FDA CONTACT REPORT, OCTOBER 24, 2002 - FDA FORM 483 FOR KIRKMAN-CAMPBELL SITE
Importance: High

Dear Roomi,

Thanks for your email. The following 17 sites had enrolled 100 or more subjects in the TREAT Study:

Site Number	PIER'S NAME	PIE'S NAME	Subjects Enrolled	Audited
1129	Anne	Kirkman-Campbell	407	Yes
96	Carl	Lang	251	Yes
1057	Egisto	Salerno	214	
403	Salim	Bakali	177	
83	Keith	Pierce	175	Yes
1622	William	Terpstra	168	
965	Rashid	Khan	168	
249	Stevan	Smallow	162	
1228	Susan	Blanchard	136	Yes
1683	Robert	Burton	131	
469	Vincent	Sghiatti	123	
606	Romulo	Tengco	121	Yes
430	Linda	Freilich	118	
759	Manjeet	Kaur Achreja	116	
479	Michael	Milstein	110	
211	James	Shoemaker	109	Yes
498	Jorge	Guerrero	105	

The Audit Plan for this study required, ten site audits, one monitoring system audit [at PPD] and one CSR audit. In addition

one FDA Inspection Preparation audit was conducted at site number 1129. The audit sites were selected based upon the number of subjects enrolled and/or significant GCP issues identified during monitoring. The following sites were audited: 1129 Kirkman-Campbell, Anne, p02411 site 1129e.pdf FMR3647 (Ketek) Aventis - Confidential

Andrew Garner, MD

This site was audited on March 27-28, 2002. The site making changes to the "payment for participation" section of the IRB approved ICF; the site throwing away the ICFs for subjects 001 to 017; in several instances the person obtaining consent dating the ICF several days after the subject and sometimes earlier than the subject; use of photocopy of the PI's signature; and other problems pertaining to informed consent and protocol adherence were the significant issues that required corrective action.

Anne Kirkman-Campbell, MD

This site was audited on Jan. 17-18, 2002. The Study Coordinator entering the date for the PI and/or the subjects on the ICFs; the PI entering the date for the person obtaining the consent and/or the subjects; partial compliance to the CFR 312.62 requirement that the case history of each individual shall document that informed consent was obtained prior to participation in the study; and other problems pertaining to informed consent were significant issues that required corrective action.

Carl Lang, MD

This site was audited on Feb. 19-20, 2002. The Principal Investigator (PI) entered the date for some of the subjects on the ICF; the PI had obtained consent from all the subjects enrolled and dated his signatures on the ICF several day(s) after the subjects in some instances; non compliance to the CFR 312.62 requirement that the case history of each individual shall document that informed consent was obtained prior to participation in the study; and other problems pertaining to informed consent and protocol adherence were significant issues that required corrective action.

James Shoemaker, MD

This site was audited on April 8-9, 2002. The person obtaining consent dating the Informed Consent Forms (ICFs) for the Principal Investigator (PI); subjects 027 and 036 not entering the date on the ICFs; no documentation available to verify that the site had screened the Women of Child Bearing Potential (WOCBP) subjects for pregnancy before enrolling them in the study; and other problems pertaining to informed consent and protocol adherence were significant issues that required corrective action.

Keith Pierce, MD

This site was audited on Dec. 13-14, 2001. The enrollment of Subject P-G 066 before obtaining informed consent; non compliance to the CFR 312.62 requirement that the case history of each individual shall document that informed consent was obtained prior to participation in the study; the person conducting the informed consent discussion not signing the informed consent form in several instances; and other problems pertaining to informed consent were significant issues that required corrective action.

Romulo Tengco, MD

This site was audited on Mar. 11-12, 2002. The Principal Investigator (PI) entering the date for some of the subjects on the ICF; the subject 013 not signing or dating the ICF [the subject only printed name in signature section]; and other problems pertaining to informed consent were significant issues that required corrective action.

Samuel Stone, MD

This site was audited on Feb. 7-8, 2002. At this site there were several problems pertaining to informed consent that were significant issues that required corrective action. One subject (010) has not signed the informed consent, and another subject (024) was randomized before obtaining consent and this subject had subsequently refused to participate in the study. The Clinic Nurse, Annette McDaniel who obtained consent from all subjects randomized the subjects in the IVRS while the subjects were reading the consent and had not yet signed the consent. She also entered the date for the PI on the ICFs.

Susan Blanchard, MD

This site was audited on Jan. 15-16, 2002. The Principal Investigator (PI) entering the date for the subjects on the Informed Consent Forms; the randomization of subject 047 in the IVRS while the subject was reading the consent and had not yet signed the consent; no proper documentation available to verify that the site had screened the Women of Child Bearing Potential (WOCBP) subjects for pregnancy before enrolling them in the study; and other problems pertaining to informed consent and protocol adherence were significant issues that required corrective action.

Jy Weiss, MD

This site was audited on April 4-5, 2002. The site making changes to the "payment for participation" section of the IRB approved ICF; the person obtaining consent dating the ICF several days after the subject; the person obtaining

consent dating the ICF for the subject; and other problems pertaining to informed consent and protocol adherence were significant issues that required corrective action.

1129 Kirkman-Campbell, Anne p02412
Site 1129e.pdf

HMR3647 (Ketek)
Aventis - Confidential

Luis Reznick, MD

This site was audited on February 18, 2002 by Cheryl Curet and Gerard Marini.

For the eleven of thirteen audits that have been closed in QAAD, the audit close out memo listing all significant audit findings with descriptions and recommendations, responses and response categories was sent electronically to the following responsible persons in all cases:

- Nadine Grethe, Study Manager
- Roomi Nusrat, Global Clinical Director
- Burno Leroy, Global Project Leader
- Gerard Marini, Head of GCP North American Operations Center

I am resending the eleven audit close out memos [attached to this email] for your reference.

HMR3647A/ 3014:
AUDIT CLOSE-OU...AUDIT CLOSE-OU...AUDIT CLOSE-OU...AUDIT CLOSE-OU...AUDIT CLOSE-OU...AUDIT CLOSE-OU...AUDIT CLOSE-OU...

HMR3647A/ 3014: HMR3647A/ 3014: HMR3647A/ 3014: HMR3647A/ 3014:
AUDIT CLOSE-OU...AUDIT CLOSE-OU...AUDIT CLOSE-OU...AUDIT CLOSE-OU...

Thanks and regards

Ranjan Khosla, MBBS, MD, CQA
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Phone: 908 541 5476
908 231 3725

-----Original Message-----

From: Nusrat, Roomi PH/US
Sent: Tuesday, October 29, 2002 8:05 AM
To: Grethe, Nadine I. PH/US; Shoemaker, Mike PH/US; Khosla, Ranjan PH/US; Grethe, Nadine I. PH/US
Subject: FW: KETEK ADULT NDA 21-144: FDA CONTACT REPORT, OCTOBER 24, 2002 - FDA FORM 483 FOR KIRKMAN-CAMPBELL SITE
Importance: High

Dear All:

For the sake of comparison, how many sites enrolled over 100 subjects and did any have similar audit problems? Are there risk issues with other high enrollers?

Thank you.
Roomi

-----Original Message-----

From: Shoemaker, Mike PH/US
Sent: Friday, October 25, 2002 3:23 PM
To: Bell, Larry PH/US; Rajfer, Sol PH/US
Cc: Caffe, Steve PH/US; Quigley, Mark PH/US; Bryers, Paul PH/US; Nusrat, Roomi PH/US; Leroy, Bruno PH/US; Grethe, Nadine I. PH/US; Frau, Lourdes PH/US; Crowley, Carol J. PH/US; Khosla, Ranjan PH/US; Aschenbrenner, Michael PH/US; Marini, Gerard PH/US
Subject: RE: KETEK ADULT NDA 21-144: FDA CONTACT REPORT, OCTOBER 24, 2002 - FDA FORM 483 FOR KIRKMAN-CAMPBELL SITE
Importance: High

We are pursuing follow up with the site to assist in generating a response to the 483 observations. A conference call with Dr. Campbell is scheduled for this afternoon.

I have provided background addressing pertinent questions below:

Was monitoring/auditing executed per plan?

QAQC_1129021205

A total of 9376 (38%) of 24434 patients were monitored at 942 (50%) of the 1872 sites that enrolled at least one patient. The target of 25% of the first 2000 patients was exceeded at 29%. Per plan the monitoring rate was to be reduced to 5% if there were no observations of unreported AESIs. The sample rate was not reduced following the first 2000 patients. A total of three monitoring visits were performed at Dr. Campbell's site covering 109 of the 407 patients enrolled. Two of these were performed post enrollment as audit follow up. Ten investigator site audits were planned and executed targeting high enrollers. In addition, a system audit of PPD was performed to assess monitoring timing and frequency relative to the monitoring plan. All ten site audits were conducted during study conduct. Dr. Campbell's site was included.

Were deficiencies cited in 483 known?

29 November 2001, first monitoring visit conducted. Three of 65 patients enrolled were monitored post visit 2. ICFs for all enrolled patients were reviewed. Dating deficiency for investigator signature noted. Corrective action recommended and implemented.

17-18 January 2002, GCP QA site audit conducted. 327 patients enrolled at that time. ICF dating practices for subjects, SAE/AESI reporting and enrollment of PI staff were noted as deficiencies. Escalated monitoring and retraining recommended and implemented.

18-21 February 2002, second monitoring visit conducted. Additional 36 of 407 patients enrolled were monitored. Deficiencies with diagnosis documentation, randomization clustering, monitor concern with similarities in lab values across patient were noted and reported to Aventis on 27 February.

1-5 April, 2002 third monitoring visit conducted. Additional 70 patients were monitored. New deficiencies noted included enrolling patients with PCN/ERY allergy, new antibiotic therapy noted in some patients and DCF generated.

8-9 October 2002 investigator site inspection prep visit performed.

Was appropriate action taken?

Intervention to stop enrollment was not triggered by the nature of observations in the first monitoring visit or the January audit. Enrollment for the protocol was closed 29 January 2002 prior to the February monitoring visit.

Following notification of February monitoring findings, deficiencies noted were addressed directly to the investigator site and a description and explanation was documented in the investigator study file and/or chart. Deficiencies involving protocol violation were notified to the IRB. The lab values were evaluated internally by the study team and concluded there were no unexpected patterns detected in the values reported.

Efforts have been focused to make the deficiencies transparent at the site and demonstrate diligence in implementing corrective actions. Though numerous deficiencies were found, no known deficiencies were interpreted to conclude that the patients did not exist, were not consented, did not receive drug and were not evaluated per protocol with the exception of noted protocol violations. As such, no action was taken to censor data in the report.

Mike

-----Original Message-----

From: Bryers, Paul PH/US
Sent: Thursday, October 24, 2002 6:01 PM
To: Leroy, Bruno PH/US; Pakulski, John PH/US; Smith, Michael P. PH/US; Ortiz, Alis PH/US; Lee, Monica PH/US; Thien Aubert, Huguette PH/FR; Montay, Guy PH/FR; Jenkins, Stephen PH/US/EXT; Yee, YingCheung PH/US; Bryskier, Andre PH/FR; Bhargava, Vijay PH/US; Shi, Jun PH/US; Vacheron, Francoise PH/FR; Nusrat, Roomi PH/US; Mauriello, Diane PH/US/EXT; Stager, William PH/US; Goedde, Michael PH/US; Rangaraju, Manickam PH/FR; McFeeters, Glenda PH/US/EXT; Sharma, Kristen PH/US; Dhanani, Zahra PH/US; Patel, Sima PH/US; Bielen, Stanley PH/US; Vigdorth, Ellen, Quintiles; Nickel, Wolf-Ulrich PH/US; Pitcher, Julie PH/US; Grethe, Nadine I. PH/US; Staropoli, Antonia PH/US; Villa, Raul PH/US; Novick, Bill PH/US/EXT; Jenkins, Stephen PH/US/EXT
Cc: Bell, Larry PH/US; Caffè, Steve PH/US; Scheeren, Joseph PH/US; Quigley, Mark PH/US; Shoemaker, Mike PH/US; Aschenbrenner, Michael PH/US; Frau, Lourdes PH/US; Lagarenne, Paul PH/US; Boyd, James PH/US; Setescak, Linda L. PH/US; Grelet, Danielle PH/FR; Desesquelle, Christian PH/FR; Gallay, Michel PH/FR; Shah, Dhiren PH/US; Aclouque, Marc