

Bioresearch Monitoring Inspection Results Memorandum - TachoSil, March 17, 2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE March 17, 2010
FROM Lillian Ortega, Bioresearch Monitoring, HFM-664
Division of Inspections and Surveillance
Office of Compliance and Biologics Quality
THROUGH Patricia Holobaugh, Bioresearch Monitoring Branch Chief, HFM-664
TO Natalya Ananyeva, HFM-475, Chairperson
Kimberly Lindsey, HFM-475, Clinical Reviewer
Jie Hie, HFM-380, RPM
SUBJECT Bioresearch Monitoring Inspection Results
Sponsor: Nycomed Danmark Aps
Product: Fibrin Sealant Patch
STN: 125351/0

SUMMARY STATEMENT

The results of Bioresearch Monitoring inspections of protocols **TC-023-IM** and **---(b)(4)---** at five (5) foreign clinical investigator sites did not reveal problems that impact the data submitted in the application.

The results of the Bioresearch Monitoring inspection of protocol **TC-019-IN** confirmed the sponsor's audit findings and also revealed additional violations that impact the data submitted in the application including informed consent, enrollment and randomization, investigational drug accountability and protocol specific training records.

BACKGROUND

There were six (6) foreign clinical investigator (CI) inspections performed in support of the Biologics License Application (BLA) and were conducted in accordance with FDA's Compliance Program Guidance manual 7348.811, Inspection Program for Clinical Investigators. The inspections represented 44% of the total subjects enrolled in **TC-023-IM**, 35% of the total subjects enrolled in **---(b)(4)---** and 69% of the total subjects enrolled in **TC-019-IN**. The inspection assignment included specific questions in reference to the study protocol and verification of the study data on safety and efficacy endpoints submitted by the sponsor in the BLA.

The review committee requested an inspection of site TC019-IN-GBR013-01. The sponsor placed study SiteTC019-IN-GBR013-01 on suspension in January 2007 and

notified the site in July 2007 that the study was permanently discontinued. The sponsor halted the study due to the site's inability to adequately comply with Good Clinical Practices, such as delayed reporting of a fatal serious adverse event (SAE) and delayed verification of source data.

Site#	Location	Number of Subjects Enrolled	Form FDA 483 Issued?	Inspection Final Classification
TC-019-IN-GBR013-01	Birmingham, UK	11	Y	OAI
----- (b)(4) -----	Vienna, Austria	42	Y	VAI
----- (b)(4) -----	Odense, Denmark	35	Y	VAI
----- (b)(4) -----	Freiburg, Germany	27	Y	VAI
TC023IM-DEU038	Leipzig, Germany	26	N	NAI
TC023IM-DEU039	Munich, Germany	26	Y	VAI

NAI – No Action Indicated ; VAI – Voluntary Action Indicated ; OAI – Official Action Indicated ; EIR – Establishment Inspection Report

Inspected Protocols: TC-019-IN, --- (b)(4) --- and TC-023-IM

STUDY TITLES:

- A prospective, multi-centre, phase III-b study of TachoSil® in pediatric patients scheduled for resection of the liver with or without segmental liver transplantation. TC-019-IN Version 1.0
- ----- (b)(4) -----

- A randomized open label, parallel-group, multi-center trial to compare the efficacy and safety of Tachosil versus standard haemostatic treatment in cardiovascular surgery. TC-023-IM Version 1.0

FINANCIAL DISCLOSURE: The Clinical Investigator Compliance Program directs the FDA investigator to ask the clinical investigator if and when he/she disclosed information about his/her financial interests to the sponsor and/or interests of any subinvestigators, spouse(s) and dependent children, and if and when the information was updated. The inspections were conducted in accordance with the compliance program.

SPONSOR/MONITOR ISSUES: The data recorded at the site in the source document is not reflected in the data submitted by the sponsor in the BLA supplement. The inspection revealed the Informed Consent Document for subject No. - (b)(6) - from **Site TC-019IN-GBR013-01** was signed and dated May 6, 2006, the day after surgery was performed. The BLA Disposition data indicates subject No. - (b)(6) - from **Site TC-019IN-GBR013-01** was consented the day of surgery May 05, 2006.

The BLA Disposition data indicates subject No. - (b)(6) - from **Site - (b)(4) -IM-0006** was randomized even though BLA Inclusion-Exclusion data indicates the subject met an exclusionary event. The BLA data submitted by the sponsor included the adverse event

experienced by the subject but did not report the protocol deviation. The monitoring report on site did indicate the clinical investigator did inform the monitor of the protocol violation.

NOTEWORTHY INSPECTIONAL FINDINGS

TC-023IM-DEU039: The clinical investigator administered at least 16 Tachosil sponges to at least three (3) patients not screened for eligibility, properly consented, or otherwise enrolled in the study. The Site and Staff Delegation log did not list the names of several surgeons who evaluated subjects' bleeding and hemostasis and also applied the study drug; the same surgeons had no documentation showing protocol-specific training.

-(b)(4)-IM-0001: Nine (9) of 19 subjects reviewed had no protocol required source documentation for the intensity and/or presence of ----(b)(4)----. Nine (9) subjects reviewed did not have protocol required chest x-rays on the day of or the day following chest drain removal or upon hospital discharge, and/or clinical laboratory tests during screening or upon hospital discharge.

-(b)(4)-IM-0003: The clinical investigator (CI) reported an SAE (death) to the sponsor 6 days after the subject died, not within 24 hours as required by the protocol; the CI reported the death during a study monitor visit. Nine (9) subjects reviewed had incomplete informed consent documents; four subjects were consented with the wrong version document which did not include an additional risk statement regarding developing antibodies to the active substance contained within the investigational drug. Five (5) subjects had no clinical laboratory testing conducted during screening and/or upon discharge.

-(b)(4)-IM-0006: The clinical investigator did not report two (2) AEs to the sponsor until after the study monitor noted the events during a routine visit that took place several months after AE occurrence. The CI randomized one subject to the standard surgical treatment group, but the subject met the protocol exclusion criteria. At least 15 subjects did not have protocol-required chest X-rays and/or clinical laboratory tests on the day of, or the day following chest drain removal, or upon hospital discharge.

TC-019-IN-GBR013-01: The clinical investigator did not identify, document or report at least two (2) SAEs including post procedural hemorrhage and multiple organ failure that led to death until a monitor visit that took place approximately four (4) months after the events occurred. Three (3) subjects were randomized and treated with Tachosil, but those subjects met exclusion criteria for enrollment. The CI did not obtain informed consent from at least two (2) subjects prior to study drug administration; the site also consented another potential subject during the sponsor-mandated study suspension period. Seven (7) of 11 subjects reviewed had no source documentation to support data recorded in the "Application of Tachosil" and Haemostatic Efficacy" section of the case report form. According to the study site coordinator, she "completed the CRF after the subjects had surgery (could be anywhere from 2-3 days later)" and she would "ask the surgeons whether or not the subjects achieved hemostasis and record the verbal response on the CRF". The "Drug Accountability Per Site" form showed five (5) packs of Tachosil sponges were administered to patients not enrolled in the study. A potential subject was consented April 2007 after the study was put on hold; the consent was signed by a physician not listed on the Site Participation Log or Site Training log.

BIMO ADMINISTRATIVE FOLLOW-UP

Informational letters were/will be issued to the clinical investigators at all inspected sites. Please contact me at 301-827-6335 if you have any questions about this memorandum or any aspects of Bioresearch Monitoring.

Lillian Ortega
Consumer Safety Officer