



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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MEMORANDUM

**DATE:** March 3, 2010 (updated on March 31, 2010 after the final pediatric review committee meeting for review of the pediatric deferral plan)

**FROM:** Kimberly Lindsey, MD, Medical Officer, Clinical Review Branch,  
Division of Hematology, OBRR

**SUBJECT:** STN 125351.00 TachoSil hemostatic pad final clinical review memo

**SPONSOR:** Nycomed Danmark ApS (Nycomed)

**TO:** Nisha Jain, MD, Acting Chief, Clinical Review Branch

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**Title and General Information:**

**BLA/NDA #:** STN 125351

**Related IND #(s):** Not applicable

**Reviewer Name and Division:** Kimberly Lindsey, MD, CRB/DH

**Submission Received by FDA:** June 5, 2009

**PDUFA completion date:** April 5, 2010

**Date of submission Final review completion:** March 3, 2010

**Product:**

**Proper Name:** TachoSil

**Product Formulation(s) Including Adjuvants, Preservatives, etc.:**  
combination product collagen pad coated with human fibrinogen and thrombin

**Applicant:** Nycomed Danmark ApS (Nycomed)

**Pharmacologic Category:** topical hemostatic agent (or local hemostatics)

**Proposed Indication(s):** TachoSil is indicated as an adjunct to hemostasis in cardiovascular surgery

**Proposed Populations(s):** for hemostatic indication, adult and pediatric populations

**Dosage Form(s) and Route(s) of Administration:** topical

**Important Related Products:** thrombin, fibrinogen and collagen

**Reviewer recommendation:**

*Based on the clinical information submitted to the application, approval is recommended. Additional information regarding immunogenicity, viral sero-conversion and adverse events will be obtained from a recently reviewed IND study (IND (b)(4)) in which TachoSil is being evaluated in ----(b)(4)----- surgery. This study includes adults and pediatric patients. With FDA input, this adequate and well controlled study will gather information that would be requested as part of additional safety information. The additional safety information obtained from the IND study is not deemed sufficient to preclude approval of this biologics license application.*

***Note: Throughout this clinical memorandum, reviewer comments are noted in italicized type.***

**Executive Summary:**

The TachoSil patch is a “ready to use” degradable surgical patch that has been developed for topical use as an adjunctive treatment for achieving hemostasis -----(b)(4)-----. The patch consists of a dry (b)(4) collagen carrier material made of equine tendons. The collagen patch is coated with a fixed combination of human fibrinogen and human thrombin. The components of TachoSil are degraded and phagocytosed approximately - (b)(4)- months after application.

TachoSil was first approved by the European Commission on June 8, 2004 for “supportive treatment in surgery for improvement of hemostasis where standard techniques are insufficient”. In February 2009, the European Commission approved TachoSil for supportive” treatment in surgery for improvement of hemostasis, to promote tissue sealing, and for suture support in vascular surgery where standard techniques are insufficient”. This Biologics License Application (BLA) represents the first regulatory submission for marketing approval for this product in the United States

The clinical development plan consists of 11 clinical studies in which the TachoSil patch was evaluated in a variety of surgical subspecialties. None of these studies was conducted under US Investigational New Drug (IND) applications. The data from this clinical program was intended to support the following indications:

- 1). TachoSil is indicated as an adjunct to hemostasis in cardiovascular surgery
- 2). -----(b)(4)-----
- 3). -----(b)(4)-----

**Note: -----(b)(4)-----  
subsequent to the FDA issued information request letter dated 12/1/2009. Therefore, this final clinical review memo only takes into consideration information intended to support approval for the hemostatic indication sought by the sponsor.**

Although Nycomed intends to produce the TachoSil patch, the patch will be distributed

by Baxter Healthcare upon US approval.

The sponsor intends that the clinical data submitted in this BLA support the approval of TachoSil for the following indications:

- TachoSil is indicated as an adjunct to hemostasis in cardiovascular surgery;  
------(b)(4)-----

One of the 11 clinical studies is intended to provide pivotal data to this BLA for the hemostatic indication in cardiovascular surgery: TC-023 IM :

TC-023-IM was a Phase 3, multicenter, open-label, randomized, controlled trial comparing TachoSil and standard hemostatic fleece to demonstrate efficacy and safety of TachoSil versus standard surgical treatment of hemorrhage in cardiovascular surgery. Randomization was done following the planned surgical procedure and attainment of primary hemostasis. Only patients with residual hemorrhage from the heart muscle, the pericardium, a major vessel or vascular bed requiring supportive hemostatic treatment were eligible for randomization. The ITT dataset consisted of all randomized subjects. The primary and secondary efficacy endpoints were the proportion of patients with hemostasis at 3 minutes, and the proportion of patients with hemostasis at 6 minutes respectively.

Overall for the pivotal study TC 023 IM the sponsor met their pre-specified efficacy endpoints. No major safety concerns were identified in for hemostasis indication.

Studies -----(b)(4)----- are all intended to be supportive studies for the hemostatic indication. These clinical studies were multicenter, open-label, randomized, controlled, parallel-group studies designed to compare the efficacy and safety of TachoSil with comparator treatment as secondary management of intraoperative hemorrhage after primary surgical hemostatic procedures in adult patients undergoing -----(b)(4)----- The comparator treatments used in these studies were the -----(b)(4)----- . The integrated analysis for all four hemostasis studies included a total of 270 patients who received TachoSil and 274 patients in Standard group. TachoSil proved to be more effective than standard or control methods to achieve hemostasis in all studies. The hemostatic effect of TachoSil was larger in the -----(b)(4)----- because the standard group had a longer time to hemostasis. Both the standard and TachoSil groups had similar adverse event profiles.

**Product development rationale:**

The sponsor states that TachoSil was developed to meet various surgical needs. Hemostasis -----(b)(4)----- are indeed critical elements of surgical technique. Hemorrhage and -----(b)(4)----- are not infrequently difficult to control by conventional surgical techniques such as suturing or electrocoagulation. Sometimes the surgical techniques are traumatic to tissue and use of

traditional methods to achieve hemostasis are impractical due to inaccessibility to the bleeding area.

----- (b)(4) -----  
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**The sponsor intends that the clinical data submitted in this BLA support the approval of TachoSil for the following indications:**

- **TachoSil is indicated as an adjunct to hemostasis in cardiovascular surgery;**  
----- (b)(4) -----

**Background:**

TachoSil (also referred to as TachoSil and formerly named TachoComb S) is intended to be marketed in the United States as a ready-to-use, degradable fibrin sealant collagen patch for topical use to support intraoperative hemostasis and ----(b)(4)----- . The TachoSil patch is coated with human fibrinogen and human thrombin.

TachoSil was initially developed with the name of TachoComb S, a result of further development of the aprotinin containing predecessor products, TachoComb and TachoComb H, which were marketed in Europe at the time of obtaining marketing authorization (June 2004) for TachoComb S. The European authorities required a change of the name to avoid any potential confusion between products during the market launch, and the brand name of TachoSil was accepted instead. As a result, the product name of TachoComb S appears in the initial studies. TachoComb S is identical to TachoSil. It should be noted that the abbreviation TC-S is used for TachoSil in some study reports included in the BLA.

TachoSil was first approved by the European Commission on June 8, 2004 for supportive treatment in surgery for improvement of hemostasis where standard techniques are insufficient. In February 2009, the European Commission approved TachoSil for supportive treatment in surgery for improvement of hemostasis, to promote tissue sealing, and for suture support in vascular surgery where standard techniques are insufficient. This Biologics License Application (BLA) represents the first regulatory submission for marketing approval for this product in the United States.

According to the sponsor, when TachoSil is in contact with fluid (e.g. blood, other body fluids, and normal saline,) the coagulation factors in the patch dissolve and the resultant fibrinogen-thrombin reaction initiates the last step of the coagulation cascade. Fibrinogen is converted by the action of thrombin into fibrin monomers, which then polymerize into fibrin strands. The fibrin strands form a viscous and elastic clot, which facilitates adherence and attachment of the patch to the wound surface.

In order to work optimally, the patch must be lightly pressed against the tissue for

approximately 3 minutes. The patch comes in a variety of sizes and may be cut to the desired size to cover the wound surface.

**Regulatory history:**

FDA and Nycomed have held multiple pre BLA meetings associated with the development of TachoSil.

Nycomed submitted briefing packages for meetings with FDA on the following dates:

**September 21, 2004-** Primary objective of the Type B meeting was to gain concurrence with the Agency that the TachoSil development program was sufficiently complete to support a BLA submission. In addition, Nycomed shared -----(b)(4)-----  
----- of human fibrinogen and human thrombin for the manufacture of TachoSil.

FDA recommended to Nycomed 1.) “that manufacture of the product for U.S. market must be separated from product for Europe market through means of physical separation and/or cleaning validation” and 2.) provided preliminary recommendations for qualification of slaughter-houses to include “the details regarding sanitary conditions of tendon collection and criteria for the selection and elimination of animals”

**June 29, 2007-** Teleconference between Nycomed and FDA to discuss a nonclinical study comparing TachoSil with TachoComb H, TachoComb and the collagen fleece (Tachotop)

**April 1, 2008-** Type C meeting to discuss additional guidance from the Agency regarding the validation strategy and resource planning for the outstanding CMC issues identified in the prior meeting with FDA. In the interim since the pre-BLA meeting, Nycomed constructed a dedicated and identical manufacturing suite for manufacture of the proposed U.S. product, next to and segregated from the manufacturing suite for manufacture of the currently marketed EU product in order to meet the Division's requirements. In conjunction to the construction of the dedicated facility, Nycomed developed a strategy for the provision of the validation information for the manufacture of the drug product in the BLA application while completing the cGMP installation qualification in the new dedicated manufacture suite where the U.S. commercial product is to be manufactured.

**May 14, 2008-** Teleconference to discuss cleaning validation and change- over procedures.

**June 26, 2008-** Planned meeting to discuss clinical data to support licensure of TachoSil (meeting postponed by FDA)

**July 24, 2008:** Teleconference in which FDA requested that the sponsor reschedule the meeting due to a need for specifying the regulatory strategy and provide a better overview of the development program for TachoSil.

**November 21, 2008-** Type B meeting with FDA to address clinical development program and regulatory strategy to support licensure of TachoSil.

This Biologics Licensing Application was submitted to the FDA on June 5, 2009. There are 2 companion BLA's associated with TachoSil. The sponsor has submitted separate BLA's for the manufacture of the human thrombin and the human fibrinogen. Because TachoSil is a device and biologic combination product, it is being reviewed primarily by CBER (for the primary mode of action which was determined to be the biological components of thrombin and fibrinogen) and CDRH is the consulting center for the device component (collagen).

**Submission history:** (by CBER receipt dates)

**May 29, 2009-** Sponsor submits original BLA for TachoSil

**July 1, 2009-** Sponsor submits proprietary name request

**August 3, 2009-** Teleconference between FDA and sponsor regarding additional statistical information – raw datasets and corresponding supporting documentation.

**September 18, 2009-** Sponsor submits raw dataset and corresponding supporting information as per FDA's request on August 3, 2009

**October 1, 2009-** Sponsor submits 120 day safety update to the integrated summary of safety in module 5.3.5.3 and to the Summary of Clinical Safety in module 2.7.4

**November 25, 2009-** Information request regarding clinical studies -----(b)(4)-----  
----- studies), statistical, preclinical, CMC, DMPQ and pharmacovigilance.

**November 30, 2009-** Administrative correspondence change in contact US agent

**December 21, 2009-** Sponsor responds to information request dated November 25, 2009

**January 25, 2010-** Sponsor submits updated stability data

**February 5, 2010-** -----(b)(4)----- and updated draft package insert for the hemostatic indication only

**February 24, 2010-** Sponsor submits additional stability data

**Financial Certification and Disclosure:**

The sponsor reports financial disclosure information for many investigators at multiple sites.

On the disclosure form the sponsor acknowledged that they “have not entered into any

financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a)". They also certify that "each listed clinical investigator required to disclose to the sponsor whether the investigator had proprietary interest in the product or significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such interests". Nycomed further certified that "no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f)".

However, the sponsor also notes on page 22/22 (section 1.3.4 Financial certification and disclosure) that financial disclosure information was not obtained for several investigators at multiple sites. Nycomed states, "The reason for not having financial disclosure forms completed for all investigators is that the trials were not run under an IND, and therefore financial disclosure was not obtained for all investigators during the trial. The reason that we were not able to obtain financial disclosure forms after trial completion is that investigators have left the investigational sites, or that they are for other reasons not able to get in contact with despite repeated phone calls have been made to the sites concerned. Additionally, recommended letters have been sent to investigators where financial disclosures are missing but only few have responded. None of the above investigators have indicated that they refused to complete a FDF (financial disclosure form) due to conflicts of interest."

**Pediatric Deferral Plan:**

*The pediatric deferral plan was submitted for the adjunct to hemostasis indication. The deferral plan was presented to the pediatric review committee (PeRC) on March 10, 2010.*

*Since the initial indication for TachoSil is in cardiovascular surgery and the pediatric deferral plan is for liver surgery, the application is incomplete for taking final action in terms of meeting PREA requirements. The sponsor needs to submit a pediatric deferral plan to study use of TachoSil in pediatric patients undergoing cardiovascular surgery and an overall plan for obtaining -----(b)(4)----- to hemostasis indication in pediatrics. They should also include how they intend to extrapolate the information in the adult studies to the pediatric studies since the safety numbers for pediatric subjects will be small.*

*The PeRC recommended that TachoSil be reviewed at a later date to provide the review team with time to obtain additional information from the Sponsor.*

*On March 15, 2010 the sponsor submitted the overall general investigation plan for the pediatric population and a pediatric plan for evaluating TachoSil in pediatric patients ages 0-16 years undergoing hepatic resection surgery:*

*The following information is included in the Pediatric Plan submitted by Nycomed to FDA on March 15, 2010:*

- 1. Pediatric Strategy in Cardiovascular Surgery*
- 2. Proposed Clinical Study Design*
- 3. Timeline for the Completion of the Clinical Study*
- 4. Request for Deferral of Conducting the Clinical Study*

Nycomed does not consider it “feasible to conduct a pediatric study in cardiovascular surgery.” Nycomed cites “complexity of the patients, the high frequency of co-morbidities, the critical care setting, and the large number of factors with impact on outcome makes the needed patient number to control for background variability particularly high.” Nycomed is concerned that an “unnecessary number of children would have to be enrolled in a trial in order to draw firm conclusions”.

Nycomed intends to use a bridging and extrapolation strategy for the PREA requirements based on data obtained so far and data to be obtained with TachoSil in liver surgery.

Nycomed already has pediatric data from the study TC-019- IN which they plan to pool with the planned pediatric data from the upcoming US liver study, -----(b)(4)----- to be conducted under IND (b)(4) for efficacy. Additionally, Nycomed has data for adults from -(b)(4-) trials conducted in Europe -----(b)(4)----- with a total of 119 TachoSil treated patients. These data are included in the current BLA. Nycomed plans to combine these data with the data to be obtained from the --- (b)(4)----- study in ----- --- (b)(4)-----.

The planned US pediatric study (protocol -----(b)(4)-----, under US –BB-IND- (b)(4)- is briefly described below:

Study title: ----- ----- (b)(4) ----- ----- ----- ----- (b)(4) ----- ----- ----- ----- ----- ----- (b)(4) ----- -----
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In the integrated analysis of safety and efficacy data from adult patients receiving TachoSil from relevant subpopulations from studies ----- (b)(4) ----- will be compared to pediatric patients receiving ----- (b)(4) -----.

The complete dataset from clinical TachoSil studies in hemostasis intended to provide a basis for the following bridging and extrapolation of TachoSil data consists of the following:

1. Bridging from adult data in------(b)(4)----- to adult data in cardiovascular surgery (TC-023-IM).
2. Extrapolation of safety and efficacy data from adults to children based on studies -----(b)(4)----- and TC-019-IN,
3. Based on the above bridging (1) and extrapolation (2), the sponsor plans to extrapolate safety and efficacy data of TachoSil in children undergoing -----(b)(4)----- to safety and efficacy data on children undergoing cardiovascular surgery (TC-023-IM).

*The bridging and extrapolation will be done by simple comparisons of outcome variables, e.g. a comparison of proportion of patients with hemostasis at 3 minutes, with confidence intervals, across age groups and organs.*

*The final study protocol will be submitted in 2010 and the study is planned to be initiated by December 2010. This information was submitted to the PeRC in advance of the scheduled March 24th, 2010 meeting.*

*On March 23, 2010 the review division was notified that the pediatric information on TachoSil would not be reviewed on March 24, 2010. This review was rescheduled for March 31, 2010.*

*On March 31, 2010 TachoSil was re-presented to the PeRC. The sponsor noted that they did not think it was feasible to study pediatric patients undergoing cardiovascular surgery due to the “complexity of the patients, the high frequency of co-morbidities, the critical care setting, and the large number of factors with impact on outcome makes the needed patient number to control for background variability particularly high.”*

*The PeRC disagreed with the sponsor’s rationale for not conducting a pediatric cardiovascular surgery study and recommended that the Division get adjunct to hemostasis utilization data for cardiovascular surgery in pediatric patients. Although not a requirement, the PeRC would like to have follow-up regarding the utilization data and whether or not the review team will require a cardiovascular surgery study in the pediatric population.*

*For administrative purposes the sponsor has met PREA requirements. Since the sponsor is pursuing -----(b)(4)----- hemostasis indication in the pediatric population, the review division will continue discussions regarding whether or not extrapolation is feasible once utilization data have been reviewed.*

**Clinical Development Program:**

A total of 11 clinical studies (see table below) sponsored by Nycomed have been completed, of which 3 were intended to provide pivotal data to this BLA. -----

----- (b)(4) -----

----- . In this final review only one study is intended to provide pivotal data for this BLA in support of approval for an adjunct to hemostasis indication. An additional 3 studies are currently ongoing, one of which 1 is under the sponsorship of ----- (b)(4) ----- Seven of the studies have been provided to this BLA as supportive efficacy and safety data for the hemostatic --- (b)(4) --- indications sought. Of these 7 studies, 6 were controlled studies and 1 was an uncontrolled pediatric study. The sponsor provides data from 4 uncontrolled studies as additional evidence of efficacy and safety for TachoSil.

The studies were conducted over a 9 year period starting in 2000 with the initial aim of providing data to obtain marketing authorization in Europe. The development program consisted of 4 stages:

- (i) an initial series of 3 studies ----- (b)(4) ----- in 3 surgical applications ----- (b)(4) -----
- (ii) the addition of a second ----- (b)(4) -----
- (iii) 2 studies required in Europe as a post-authorization commitment (TC-018-IN and TC-019-IN) evaluating safety and pediatric use, respectively and
- (iv) studies aiming at further expanding the clinical evidence for TachoSil ----- (b)(4) --- and TC-023-IM) conducted in patients undergoing --- (b)(4) --- cardiovascular surgery, respectively.

The following table provided by the sponsor depicts the clinical program for TachoSil:

**Table 1: Completed Clinical Studies on TachoSil**

	Surgical indication	Study Code	Treatments <sup>a</sup>	N	Study Period
Controlled studies providing safety and efficacy data					
1	(b)(4)		TS vs standard surgical treatment	189	2000-2002
2			TS vs standard surgical treatment	301	2006-2007
3	Cardiovascular surgery	TC-023-IM	TS vs hemostatic fleece	120	2006-2007
Controlled studies providing safety data and supportive efficacy data					
4	(b)(4)			121	2001-2002
5				188	2002-2004
6				119	2003-2003
Uncontrolled studies providing additional safety and efficacy <sup>b</sup> data					
7	Liver resection (children)	TC-019-IN	TS (no comparator)	16	2006-2007
8	Various surgeries	TC-018-IN	TS (no comparator)	3098	2005-2008
9	(b)(4)		TS (no comparator)	154	2004-2005
10			TS (no comparator)	616 <sup>c</sup>	2005-2007
11			TS (no comparator)	169	2007-2008

<sup>a</sup> TS, TachoComb S or TachoSil.

<sup>b</sup> Efficacy data from the pediatric study TC-019-IN.

<sup>c</sup> 324 patients received treatment with TachoSil.

Study TC-023-IM is intended to provide the pivotal efficacy data for this submission; studies -----(b)(4)----- are intended to provide supportive data for hemostatic efficacy. All 4 studies are included in the Integrated Summary of Efficacy (ISE), Module 5, Section 5.3.5.3. These 4 studies provide key safety information, and safety data from all 4 studies are included in the Integrated Summary of Safety (ISS), Module 5, Section 5.3.5.3.

In addition, 1 uncontrolled study (study TC-019-IN) is intended to provide additional efficacy and safety data in pediatric patients undergoing -(b)(4)---. Four uncontrolled studies in a variety of surgical subspecialties provide additional safety data. There are currently 3 ongoing studies on TachoSil as part of the global clinical development of TachoSil:

1. -----  
------(b)(4)-----  
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In addition, there are 2 uncontrolled studies being conducted in Europe,

2. -----(b)(4)-----  
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3. -----(b)(4)-----  
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- 4.

**Table 2: Ongoing Clinical Studies on TachoSil**

	Surgical indication	Study Code	Treatments <sup>a</sup>	N (planned)
12	(b)(4)			
13				
14				

<sup>a</sup> TS, TachoSil.

Of the 3 ongoing studies, 2 are being conducted in the EU and only the ---(b)(4)----- study is being conducted in Japan.

In this BLA submission, Nycomed notes that “the outcome of the ongoing study --(b)(4)-- ---IM is decisive for a potential later clinical development of TachoSil in ---(b)(4)----- Nycomed does intend to expand the indications for TachoSil in the US to (b)(4) surgery hemostatic and -----

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**Clinical Studies:**

**Pivotal study intended to support the adjunct to hemostasis indication: TC 023 IM**

**Clinical Trial outline for Pivotal study intended to support the cardiovascular hemostasis indication: TC 23-IM (Adapted from Sponsor)**

**Title of trial:**

A randomized, open label, parallel-group, multi-centre trial to compare the efficacy and safety of TachoSil versus standard hemostatic treatment in cardiovascular surgery

**Trial centers:**

The trial was conducted at 10 sites in 5 European countries: Denmark (2), France (2), Germany (2), Italy (2) and Spain (2).

**Period of trial:**

June 2006 – Sept 2007

**Phase of development:**

Therapeutic use, Phase IV

**Target population:**

Subjects with a planned elective surgery on the heart, the ascending aorta or arch, requiring a cardiopulmonary bypass procedure were eligible if the below selection criteria applied. A total of 120 subjects were randomized.

**Objectives:**

To demonstrate efficacy and safety of TachoSil in cardiovascular surgery

**Trial Design:**

Open Label

- TachoSil was compared with standard treatment of hemorrhage in cardiovascular surgery
- Subjects were assigned to treatment by randomization, stratified by centre
- The trial was open label
- The trial configuration was parallel

**Inclusion criteria:**

All inclusion criteria must be answered “yes” for a subject to participate in the trial.

At Screening:

1. Has the subject given informed consent according to local requirements before any trial related activities? A trial related activity is any procedure that would not have been performed during the routine management of the subject. In this trial, the screening is the first trial related activity.

2. For female subjects of childbearing potential: Is the pregnancy test at screening negative (not applicable for male patients)?
3. Does the female subject of child-bearing potential use adequate contraception (contraceptive pill, contraceptive injection, contraceptive implant or intrauterine device – not applicable for male patients)?
4. Is the subject  $\geq 18$  years of age?
5. Is the following planned: An elective surgery on the heart, the ascending aorta or arch, requiring cardiopulmonary bypass procedure?

Intra operatively (after primary hemostatic treatment):

6. Is bleeding from the heart muscle, the pericardium, a major vessel or a vascular bed present and does it require supportive hemostatic treatment?
7. Has the target area (the most problematic hemorrhage area) been identified?
8. Is it possible to compress the trial treatment (TachoSil or comparator fleece material) for 3 minutes?

**Exclusion criteria:**

All exclusion criteria must be answered “no” for a subject to participate in the trial.

At Screening:

1. Has the subject participated in any other trial with an investigational drug or device within 30 days before inclusion in this trial?
2. Does the subject participate in a clinical trial concomitantly with the present trial?
3. Is the subject undergoing an emergency operation?
4. Does the subject have a history of allergic reactions after application of human fibrinogen, human thrombin and/or collagen of any origin?
5. Is the subject suffering from known coagulopathy?
6. Is the subject currently participating in or has the subject previously participated in the TC-023-IM trial?
7. Is the female subject pregnant or breast feeding (not applicable for male patients)?

Intra operatively (after primary hemostatic treatment):

8. Has liquid fibrin sealant/glue or TachoSil been applied?
9. Has disseminated intravascular coagulation (DIC) occurred, i.e. micro vascular bleeding?

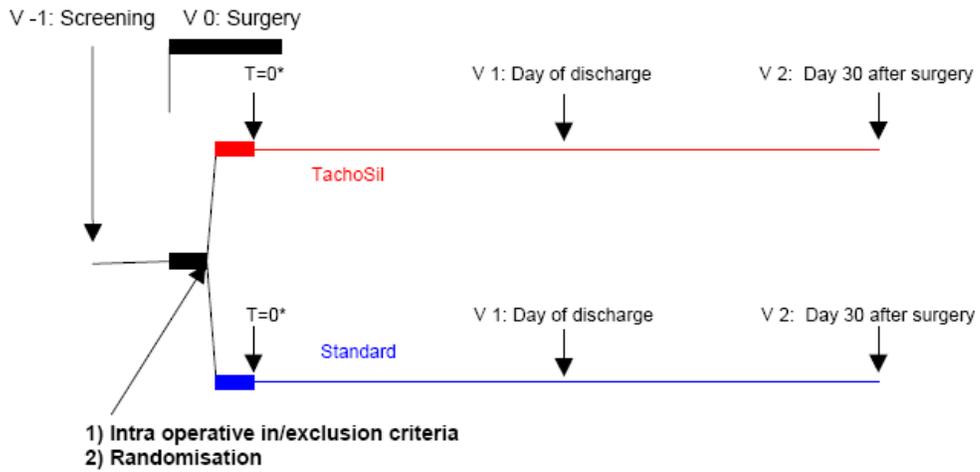
**Assignment procedures**

Subjects were randomized to open treatment with either TachoSil or standard hemostatic treatment. When a subject was eligible for participation, the Investigator called a central IVRS, which was then used to secure total allocation blinding. After receiving the user (site) ID, trial ID and age of subject to be randomized, the IVRS informed the Investigator of the subject number and the trial treatment allocated.

Subjects were evenly distributed between TachoSil and standard hemostatic treatment via block randomization. The block size was 4 subjects. The randomization list was kept at

Nycomed, Clinical Trial Supply, until the database was released.

### Design overview



\* Time=0 was defined as skin-to-skin closure.

**Standard therapy in this study was collagen fleece or cotton gauze**

## Flow Chart

Visits	Visit -1 Screening	Visit 0 Surgery	Visit 1 Discharge surgical ward	Visit 2 <sup>1</sup> Day 30 after surgery
Visit window	1-4 days before surgery		- 8 h	+/- 10 days
Informed consent	X			
Demographic data	X			
Inclusion/Exclusion criteria screening	X			
Pregnancy test	X			
Physical examination	X		x	
Vital signs	X		x	
Laboratory tests	X	X**	X	
Past and concomitant illness and medication	X	X	X	
Classification of surgery	X	(X)		
Adverse events		X	X	X
Surgical procedures		X		
Description of primary haemostatic treatment		X		
Identification of target area		X		
Evaluation of bleeding		X		
Inclusion/Exclusion criteria intra-operatively		X		
IVRS randomisation		X		
Application of randomised treatment		X		
Time to haemostasis		X		
TachoSil accountability		X		
Rescue treatment and treatment of other areas		X		
Expert opinion		X		
Description of surgery		X		
Body temperature		X	X	
Post operative drain volume (ml)			X	
Time of removal of drains			X	
Post operative blood transfusion			X	

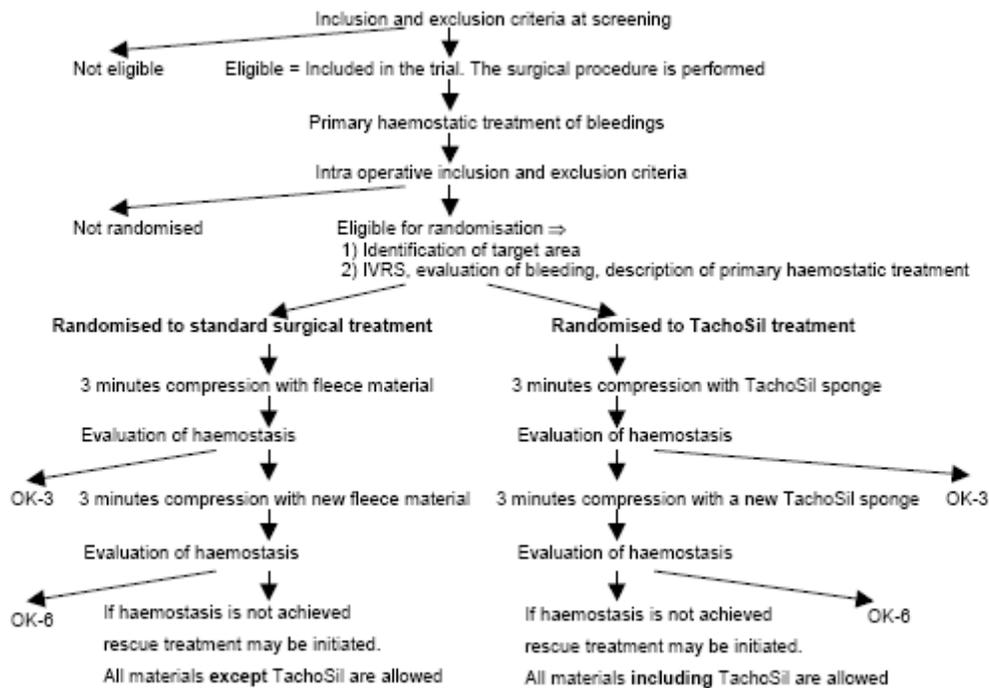
\* Expert opinion (according to sponsor): The investigator estimated the number and size of TachoSil sponges or fibrin glue product and volume that would have been used during this surgery if the subject was not a trial subject.

Visits	Visit -1 Screening	Visit 0 Surgery	Visit 1 Discharge surgical ward	Visit 2* Day 30 after surgery
Visit window	1-4 days before surgery		- 8 h	+/- 10 days
Need of re-operation with reason			X	
Other post operative complications			X	
Time of discharge			X	
End of trial form				X

\*: Visit 2 (Day 30 after surgery) could be performed as a telephone visit

\*\* : At Visit 0, only ACT was measured.

### Detailed flow chart for randomisation and trial treatment



OK-3: If hemostasis was achieved after 3 min, the time to hemostasis was recorded as 3 min.

OK-6: If hemostasis was achieved after 6 min, the time to hemostasis was recorded as 6 min.

*Reviewer comments: It appears that the sponsor really means TTH within 3 min, 6 min rather than after? Elsewhere in the protocol the sponsor refers to the primary efficacy*

*measurement as proportion of subjects in which time to hemostasis is achieved within 3, 6 or 10 minutes.*

*The sponsor refers to the standard of care material as a fleece. However, consistent terminology for the standard of care product is lacking in the protocol. Sponsor presented a table of all subjects who received standard treatment and described what the standard treatment was. Approximately half of the patients in the “standard” group received a fleece material similar to Surgicel and the other approximate half received cotton gauze.*

*Additional analyses are not thought to be necessary for assessing the primary efficacy endpoint since there are no significant differences in the standards treatment (i.e. Gauze or Fleece- Surgicel). Ideally all subjects randomized and treated with standard treatment should have received the same product (manual compression with plain gauze, or Surgicel etc.*

### **Test product, dose and mode of administration, batch number**

TachoSil (equine collagen sponge with human fibrinogen and human thrombin); Number of sponges as needed applied to relevant surgical sites. In this trial, only the largest marketed TachoSil sponge (9.5 x 4.8 cm) was used.

### **Reference therapy**

Standard surgical treatment—collagen, fleece, (Surgicel)

### **Application of trial treatment**

#### **TachoSil**

To allow the TachoSil sponge to adhere to tissue in the target area, the area had to be cleaned from surgical debris before application of TachoSil. All bleedings in the target area had to be covered. If more than one sponge was needed at the same target area, the individual sponges were to overlap by 1-2 cm. The TachoSil sponge was to be applied so that it extended 1-2 cm beyond the margins of the wound. A sponge was to be cut with sterile scissors as needed. Any cut-off surplus pieces were discarded. The sponsor noted that due to strong affinity of collagen, and the active substances fibrin and thrombin to blood, TachoSil may stick to surgical instruments or gloves covered with blood. This could be avoided by pre-moistening surgical instruments and gloves with physiological saline. TachoSil had to be applied under aseptic conditions. After removal of TachoSil from the sterile package, the yellow, active side of the TachoSil sponge was applied to the bleeding area(s) and pressure applied for 3 min.

### **Standard hemostatic treatment**

For subjects randomized to standard haemostatic treatment, any hemostatic fleece material (without additional active coagulation stimulating compounds) could be used. The fleece was applied to the bleeding area and pressure applied for 3 min. No suturing was allowed, and no fibrin sealants, e.g. FloSeal® and Bioglue®, could be used before or during assessment of time to hemostasis

**Time to hemostasis.** After 3 min of application with pressure, hemostasis in the target area was evaluated.

If hemostasis was achieved, “time to hemostasis” was recorded as 3 min  
If hemostasis was not achieved, another piece of trial treatment (TachoSil or standard fleece material) was applied for 3 min  
If hemostasis was achieved, “time to hemostasis” was recorded as 6 min  
If after 6 min, hemostasis was not achieved, rescue treatment could be initiated

**TachoSil accountability:** The number of TachoSil sponges used and the pack number(s) on the box (es) were recorded and the tear-off labels inserted in the CRF.

**Rescue treatment and treatment of other areas:** If hemostasis was not achieved within 6 min after the first application of trial treatment, rescue treatment could be initiated. Subjects in both treatment arms could be treated with any method and agent including traditional surgical methods, fibrin sealants or other haemostatic material. The subjects in the standard group could, however, NOT be treated with TachoSil (for reasons of safety analysis).

Subjects that received rescue treatment continued in the trial. For areas other than the target area, the allowed treatment was the same as specified for rescue treatment. The number of TachoSil sponges or fibrin glue (ml) used as rescue treatment and as treatment of other areas were recorded in the CRF.

**Description of surgery:** In addition to the primary endpoint, the following was recorded in the patient medical records and subsequently entered in the CRF:

- The following time points during surgery:
  - Time of incision
  - Time of start and end of Extra Corporal Circulation (ECC)
  - Time of protamine infusion
  - Time of application of trial treatment
  - Time of skin-to-skin closure. Note that this was defined as time = 0
- Was aprotinin or an alternative inhibitor of fibrinolysis (type) used?
- Need of intra-operative transfusion(s) (whole blood, packed red blood cells (RBC), platelets, fresh frozen plasma and/or other), units and time of transfusion

**Body temperature** was obtained in the ear in the evening after surgery. Subjects with elevated body temperature (any measurement > 38.5°C) had to be evaluated on an individual basis to clarify the cause of the elevated body temperature. The evaluation should be based on diagnostic tests and clinical signs.

### **Past and Concomitant Illness and Medication:**

#### **Definitions:**

**Concomitant illness** any illness that was present at the start of the trial

**Concomitant medication** any medication other than the trial product that was taken during the trial - including screening and run-in.

Prophylactic anticoagulation should be recorded if anticoagulant treatment was stopped within two days before surgery. During surgery, several drugs could be administered to control anesthesia, blood pressure, coagulation status etc. Only the drugs had to be

recorded whereas dose changes should not be recorded.

A worsening in severity or frequency of a concomitant illness as well as any new illness diagnosed during the trial, must be regarded as AEs whether or not they were considered to be related to the trial product and must be reported as such. Any changes in concomitant medication or treatment procedures had to be recorded at each visit.

**Criteria for evaluation:**

Efficacy: Primary/secondary efficacy endpoints: Proportion of subjects achieving hemostasis after 3 min/6 min (ITT).

Time to hemostasis was measured on the general watch present in the surgical theatre. Three minutes after application the investigator evaluated if acceptable hemostasis in the target area was achieved. If hemostasis was achieved, “time to hemostasis” was recorded as 3 min. If hemostasis was not achieved, another trial treatment (TachoSil or standard fleece material) was applied for 3 min. If hemostasis was achieved, “time to hemostasis” was recorded as 6 min. If after 6 min, hemostasis was not achieved, “time to hemostasis” was recorded as not achieved after 6 minutes.

**Primary efficacy endpoint:**

- Proportion of subjects achieving hemostasis after 3 min (ITT, PP).

**Secondary efficacy endpoint**

- Proportion of subjects achieving hemostasis after 6 min (ITT).

**Other endpoints**

- Incidence of re-operation due to bleeding complications
- Post-operative transfusion (type and number of units)
- Duration of drainage (hours)
- Post-operative drainage volume (ml)
- Body temperature.

**Other variables:** duration of drainage; post-operative drainage volume; post-operative transfusions.

**Safety:** Adverse events; laboratory tests; body temperature; vital signs.

Protocol definition of adverse event: An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

It should be noted that the protocol specified that the following not be recorded as adverse events (AEs):

- A pre-planned procedure recorded at screening unless the condition for which the procedure was planned had worsened since screening. Complications to pre-planned procedures should, however, be recorded as AEs

- A pre-existing condition found as a result of screening procedures
- Post-operative nausea, vomiting or pain that the Investigator considered common and expectable post-operative findings, treated or untreated. Any post-operative event considered by the Investigator as either uncommon, unexpected or both had to be recorded as an AE

**Statistical methods**

Evaluability of subjects for analysis:

The ITT population was defined as all randomized subjects. The safety population consisted of all subjects randomized and given trial treatment.

The sponsor cites the following as legitimate reasons for excluding subjects from the per protocol population:

- Impossible to compress the randomized treatment to the target area
- If subjects develop DIC

**Sample size calculation:**

Based on published papers with competing products (Costasis and FloSeal) the sponsor’s assumptions for hemostasis are given in the table below.

The null hypothesis was no difference between TachoSil and standard haemostatic treatment, the alternative that they differed. To achieve 90% power in a 2-sided continuity corrected chi-square test with a significance level of 5%, 61 subjects were required per treatment group for 90% power, 2-sided continuity corrected chi-square test with a significance level of 5%.

	3 min
TachoSil	75%
Control	45%
N*	<b>61</b>

A total of 120 subjects were randomized.

A test level of alpha =5% was used throughout to determine statistical significance.

**Primary Efficacy Endpoint:**

The primary efficacy endpoint was the proportion of subjects achieving hemostasis at 3 minutes in the target area. This was analyzed using the Cochran-Mantel-Haenszel test controlling for center (data from small centers were pooled) and by the Breslow-Day test to test for homogeneity of odds ratios, i.e. treatment effect, across centers.

The null hypothesis was difference between treatments against the alternative that they differ. Subjects with missing time to hemostasis were counted in the group of subjects not

having hemostasis at 3 min (in the ITT population – for the PP population missing time to hemostasis were left missing, i.e. not included in the analysis). The primary analysis was performed on both the ITT and the PP population to check the sensitivity of the analysis; however, emphasis was on the ITT population.

### **Secondary Efficacy Endpoints:**

The secondary efficacy endpoint was the proportion of subjects achieving hemostasis after 6 minutes. This analysis was done on the ITT population only. However, if more than 10% of the ITT population was excluded from the PP population, this analysis was to be performed for the PP population as well.

### **Endpoints summarized with descriptive statistics**

Summaries were by treatment group and giving mean, standard deviation, median, min, max, and number (n) or proportion (%) as appropriate.

- Incidence of re-operation due to bleeding complications
- Duration of drainage (h) Duration of drainage was measured as time (in minutes) from T = 0 to time of drain removal.
- Post-operative need for transfusion (units). The post-operative need for transfusion was measured as number of units of whole blood, packed RBC, platelets and/or fresh frozen plasma. Summaries were by type of transfusion.
- Post-operative drainage volume (ml). The post-operative drainage volume was measured every hour from T = 0 until removal of the drain. In addition to the summary, the drainage volume was plotted by treatment versus time since operation.
- Blood tests and vital signs. The results from the blood tests and vital signs were summarized by descriptive statistics. Changes from screening in the variables measured in the blood were compared between treatments by means of Mann-Whitney test.
- Body temperature. Body temperature was presented graphically. The mean body temperature was plotted by treatment and with standard errors vs. time of measurement (first morning post operation, first evening post operation, second morning etc. to fifth evening post operation). Cases with elevated body temperature (any measurement > 38.5°C) were evaluated on an individual basis to clarify the cause of the elevated body temperature. The evaluation was based on blood variables and clinical signs.

### **Clinical laboratory adverse event**

Any clinical laboratory abnormality that suggested a disease and/or organ toxicity and was of a severity, which required active management, i.e. change of dose, medical treatment, discontinuation of product, more frequent follow-up or diagnostic investigation.

### **Serious Adverse Event**

A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose

- resulted in death
- was life-threatening. Life-threatening in the definition of an SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe
- required hospitalization or prolongation of existing hospitalization\*
- resulted in persistent or significant disability/incapacity
- was a congenital anomaly/birth defect
- was a medical important AE that is not immediately life-threatening or does not result in death or require hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

\* Only in-patient hospitalization including over night admission was regarded as an SAE.

**Interim Analyses:** None

**Protocol Amendments:**

There was only one amendment and it was “non-substantial” consisting of primarily minor clarifications.

### **TC 23-IM TRIAL RESULTS:**

This pivotal trial was completed with 119 subjects receiving trial treatment (59 randomized to TachoSil and 60 to standard treatment (ITT); 62 subjects received TachoSil and 57 standard treatment (the AT and safety analysis sets)). Nine subjects were excluded from the PP analysis set.

74% of the subjects were male. Mean (range) age was 67 (23 – 86) years. The BMI was 27.1 (16.5 – 50.2) kg/m<sup>2</sup>. No baseline variable, i.e. blood pressure, heart rate differed between trial treatments. The two trial treatment groups were also similar regarding surgical variables.

*Reviewer comments: Reviewer agrees that the majority of subjects were male and that the surgical variables for primary hemostatic treatment, target bleeding site and type of bleeding were generally similar between the two groups. Specific tables showing the comparison of the surgical variables follow below.*

### **Efficacy results:**

**Proportion of subjects achieving hemostasis after 3 minutes (primary efficacy endpoint).**

The proportion (95% CI) of subjects with hemostasis at 3 min was 0.75 (0.64 – 0.86) for TachoSil and 0.33 (0.21 – 0.45) for standard treatment; the difference was statistically significant ( $p < 0.0001$ ). In the PP population a similar result was seen.

Table 25 a: Primary Endpoint, Proportion of Subjects Achieving Hemostasis after 3 minutes, ITT

Cochran- Mantel- Haenszel test stratifying by center testing for association between treatment and hemostasis at 3 minutes

Treatment	Total number of patients	Proportion , p, With hemostasis	95% CI for p	P value
TachoSil	59	0.746	[0.635: 0.857]	<.0001
Standard	60	0.333	[0.214: 0.453]	

Breslow-day test for homogeneity of odds ratios across centers:  
Chi Square = 0.248, df=4, p=0.993

Table 25b: Primary Endpoint, Proportion of Subjects Achieving Hemostasis after 3 minutes, PP  
Cochran-Mantel-Haenszel test stratifying by center testing for association between treatment and hemostasis at 3 minutes

Treatment	Total number of patients	Proportion , p, With hemostasis	95% CI for p	P value
TachoSil	69	0.746	[0.636: 0.857]	<.0001
Standard	62	0.346	[0.217: 0.475]	

Breslow-day test for homogeneity of odds ratios across centers:  
Chi Square = 0.669, df=4, p=0.956

Proportion of subjects achieving hemostasis after 6 min (secondary efficacy endpoint).

The proportion of subjects achieving hemostasis after 6 min (secondary efficacy endpoint). The proportion (95%CI) of subjects with hemostasis at 6 min was 0.95 (0.89-1.0) for TachoSil and 0.72 (0.60-0.83) for standard treatment, the difference was statistically significant.

Table 26: Secondary Endpoint, Proportion of Subjects Achieving Hemostasis after 6 minutes, ITT  
Cochran-Mantel-Haenszel test stratifying by center testing for association between treatment and hemostasis at 6 minutes

Treatment	Total number of patients	Proportion , p, With hemostasis	95% CI for p	P value
TachoSil	59	0.949	[0.893: 1.000]	0.0005
Standard	60	0.717	[0.603: 0.81]	

Breslow-day test for homogeneity of odds ratios across centers:  
Chi Square = 4.378, df=4, p=0.357

*Reviewer comment: FDA statistical analyses confirm sponsor’s results for the primary efficacy endpoint. See statistical memo Chunrong, Cheng, PhD.*

**Treatment Failures:**

Three (5%) of subjects treated with TachoSil and 17 (28%) of standard treatment subjects were deemed treatment failures and had to receive rescue treatments. The 3 TachoSil subjects had one of the following “rescue” treatments: fibrin glue, suture, or suture and TachoSil.

**Reoperations:**

Three (5%) TachoSil subjects and eight (14%) standard treatment subjects needed reoperation. None of these re-operations were judged by the sponsor to be related to trial treatment. For the TachoSil subjects, re-operation was needed due to iatrogenic puncture of the heart resulting in cardiac tamponade, revision of a subcutaneous hematoma and bleeding from the sternal marrow.

*Reviewer comment: Reviewer agrees that TachoSil would not be expected to have caused bleeding from a puncture in the heart. It is possible that hemostatic failure of TachoSil could lead to a subcutaneous hematoma and sternal marrow bleeding if TachoSil was applied to these locations. Sternal marrow is not listed as a target bleeding site for the protocol. The investigator should not have applied TachoSil to any sternal marrow and left it in situ as this could have increased the potential for failure to achieve proper wound closure. It is not clear by the information provided that the subcutaneous hematoma was a direct result of hemostatic failure of TachoSil*

**Safety results:**

Two TachoSil subjects and 2 standard treatment subjects died. The time of death varied between two and 25 days after surgery. No death was considered by the sponsor to be related to trial treatment; all deaths were judged by the sponsor to be related to the underlying illness or to complications of surgery.

**Subject Disposition:**

Total number of subjects screened: 326

	TachoSil	Standard	Total
Randomized	59	61	120 (100%)
Completing surgery	59	60	119 (99%)
Completing discharge	58	58	116 (97%)
Completing follow-up	55	54	109 (91%)
Discontinued	4	6	10 (8%)
Due to adverse event	2	1	3 (3%)
Due to other	2	5	7 (6%)
ITT	59	60	119 (99%)
PP	59	52	111 (93%)
AT	62	57	119 (99%)

One hundred nineteen (119) randomized subjects that received trial treatment. They constitute the ITT and the safety (equal to the AT) analysis sets. The ITT and AT analysis sets differ in the distribution of trial treatments (59/60 vs. 62/57) since three subjects received TachoSil instead of standard treatment.

## Demographics and baseline characteristics:

Variable	Unit	TachoSil	Standard	All subjects
Sex				
Male	%	76	72	74
Female		24	28	26
Age	years	65 (23 - 82)	68 (36 - 86)	67 (23 - 86)
Age > 65 years	%	59	65	62
Height	cm	170 (150 - 196)	170 (155 - 186)	170 (150 - 196)
Weight	kg	77 (46 - 145)	79 (45 - 118)	78 (45 - 145)

Variable	Unit	TachoSil	Standard	All subjects
Body Mass Index	kg/m <sup>2</sup>	26.8 (18.3 - 50.2)	27.4 (16.5 - 37.2)	27.1 (16.5 - 50.2)
Blood pressure*				
Systolic	mmHg	128 (100 - 170)	128 (90 - 183)	128 (90 - 183)
Diastolic		74 (40 - 102)	73 (50 - 93)	73 (40 - 102)
Heart rate*	beats/min	71 (50 - 114)	73 (46 - 96)	72 (46 - 114)

Variables are presented as percentage or mean (range). \*: Data for the AT analysis set.

The table below presents the surgical variables by trial treatment and overall.

Primary haemostatic treatment	Unit	TachoSil	Standard	All subjects
Suturing		73	72	72
None	%	17	20	18
Electro coagulation		10	8	9

Variables are presented as percentage; Data from [Tables 13, Appendix 4.1](#)

Primary hemostatic treatment was predominantly suturing, there was no difference between the primary hemostatic treatments performed in the two groups.

Surgical variable	Unit	TachoSil	Standard	All subjects
Target area	%			
Aorta		59	53	56
Right ventricle		19	13	16
Right atrium		9	17	13
Site of bleeding	%			
Vessel		73	63	68
Tissue		27	37	32
Type of bleeding	%			
Arterial		81	67	74
Venous		19	33	26
Severity of bleeding	%			
Mild (oozing)		32	40	36
Moderate		59	57	58
Severe		9	3	6

Variables are presented as percentage; Data from [Tables 13, Appendix 4.1](#)

The bleedings treated in the trial were mainly vascular and arterial. In the TachoSil group more bleedings were arterial than in the standard treatment group (81 versus 67%), and more bleedings in the TachoSil group were classified as severe as in the standard group (9 versus 3%).

*Reviewer comment: The protocol does not specify in objective terms, the definitions of the various bleeding intensities (mild, moderate, severe). Therefore, clinical significance of the sponsor's noted differences in severity of bleeding cannot be assessed.*

*The type of residual bleeding (i.e. after primary suturing) usually seen from the aorta in cardiovascular surgery probably represents an appropriate hemostatic challenge for the use of TachoSil as an adjunctive hemostatic treatment.*

#### **Protocol Deviations:**

One subject was randomized to standard treatment but received no trial treatment since bleeding was not longer present when allocation to trial treatment was known.

Three subjects were randomized to standard treatment but received TachoSil instead.

Exclusions from the per protocol population:

Suturing was given as standard treatment in 4 subjects

Application of TachoSil instead of standard treatment: 3 subjects

Fibrin glue (TISSUECOL) was given as standard treatment (an exclusion criterion) in one subject.

#### **Death Narratives as reported by the sponsor:**

##### TachoSil

Subject no. 1013: A 75-year old male with a medical history of myocardial infarction, chronic renal failure, hypertension, hyperlipoproteinaemia, diabetes, adipositas, triple vessel disease and symptomatic aortic stenosis underwent aortic valve replacement and left internal mammary artery to the left anterior descending bypass operation on 22 Jun 2007. During surgery, TachoSil was used for hemostasis. On postoperative day one, low cardiac output was detected and an intra-aortic balloon pump was inserted. The subject also developed acute renal failure requiring hemodialysis. Due to prolonged intubation, a tracheotomy was performed on 7 Jul 2007. Despite catecholamine and fluid therapy the subject further deteriorated and developed acute respiratory distress syndrome. Antibiotic and anti-mycotic treatment was initiated. However, the subject developed sepsis and died due to multi-organ failure on ---(b)(6)--. The reporting investigator considered the event to be not related to TachoSil. No alternative etiology was reported.

*Reviewer comment: Reviewer agrees with sponsor assessment that the event was not likely related to TachoSil.*

Subject no. 1017: A 71-year old female with a medical history of aortic stenosis, triple vessel disease and ischemic cardiomyopathy underwent aortic valve replacement and triple bypass on 28 Jun 2007. During surgery, TachoSil was used for hemostasis. Due to

hemodynamic instability, an intra-aortic balloon pump was inserted at the end of surgery. During the postoperative course, the subject developed anuria requiring hemodialysis and acute bowel ischemia. Right hemicolectomy, partial resection of the ileum and ileotransversotomy were performed on 5 Jul 2007. Sputum cultures were positive for aspergillus and candida.

Furthermore, the subject developed right leg ischemia and cerebral infarct. The catecholamine consumption remained high throughout the entire postoperative course. On --(b)(6)--- the subject died due to sepsis with multi-organ failure. Autopsy was not performed. The reporting investigator assessed the multi-organ failure to be not related to treatment with TachoSil.

*Reviewer comment: Reviewer agrees with sponsor assessment that the event was not likely related to TachoSil.*

### **Standard treatment**

Subject no. 1006: A 76-year old male with a medical history of heart failure underwent tricuspid- and mitral valve repairment with cryoablation on 30 Apr 2007. Standard treatment was used for hemostasis. During the immediate postoperative period, the subject developed ventricular tachycardia, which abated after four days and was suspected to be caused by underlying disease. On 2 May 2007, myocardial infarction developed. An attempt to stent the occluded right coronary artery failed. The following day, the subject developed respiratory insufficiency, which required prolonged intubation and subsequently a tracheostomy, which was performed on post-operative day 10 (10 May 2007). In addition to recurrent pleural effusions, pneumothorax developed on 5 May 2007 and drainage was performed. On 11 May 2007, the subject developed high grade fever (41.5 °C). Blood cultivation revealed enterococcus and antibiotic treatment was started. Due to decreased hemodynamic circulation, renal failure developed on 17 May 2007, which required hemodialysis. Despite increased doses of catecholamine, the subject died on ----(b)(6)----. The autopsy revealed that the cause of death was multi-organ failure.

Subject no. 2056: A 75-year-old female had a medical history of aortic valve stenosis, mitral valve insufficiency, atrial fibrillation, chronic renal failure, polymyalgia rheumatica, hyperlipoproteinaemia and sinusitis. On 18 Jun 2007, the subject underwent mitral valve reconstruction and aortic valve replacement. Standard treatment was used for hemostasis.

Post-operatively, on 18 Jun 2007, the subject developed non-sustained ventricular tachycardia and low-output syndrome (reported as a separate event). A short defibrillation was immediately performed and treatment with amiodarone was given. The following day, on 19 Jun 2007, the subject's cardiac condition aggravated further with a fall in blood pressure, cardiac output at 1.7 l/min and decreased pulmonary function. The subject was reintubated due to general hypoxemia caused by respiratory insufficiency (reported as a separate event). At the same day, on 19 Jun 2007, acute renal failure developed and dialysis was started. Laboratory tests performed on 18 Jun 2007 had shown elevated values of creatine kinase and creatine kinase-MB. Re-analysis performed on ---(b)(6)--- revealed a significant increase of the values and a cardiac catheter

examination was performed which revealed occlusion of the right coronary artery (reported as a separate event). Immediately, a re-operation with an aorto-coronary venous-bypass was performed, but without success. A cardiopulmonary resuscitation was performed for a few minutes but without success and the subject died. The Investigator stated the death to be due to ventricular tachycardia, myocardial infarction and pulmonary insufficiency.

**Withdrawals:**

Three subjects were withdrawn due to AEs: two in the TachoSil group and one in the standard treatment group (all due to multi-organ failure)

**SURGICAL VARIABLES:**

Surgical variables by trial treatment overall (to include identification of target area, bleeding site, severity of bleeding)

The aorta was the target area in 56% of the subjects followed by the right ventricle (16%) and the right atrium (13%).

Surgical variable	Unit	TachoSil	Standard	All subjects
Target area	%			
Aorta		59	53	56
Right ventricle		19	13	16
Right atrium		9	17	13
Site of bleeding	%			
Vessel		73	63	68
Tissue		27	37	32
Type of bleeding	%			
Arterial		81	67	74
Venous		19	33	26
Severity of bleeding	%			
Mild (oozing)		32	40	36
Moderate		59	57	58
Severe		9	3	6

Suturing was used as primary hemostatic treatment in 72% of the subjects followed by no treatment (18%), electro-coagulation (9%), clips (4%) and gauze (1%). Bleeding occurred from a vessel in 68% and from tissue in 32% of the subjects. Bleeding was arterial in 74% and venous in 26% of the subjects. Severity of bleeding was rated mild (oozing) in 36%, moderate in 58% and severe in 6% of the subjects.

Table 13: Operation- Primary Hemostatic Treatment, Target Area and Bleeding, ITT

		TachoSil		Standard		Total	
		(N=59)	%	(N=60)	%	(119)	%
		N		N		N	
Description of primary hemostatic treatment	Suturing	43	72.9	43	71.7	86	72.3
	Electro-coagulation	6	10.2	5	8.3	11	9.2
	Clips	3	5.1	2	3.3	5	4.2
	Gauze			1	1.7	1	0.8

	None	10	16.9	12	20.0	22	18.5
Identification of target area	Aorta	35	59.3	32	53.3	67	66.3
	Coronary anastomosis	2	3.4	3	5.0	5	4.2
	Internal mammary artery vascular bed	1	1.7	1	1.7	2	1.7
	Left atrium	3	5.1	2	3.3	5	4.2
	Left ventricle	3	5.1	2	3.3	5	4.2
	Right atrium	5	8.5	10	16.7	15	12.6
	Right ventricle	11	18.6	8	13.3	19	16.0
	Other	3	5.1	2	3.3	5	4.2
Bleeding occurring from	Tissue	16	27.1	22	36.7	38	31.9
	A vessel	43	72.9	38	63.3	81	68.1
Type of bleeding	Arterial	48	81.4	40	66.7	88	73.9
	Venous	11	18.6	20	33.3	31	26.1
Suture used for primary hemostatic treatment	Yes	35	59.3	36	60.0	71	59.7
	No	24	40.7	24	40.0	48	40.3
Severity of bleeding	Mild (oozing)	19	32.2	24	40.0	43	36.1
	Moderate	35	59.3	34	56.7	69	58.0
	Severe	5	8.5	2	3.3	7	5.9

### Identification of target area (detailed):

	TachoSil (n=59)		Standard (n=60)		Total (n=119)	
	N	%	N	%	N	%
Intercostal Muscle			1	1.7	1	0.8
Pulmonary artery	1	1.7	1	1.7	2	1.7
Sternum	1	1.7			1	0.8
Vena cava- inferior-superior	1	1.7			1	0.8

### Treatment Failures:

Three (5%) TachoSil and 17 (28%) standard treatment subjects were treatment failures and received rescue treatment. The three TachoSil subjects had fibrin glue, suture and suture + TachoSil, respectively. The standard treatment subjects were treated with suture alone (11 subjects) and fibrin glue (4); three subjects received suture and oxidized cellulose, suture and Bioglue® and electro-coagulation, respectively.

Table 21: Treatment failures, ITT

	TachoSil	(N=59)	Standard	(N=60)	Total	(N=119)
--	----------	--------	----------	--------	-------	---------

	N	%	N	%	N	%
Received rescue treatment	3	5	17	28	20	17

**Standard Hemostatic Treatments:**

**Table 20: Description of Fleece material used for standard hemostatic treatment, AT**

Fleece material used	n	%
Compression and fibrillar absorbable hemostatic fleece (equivalent to Surgicel)	24	42
Compression and gauze	28	49
Suture	4	7
Tissuecoll	1	2

*Reviewer comment: The sponsor did not specify that one standard fleece material be used throughout the trial. The majority of patients were treated with Surgicel fleece material or manual compression with gauze. Both are acceptable standard of care methods for an adjunct to hemostasis. Suturing is considered by FDA to be a primary method of achieving hemostasis and not an appropriate comparator for an adjunct to hemostasis trial. However, the reviewer notes that altogether TachoSil was still superior to “standard of care” adjuncts to hemostasis as well as primary measures to achieve hemostasis ( See summaries of -----(b)(4)----- was the active control.) TachoSil was shown to be superior to---(b)(4)--- which is viewed by CBER to be a primary method of hemostasis so this makes it more compelling to argue that TachoSil is an effective hemostatic agent.*

**Protamine Infusions:**

It should be noted that the time of protamine infusion (before or after trial treatment) was only available for 54 TachoSil and 53 standard treatment subjects.

Table 14 Subgroup analysis, primary endpoint by time of protamine infusion ITT  
Cochran-Mantel-Haenszel test stratifying by center testing for association between treatment and hemostasis at 3 minutes.

Treatment	Total number of patients	Proportion, p, With hemostasis	95% CI For p	P value
Subgroup : trial treatment applied BEFORE protamine infusion				
TachoSil	10	0.700	[0.416: 0.984]	0.3409
Standard	9	0.556	[0.231: 0.880]	
Subgroup: trial treatment applied DURING or AFTER protamine infusion				
TachoSil	44	0.795	[0.676: 0.915]	<0.0001
Standard	44	0.318		

During surgery, aprotinin was given to 27 (46%) of the TachoSil and 35 (58%) of the

standard treatment subjects. Other fibrinolysis inhibitors were used in 18 (31%) of the TachoSil and in 20 (33%) of the standard treatment subjects.

Most of the trial treatments were applied after reversal of heparinization with protamine infusion. However, it is worth noting that a subgroup of 19 subjects, 10 TachoSil and 9 standard treatment subjects, received the trial treatment before protamine infusion and interestingly 70% of the TachoSil subjects had hemostasis at 3 min. Standard treatment was less effective (56%) in this setting. The trial was not powered to detect a difference between these subgroups, and the difference was not statistically significant ( $p = 0.341$ ).

*Reviewer comment:*

*The sponsor seeks a claim that TachoSil is effective -----(b)(4)-----  
While this subset of 10 subjects who were treated with TachoSil before heparin reversal, did achieve satisfactory hemostasis, it should be noted that the trial was not powered to detect a difference between the two groups, so this claim should not be allowed for the labeling.*

Activated clotting time (ACT) values were obtained during surgery according to the routine of the centers for monitoring of the anticoagulation status

**Table 18: Use of Aprotinin During Surgery, ITT**

		TachoSil	Standard	Total
Use of aprotinin during surgery	YES	27 ( 46%)	35 ( 58%)	62 ( 52%)
	NO	31 ( 53%)	25 ( 42%)	56 ( 47%)
	(missing)	1 ( 2%)	0 ( 0%)	1 ( 1%)
Use of alternative fibrinolysis inhibitor	YES	18 ( 31%)	20 ( 33%)	38 ( 32%)
	NO	41 ( 69%)	39 ( 65%)	80 ( 67%)
	(missing)	0 ( 0%)	1 ( 2%)	1 ( 1%)
Specification if yes	VASOPRESSIN	0 ( 0%)	1 ( 2%)	1 ( 1%)
	TRANEXAMIC ACID	1 ( 2%)	0 ( 0%)	1 ( 1%)
	TRANEX	6 ( 10%)	9 ( 15%)	15 ( 13%)
	EXACYL (TRANEXAMIC ACID)	1 ( 2%)	0 ( 0%)	1 ( 1%)
	CYKLOKAPRON	4 ( 7%)	3 ( 5%)	7 ( 6%)
	CYCLOKAPRON	0 ( 0%)	1 ( 2%)	1 ( 1%)
	OLYKLOKAPRON	1 ( 2%)	0 ( 0%)	1 ( 1%)
	AT III	0 ( 0%)	1 ( 2%)	1 ( 1%)
	(missing)	46 ( 78%)	45 ( 75%)	91 ( 76%)

**Amount of Trial Product Used:**

**TachoSil.** The total number of TachoSil sponges used in the 62 subjects that received TachoSil (AT analysis set) was 74; 53 subjects received one sponge, 7 received 2 sponges, 1 subject received 3 sponges and 1 subject received 4 sponges. Subject mean (median) was 1.2 (1). For individual data, see Appendix 4.1.

**Standard treatment.** In the standard treatment group 28 patients were treated with compression and gauze, 24 with compression and fibrillar absorbable haemostatic fleece, 4 with suture and 1 with Tissucol®.

The sponsor provided the following table for dosing of the TachoSil patch:

**Table 19b: Drug Accountability: Number of TachoSil Sponges Used, AT**

Total number of TachoSil sponges used

1		2		3		4		All	
N	%	N	%	N	%	N	%	N	%
53	85.5	7	11.3	1	1.5	1	1.6	62	100

**Efficacy Summary:**

TachoSil was superior to standard hemostatic treatment in obtaining intra-operative hemostasis after 3 and 6 minutes.

**Adverse event summary:**

Two TachoSil and 2 standard treatment subjects died; all deaths were judged by the sponsor to be related to the underlying illness or to complications of surgery.

A total of 328 AEs were reported during the trial period: 149 events in 46 (74%)

TachoSil subjects and 179 events in 44 (77%) standard subjects

According to the sponsor’s definitions of adverse event ratings, severity was considered mild for 135 (70 after TachoSil/65 after standard), moderate for 151 (64/87) and severe for 42 (15/27) of the AEs. One AE was considered by the sponsor to be possibly related to trial medication: pyrexia after TachoSil, which was non-serious and of mild severity. No AEs were classified by the sponsor as probably related.

The most frequently reported AEs were supraventricular arrhythmias (including atrial fibrillation, atrial flutter and supraventricular tachycardia). (20 in TachoSil/16 in standard treatment subjects).

*Reviewer comment: Reviewer agrees with the most frequently reported AEs. This is not unexpected in this surgical patient population.*

Fifty-eight SAEs were reported: 15 events in eight TachoSil subjects and 43 events in 18 standard subjects. Thirteen events occurred in more than one subject.

Of the 58 SAEs, the severity was mild for seven (2/5), moderate for 22 (7/15) and severe for 29 (6/23). No SAEs were considered possibly or probably related to treatment with TachoSil or standard treatment.

Adverse event reporting (Source: sponsor)

N = number of subjects exposed to treatment n = number of subjects with event % = number of subjects with event per subjects exposed, in percent E = number of events		Treatment						Total (E)
		TachoSil N = 62			Standard N = 57			
		n	%	E	n	%	E	
<b>SOC</b>	<b>PT</b>							
<b>Cardiac disorder</b>	Atrial fibrillation	18	29	18	14	25	14	32
	Tachyarrhythmia	4	6	4	4	7	4	8
	Pericardial effusion	3	5	3	4	7	4	7
	Low cardiac output syndr.	2	3	2	2	4	2	4
	Bradycardia	1	2	1	3	5	3	4
	AV block third degree	0	0	0	4	7	4	4
	Cardiac tamponade	1	2	2	1	2	1	3
	Atrial flutter	2	3	2	0	0	0	2
	Myocardial infarction	0	0	0	2	4	2	2
	Supraventr. tachycardia	0	0	0	2	4	2	2
Ventricular tachycardia	0	0	0	2	4	2	2	
<b>Respiratory, thoracic and mediastinal disorders</b>	Pleural effusion	14	23	14	11	19	14	28
	Pneumothorax	4	6	4	4	7	5	9
	Cough	2	3	2	1	2	1	3
	Respiratory failure	0	0	0	3	5	3	3
	Asthma	2	3	2	0	0	0	2
	Pulmonary congestion	2	3	2	0	0	0	2
	Dyspnoea	1	2	1	1	2	1	2
<b>Blood and lymphatic system disorder</b>	Haemorrhagic anaemia	5	8	5	6	11	6	11
	Anaemia	3	5	3	1	2	1	4
	Abnormal clotting factor	2	3	2	2	4	2	4
	Coagulopathy	1	2	1	1	2	1	2
	Thrombocytopenia	1	2	1	1	2	1	2
<b>Gastrointestinal disorders</b>	Nausea	8	13	8	5	9	5	13
	Constipation	3	5	3	3	5	3	6
	Vomiting	1	2	1	1	2	1	2
<b>Metabolism and nutrition disorders</b>	Hyperglycaemia	6	10	6	7	12	7	13
	Fluid overload	1	2	1	1	2	1	2
	Hypokalaemia	1	2	1	1	2	1	2
	Hyperuricaemia	0	0	0	2	4	2	2
<b>Renal and urinary disorders</b>	Renal failure acute	3	5	3	2	4	2	5
	Haematuria	2	3	2	1	2	1	3
	Polyuria	1	2	1	1	2	1	2
	Tubulointerstitial nephritis	1	2	1	1	2	1	2
<b>General disorders</b>	Pyrexia	4	6	4	3	5	3	7
	Multi-organ failure	2	3	2	1	2	1	3

N = number of subjects exposed to treatment n = number of subjects with event % = number of subjects with event per subjects exposed, in percent E = number of events		Treatment						Total (E)
		TachoSil N = 62			Standard N = 57			
		n	%	E	n	%	E	
<b>SOC</b>	<b>PT</b>							
<b>Psychiatric disorders</b>	Sleep disorder	3	5	3	1	2	1	4
	Psychotic disorder	0	0	0	4	7	4	4
	Mental disorder due to general medical condition	0	0	0	2	4	2	2
<b>Vascular disorders</b>	Hypotension	2	3	2	5	9	5	7
	Hypertension	1	2	1	1	2	1	2
<b>Infections and infestations</b>	Wound infection	4	6	4	0	0	0	4
	Sepsis	0	0	0	2	4	2	2
<b>Injury, poisoning and procedural complications</b>	Post-proced. haemorrhage	3	5	3	3	5	3	6
<b>Nervous system disorders</b>	Disturbance in attention	1	2	1	2	4	2	3
	Convulsion	1	2	1	1	2	1	2
	Somnolence	0	0	0	2	4	2	2
<b>Investigations</b>	Haemoglobin decreased	0	0	0	3	5	3	3
	CRP increased	0	0	0	2	4	2	2
<b>Skin and subcutaneous tissue disorders</b>	Subcutaneous emphysema	1	2	1	1	2	1	2

Data from [Table 34](#)

*Reviewer comment: Reviewer disagrees with sponsor's reporting of pleural effusions. See reviewer assessment tables for AEs below.*

#### **Adverse event reporting: Reviewer Assessment (TachoSil N= 62, Comparator N= 57)**

Product:	Study No.: TC 23 M Hemostasis			
Treatment Emergent AEs	Test (No of subjects)	Test (No. of events)	Control (No. of subjects)	Control (No. of events)
<b>Death</b>	2	2	2	2
<b>Hypertension/BP increased/hypertensive crisis/malignant hypertension/systolic hypertension/SVR increased</b>	1	1	1	1
Hypertension	1	1	1	1
<b>Pulmonary hypertension</b>	1	1	0	0
<b>Chest</b>	0	0	1	1

**pain/pressure/tightness**

Product:	Study No.: TC 23 M Hemostasis			
Treatment Emergent AEs	Test (No of subjects)	Test (No. of events)	Control (No. of subjects)	Control (No. of events)
<b>CHF, etc</b>	<b>5</b>	<b>5</b>	<b>10</b>	<b>10</b>
Congestive cardiac failure	0	0	0	0
Cardiac failure	0	0	0	0
Cardiorespiratory failure	0	0	0	0
Left ventricular failure	0	0	0	0
Pulmonary edema	0	0	0	0
Acute circulatory failure	0	0	1	1
Cardiac index decreased	0	0	0	0
Cardiac output decreased	2	2	2	2
CVP increased	0	0	0	0
Fluid overload	1	1	1	1
Cardiac tamponade	1	1	1	1
Hypotension	1	1	5	5
<b>Pericardial effusion</b>	<b>3</b>	<b>3</b>	<b>4</b>	<b>4</b>
<b>Card. arrest, etc</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>1</b>
Cardiorespiratory arrest	1	1	0	0
Cardiac arrest	0	0	1	1
Ventricular fibrillation	0	0	0	0

Product:	Study No.: TC 23 M Hemostasis			
Treatment	Test	Test	Control	Control
Emergent AEs	(No of subjects)	(No. of events)	(No. of subjects)	(No. of events)
<b>MI, etc</b>	<b>0</b>	<b>0</b>	<b>2</b>	<b>2</b>
Myocardial infarction	0	0	2	2
Myocardial ischemia	0	0	0	0
Angina pectoris	0	0	0	0
Unstable angina	0	0	0	0
<b>Cardiac arrhythmias</b>	<b>27</b>	<b>27</b>	<b>31</b>	<b>31</b>
arrhythmia	0	0	0	0
Atrial fibrillation	18	18	14	14
Atrial flutter	2	2	0	0
bradycardia	1	1	3	3
tachycardia	4	4	4	4
V-extrasystoles	0	0	0	0
Supraventricular tachycardia	0	0	2	2
V-tach/ V fib	0	0	3	3
Atrial tachycardia	0	0	0	0
AV block	1	1	4	4
Bundle branch block	1	1	1	1
Sinus tachycardia	0	0	0	0

Product:	Study No.: TC 23 M Hemostasis			
Treatment	Test	Test	Control	Control
Emergent AEs	(No of subjects)	(No. of events)	(No. of subjects)	(No. of events)
<b>CVA, TIA, cerebral infarct, etc</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>
Cerebrovascular accident	0	0	1	1
Hemiparesis	0	0	0	0
Cerebral infarction	1	1	0	0
Cerebral hemorrhage	1	1	2	2
Cerebral atrophy	1	1	0	0
Cerebral Dysfunction	0	0	0	0
Vasovagal syncope	0	0	0	0
Paresis	0	0	0	0
Cervical root pain	1	1	0	0
Brain contusion	0	0	1	1

Product:	Study No.: TC 23 M Hemostasis			
Treatment Emergent AEs	Test (No of subjects)	Test (No. of events)	Control (No. of subjects)	Control (No. of events)
<b>Pneumonia, aspiration pneumonia, respiratory failure/insufficiency</b>	2	2	2	2
Pneumonia	1	1	2	2
Pneumonitis	0	0	0	0
Bronchitis	0	0	0	0
Pneumonia- aspiration	0	0	0	0
Bronchopulmonary aspergillosis	1	1	0	0
<b>Respiratory distress.etc</b>	20	20	19	26
ARDS	0	0	0	0
Respiratory distress	0	0	0	0
Dyspnea	1	1	1	1
Atelectasis	0	0	0	0
Respiratory failure	0	0	4	4
Pleural effusion	13	13	12	15
Pulmonary congestion	2	2	0	0
Pneumothorax	4	4	3	5
Hemothorax	0	0	1	1

Product: Treatment Emergent AEs	Study No.: TC 23 M Hemostasis			
	Test (No. of subjects)	Test (No. of events)	Control (No. of subjects)	Control (No. of events)
<b>Oliguria, etc.</b>	6	6	4	4
Oliguria				
Renal failure- acute	3	3	2	2
Renal failure- chronic	0	0	0	0
Renal failure	0	0	1	1
Renal impairment	1	1	0	0
Anuria	1	1	0	0
Dialysis	0	0	0	0
Urinary hesitation	0	0	0	0
Urinary retention	0	0	0	0
Acute tubular necrosis	1	1	1	1
<b>Hypoxia, etc.</b>	0	0	0	0
<b>Hypovolemia</b>	0	0	1	1
Hypovolemia	0	0	1	1
Hypovolemic shock	0	0	0	0
Dehydration	0	0	0	0

Product:	Study No.: TC 23 M Hemostasis			
Treatment Emergent AEs	Test (No. of subjects)	Test (No. of events)	Control (No. of subjects)	Control (No. of events)
<b>Gastrointestinal pain, nausea, vomiting</b>	10	10	6	6
Vomiting	0	0	0	0
Abdominal distension	0	0	0	0
Nausea	9	9	5	5
Vomiting	1	1	1	1
Post-operative nausea	0	0	0	0

Product:	Study No.: TC 23 M Hemostasis			
Treatment Emergent AEs	Test (No of subjects)	Test (No. of events)	Control (No. of subjects)	Control (No. of events)
<b>Coagulation</b>	<b>5</b>	<b>5</b>	<b>4</b>	<b>4</b>
Coagulation disorder	4	4	3	3
DIC	0	0	0	0
Thrombocytopenia	1	1	1	1
<b>Thromboembolic events</b>	<b>0</b>	<b>0</b>	<b>2</b>	<b>2</b>
Thrombosis	0	0	1	1
Arterial thrombosis-limb	0	0	0	0
DVT	0	0	0	0
Pulmonary embolism			1	1
Thromboembolism	0	0	0	0
Thrombophlebitis-deep	0	0	0	0

Product:	Study No.: TC 23 M Hemostasis			
Treatment Emergent AEs	Test (No of subjects)	Test (No. of events)	Control (No. of subjects)	Control (No. of events)
<b>Hemorrhage/bleeding</b>	<b>15</b>	<b>15</b>	<b>15</b>	<b>15</b>
anemia	3	3	7	7
Duodenal ulcer hemorrhage	0	0	0	0
Gastric ulcer hemorrhage	0	0	0	0
GI hemorrhage	0	0	0	0
Rectal hemorrhage	0	0	0	0
Exsanguination	0	0	0	0
Hemorrhage	1	1	1	1
Ulcer hemorrhage	0	0	0	0
Intra-operative hemorrhage	0	0	0	0
Post-op hemorrhage	9	9	3	3
Secondary anemia	0	0	0	0
Hemoglobin decreased	0	0	3	3
Vaginal hemorrhage	0	0	0	0
Anemia aggravated	0	0	0	0
Hematuria	2	2	1	1

Product:	Study No.: TC 23 M Hemostasis			
Treatment Emergent AEs	Test (No of subjects)	Test (No. of events)	Control (No. of subjects)	Control (No. of events)
<b>Sepsis/septic shock</b>	3	3	2	2
Sepsis	0	0	2	2
Septic shock	0	0	0	0
Multiple organ failure	2	2	0	0
Bacteremia	1	1	0	0
<b>Ischemia/ischemic events</b>	0	0	1	1
Intestinal infarction	0	0	0	0
Intestinal ischemia	0	0	0	0
Ischemia /periph	0	0	0	0
Ischemic colitis	0	0	1	1

Product:	Study No.: TC 23 M Hemostasis			
Treatment Emergent AEs	Test (No of subjects)	Test (No. of events)	Control (No. of subjects)	Control (No. of events)
<b>Blindness</b>	1	1	0	0
<b>Pain</b>	2	2	0	0
<b>Infection</b>	6	6	12	12
Mediastinitis	6	6	1	1
Infection	0	0	11	11
<b>Pyrexia</b>	4	4	5	5

*Reviewer comments: For this pivotal study overall the adverse event profiles are similar for both the standard (control) and TachoSil groups.*

**Bioresearch Monitoring general comments pertaining to study TC 23-IM ( Source: Lillian Ortega, Consumer Safety Officer, Division of Inspections and Surveillance Bioresearch Monitoring Branch , FDA/CBER/Office of Compliance and Biologics Quality)**

TC-023: 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

Site TC023IM-DEU039: Munich, Germany

- Investigator exposed at least 3 non study subjects to the investigational Medical Product (test article). A total of sixteen TachoSil sponges were used on non study subjects, which were not screened for eligibility or properly consented.
- Several surgeons who performed critical study activities such evaluating bleeding, hemostasis and applied the investigational drug were not listed on the Site and Staff Delegation log. The surgeons did not have documentation of protocol-specific training during the inspection.

Site TC023IM-DEU038: Leipzig, Germany

- No discrepancies noted

37 pages determined not to be releasable; (b)(4),(b)(6)

**Sponsor’s Conclusion:**

The study met the primary efficacy endpoint showing that TachoSil was superior to ----- (b)(4)-- coagulator in obtaining rapid and effective hemostasis.

*Reviewer comments: Reviewer agrees that TachoSil achieved hemostasis in a shorter amount of time compared to control treatment and that the adverse event profile between the control and TachoSil groups is similar.*

**Overview of Efficacy across the trials**

Studies -----(b)(4)----- were multicenter, open-label, randomized, controlled, parallel-group studies designed to compare the efficacy and safety of TachoSil with comparator treatment as secondary management of intraoperative hemorrhage after primary surgical hemostatic procedures in adult patients undergoing -----(b)(4)----- . The comparator treatments used in these studies were the -----(b)(4)----- or standard surgical techniques -----(b)(4)----- .The FDA does not recognize these 2 comparator treatments as appropriate controls for adjunct to hemostasis studies (FDA, CBER, TachoSil pre-BLA meeting minutes, 2008). At this time, these hemostatic methods are regarded by FDA as primary methods of achieving hemostasis. All studies were conducted in the European Economic Area.

The integrated analysis for all four hemostasis studies (with the addition of the pivotal study TC 23 -IM) included a total of 270 patients who received TachoSil and 274 patients in Standard group.

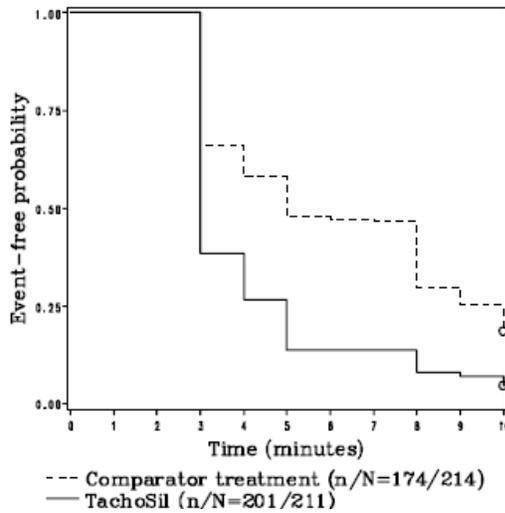
Efficacy data from above three studies and study TC-023-IM were pooled where possible. Some efficacy endpoints were not available for study TC-023-IM (Table 7), therefore, those integrated summary were only conducted on the three non-cardiovascular studies.

Excerpted from Chunrong Cheng, Ph D . Statistician, Office of Biostatistics and Epidemiology.

Primary efficacy endpoints

- In the integrated analysis of all 3 studies -----(b)(4)-----, the median time to hemostasis for patients in the TachoSil treatment group was shorter (3.0 minutes) than that for patients in the comparator treatment group (5.0 minutes). The p-value for the log-rank test was <0.001.

**Figure 1.** Time to hemostasis -----(b)(4)-----



A treatment difference was seen both in the ----(b)(4)----- studies but was larger in the (b)(4) study because of a longer time to hemostasis observed in the comparator treatment group.

- In the integrated analysis of the 4 studies, a greater percentage of patients (174 patients [64.4%]) in the TachoSil treatment group achieved hemostasis at 3 minutes than in the comparator treatment group (92 patients [33.6%]). Although there was evidence of some heterogeneity in the odds ratios across organs and regions, the overall odds ratios, whether adjusted for region or for organ, were strongly in favor of TachoSil (4.249 and 3.907, respectively).

### Secondary endpoints

The integrated analysis of 3 studies -----(b)(4)----- showed that a greater proportion of patients in the TachoSil treatment group (182 patients [86.3%]) achieved hemostasis at 5 min than in the Standard group (112 patients [52.3%]). The proportion of patients with hemostasis at 10 min was also greater in the TachoSil group (201 patients [95.3%]) than in the Standard group (174 patients [81.3%]). There was no evidence of heterogeneity in the odds ratios across organs and regions.

### Subgroup analysis

The subgroup analysis for the primary efficacy endpoint, hemostasis at 3 minutes, was conducted in the pooled data of the 4 studies.

**Table 1.** Hemostasis at 3 minutes -----(b)(4)----- TC-023-IM)

	N	Tachosil	N	Standard
Female	96	63 (66%)	106	40 (38%)
Male	174	111(64%)	168	52 (31%)
Age ≤65	158	92(58%)	154	54 (35%)
Age >65	112	82(73%)	120	38 (32%)

Dr. Cheng's comment: In study TC-023-IM, the treatment effect in females was not as

large as that in the males. Note that there were only 14 females in the TachoSil group in that study. The sex-related difference was not apparent in the integrated studies with larger sample size. Therefore, sex may not be a concern in the hemostasis indication. However, it was observed that the older subjects had better hemostasis at 3 minutes than the younger subjects.

Clinical reviewer comment: Agrees with the observed age difference, significance is not clinically apparent from these studies.

Reviewer integrated efficacy summary conclusion:

Based on the results of the pivotal cardiovascular surgery study it appears that hemostatic efficacy of TachoSil has been demonstrated. Furthermore, the supportive hemostatic studies, -----(b)(4)----- IN, used primary method of hemostasis as a control and the studies demonstrated that TachoSil was superior to even these primary hemostatic methods in terms of achieving hemostasis within 3 minutes.

### Overview of Safety across trials

The following is the reviewer’s tabulation of the integrated safety summary data from the adjunct to hemostasis studies intended to support approval of TachoSil for this indication: Studies -----(b)(4)----- and TC-023 IM ( TachoSil N=276, Comparator N=268)

Product:	Study No.: -----(b)(4)----- and 23 Hemostasis			
Treatment Emergent AEs	Test (No of subjects)	Test (No. of events)	Control (No. of subjects)	Control (No. of events)
<b>Death</b>	10	N/A	8	N/A
<b>Hypertension/BP increased/hypertensive crisis/malignant hypertension/systolic hypertension/SVR increased</b>	7	N/A	3	N/A
Hypertension	7		3	
<b>Pulmonary hypertension</b>	1	N/A	0	N/A
<b>Chest pain/pressure/tightness</b>	3	N/A	2	N/A

Product:	Study No.: -----(b)(4)----- and 23 Hemostasis			
Treatment	Test	Test	Control	Control
Emergent AEs	(No of subjects)	(No. of events)	(No. of subjects)	(No. of events)
<b>CHF, etc</b>	9	N/A	11	N/A
Congestive cardiac failure				
Cardiac failure				
Cardiorespiratory failure				
Left ventricular failure				
Pulmonary edema				
Acute circulatory failure			1	
Cardiac index decreased				
Cardiac output decreased	2		2	
CVP increased				
Fluid overload	1		1	
Cardiac tamponade	1		1	
Hypotension	4		5	
Hypervolemia	1		0	
<b>Card. arrest, etc</b>	1	N/A	1	N/A
Cardiorespiratory arrest				
Cardiac arrest	1		1	

Product:	Study No.: -----(b)(4)----- and 23 Hemostasis			
Treatment	Test	Test	Control	Control
Emergent AEs	(No of subjects)	(No. of events)	(No. of subjects)	(No. of events)
Myocardial infarction	6	N/A	2	N/A
Myocardial infarction	5		2	
Myocardial ischemia				
Angina pectoris	1		0	
Unstable angina				
<b>Cardiac arrhythmias</b>	<b>32</b>	<b>N/A</b>	<b>31</b>	<b>N/A</b>
Arrhythmia	1		0	
Atrial fibrillation	19		15	
Atrial flutter	2		0	
bradycardia	1		3	
tachycardia	7		5	
V-extrasystoles				
V-tach/ V fib	0		4	
Atrial tachycardia				
AV block	1		4	
Bundle branch block	1		0	
Sinus tachycardia				

Product:	Study No.: -----(b)(4)----- and 23 Hemostasis			
Treatment	Test	Test	Control	Control
Emergent AEs	(No of subjects)	(No. of events)	(No. of subjects)	(No. of events)
<b>CVA, TIA, cerebral infarct, etc</b>	3	N/A	3	N/A
Cerebrovascular accident	0		1	
Hemiparesis				
Cerebral infarction	1		1	
Cerebral hemorrhage	1		0	
Cerebral atrophy				
Cerebral Dysfunction				
Vasovagal syncope				
Paresis				
Cervical root pain	1		0	
Brain contusion cephalhematoma	0		1	

Product:	Study No.: -----(b)(4)----- and 23 Hemostasis			
Treatment Emergent AEs	Test (No of subjects)	Test (No. of events)	Control (No. of subjects)	Control (No. of events)
<b>Pneumonia, aspiration pneumonia, respiratory failure/insufficiency</b>	8	N/A	8	N/A
Pneumonia	7		7	
Pneumonitis				
Bronchitis	1		1	
Pneumonia- aspiration				
<b>Respiratory distress.etc</b>	35	N/A	27	N/A
ARDS	1		0	
Respiratory distress				
Dyspnea	3		2	
Atelectasis	0		1	
Respiratory failure	5		5	
Pleural effusion	18		14	
Pulmonary congestion	2		0	
Pneumothorax	6		4	
Hemothorax	0		1	

Product:	Study No.: -----(b)(4)----- and 23 Hemostasis			
Treatment	Test	Test	Control	Control
Emergent AEs	(No. of subjects)	(No. of events)	(No. of subjects)	(No. of events)
<b>Oliguria, etc.</b>	15	N/A	8	N/A
Oliguria	2		1	
Renal failure-acute	4		1	
Renal failure-chronic				
Renal failure	2		1	
Renal impairment	1		0	
Anuria	1		1	
Dialysis				
Urinary hesitation				
Urinary retention	1		0	
Acute tubular necrosis	1		1	
Hematuria	2		2	
Polyuria	1		1	
<b>Hypovolemia</b>	1	N/A	2	N/A
Hypovolemia	1		2	
Hypovolemic shock				
Dehydration				

Product:	Study No.: -----(b)(4)----- and 23 Hemostasis			
Treatment	Test	Test	Control	Control
Emergent AEs	(No. of subjects)	(No. of events)	(No. of subjects)	(No. of events)
<b>Gastrointestinal pain, nausea, vomiting</b>	16	N/A	14	N/A
Vomiting	2		2	
Abdominal distension				
Nausea	11		9	
Vomiting aggravated				
Post-operative nausea				
Abdominal pain	2		1	
GI hemorrhage	1		2	
<b>Hepatobiliary Disorders</b>	4	N/A	5	N/A
Hepatic failure	3		4	
Pancreatitis	0		1	
Hepatorenal syndrome	1		0	

Product:	Study No.: -----(b)(4)----- and 23 Hemostasis			
Treatment	Test	Test	Control	Control
Emergent AEs	(No of subjects)	(No. of events)	(No. of subjects)	(No. of events)
<b>Coagulation</b>	10	N/A	10	N/A
Hemorrhagic anemia	5		6	
Abnormal clotting factor	2		2	
Thrombocytopenia	1		1	
Hemorrhagic diathesis	1		0	
Coagulopathy	1		1	
<b>Thromboembolic events</b>	0	N/A	3	N/A
Thrombosis	0		1	
Arterial thrombosis-limb DVT	0		1	
Pulmonary embolism	0		1	
Thromboembolism				
Thrombophlebitis-deep				

Product:	Study No.: -----(b)(4)----- and 23 Hemostasis			
Treatment Emergent AEs	Test (No of subjects)	Test (No. of events)	Control (No. of subjects)	Control (No. of events)
<b>Hemorrhage/bleeding</b>	21	N/A	22	N/A
anemia	4		2	
Duodenal ulcer				
hemorrhage				
Gastric ulcer				
hemorrhage				
GI hemorrhage				
Rectal hemorrhage				
Exsanguination				
Hemorrhage	1		1	
Ulcer hemorrhage				
Intra-operative hemorrhage				
Post-op hemorrhage	7		8	
Secondary anemia (post op anemia)	1		1	
Hemoglobin decreased			3	
Vaginal hemorrhage				
Anemia aggravated				
Hematuria	2		1	
Post op hematoma	3		3	
Renal hematoma	3		3	

Product:	Study No.: -----(b)(4)----- and 23 Hemostasis			
Treatment	Test	Test	Control	Control
Emergent AEs	(No of subjects)	(No. of events)	(No. of subjects)	(No. of events)
<b>Sepsis/septic shock</b>	6	N/A	5	N/A
Sepsis	1		1	
Septic shock	1		1	
Multiple organ failure	3		2	
Bacteremia	1		1	
<b>Ischemia/ischemic events</b>	1	N/A	0	N/A
Intestinal infarction				
Intestinal ischemia				
Ischemia /periph ischemia				
Ischemic colitis	1		0	

Product:	Study No.: -----(b)(4)----- and 23 Hemostasis			
Treatment	Test	Test	Control	Control
Emergent AEs	(No of subjects)	(No. of events)	(No. of subjects)	(No. of events)
<b>General disorders</b>	27	N/A	19	N/A
<b>Pain (NOS)</b>	5		5	
<b>Pyrexia</b>	22		14	

Product:	Study No.: -----(b)(4)----- and 23 Hemostasis			
Treatment	Test	Test	Control	Control
Emergent AEs	(No of subjects)	(No. of events)	(No. of subjects)	(No. of events)
<b>Skin disorders</b>	3	N/A	2	N/A
Pruritus	2		0	
Rash	1	N/A	0	N/A
<b>Immune system</b>		N/A	0	N/A
Anaphylactic	0		1	
Drug Hypersensitivity	0		1	

Product:	Study No.: -----(b)(4)----- and 23 Hemostasis			
Treatment	Test	Test	Control	Control
Emergent AEs	(No of subjects)	(No. of events)	(No. of subjects)	(No. of events)
<b>Infection</b>	26	N/A	26	N/A
Wound infection	10		3	
Urinary tract infection	5		5	
Cystitis	3		3	
Abdominal abscess	1		4	
Biliary abscess	1		1	
Liver abscess	1		1	
Oral candidiasis	1		2	
Post procedural infection (NOS)	0		3	
Post operative abscess (NOS)	2		0	
Wound abscess	1		1	
Abscess	1		2	
Acinetobacter infection	0		1	

*Reviewer assessment for integrated summary of safety:*

*Reviewer notes, as does the sponsor, that the numbers of reported pyrexia and infection adverse events are higher in the TachoSil group compared to the control. The significance of this is not apparent from the safety review. Generally the adverse event profiles of the TachoSil and control groups are similar. No safety issues identified to preclude approval of the BLA from the clinical perspective.*

### **Immunogenicity**

FDA noted concerns about potential safety issues arising from immunogenicity due to the equine origin of the collagen sponge in an information request communication dated November 25, 2009:

Q15. The equine origin of the collagen sponge and the possibility that gamma irradiation may cause formation of neoepitopes in active substances of TachoSil raise a potential safety concern.

a. You conducted several preclinical toxicity and immunogenicity studies using TachoSil and its predecessors or individual components of the fibrin sealant patch. These studies contain major deficiencies. Specifically, the studies lack systematic evaluation of relevant immunogenic endpoints that should include, but not be limited to, antibody formation (neutralizing, across-reacting, etc.), relevant time points after exposure to the product, dosing at toxic levels (after establishing the Maximal Tolerated Dose, MTD), etc. Please comment.

Q16. You identified clinical assessments to include pyrexia, rash, pruritus, eosinophilia and increased white blood cell count as evidence of immunological reactions. Our major clinical concern regarding potential immunogenicity of TachoSil, however, is predicated on the possibility that TachoSil usage will result in the development of antibodies (neutralizing and non-neutralizing antibodies) against thrombin and fibrinogen or equine collagen that would lead to decreased efficacy of the product and possible bleeding complications. This concern is also based on the slow rate of resorption of the TachoSil Patch (b)(4) months) and the possibility of presence of a considerable amount of non-active/ denatured thrombin due to initial overages of thrombin and losses during the manufacturing process.

In our pre-BLA discussions, we requested that you assess immunogenicity of your product. We did not see a prospective plan incorporated in your clinical protocols (in particular, pivotal studies TC-023-IM and ---(b)(4)--- intended to support initial US licensure) to monitor the formation of antibodies to thrombin, fibrinogen or collagen. You should assess immunogenicity with biochemical laboratory parameters in conjunction with clinical parameters.

a. Please provide the protocol for sensitive validated immunogenicity assays for monitoring antibody formation and determination of antibody titers (e.g. (b)(4)) you will use in the clinical studies evaluating safety and efficacy of TachoSil. You should validate the method(s) according to ICH guidelines Q2A and Q2B. Please note that the time intervals for blood collection must correlate with the physicochemical resorptive properties of TachoSil.

Immunogenicity in terms of assays for monitoring antibody formation and determination of antibody titers (e.g. (b)(4)) got thrombin, fibrinogen and collagen was not formally studied in the pivotal and supportive studies (i.e. -----(b)(4)-----, TC23-IN ) submitted to this application.

The sponsor has provided a protocol for assay development, pre-validation and validation for TachoSil and the assay will be implemented in their US IND studies.

Nycomed also presented preclinical data (SR UL/5161) to suggest that they have sufficient information to conclude that gamma irradiation of TachoSil does not cause formation of neoepitopes.

Since the EU marketing authorization of TachoSil in 2004, the sponsor notes that immunogenicity has not presented a safety problem. In the BLA the sponsor presents a legacy study report of immunologic events summarized from preclinical and clinical data (section 5.3.5.4.1 of Module 5). It is important for the purposes of the legacy report review to note that TachoSil does not contain bovine thrombin or aprotinin.

The clinical information regarding immunogenicity comes from several sources: clinical study reports, survey of the AER (adverse event report) list and published studies. The summaries for clinical studies and AER lists taken directly from the legacy report are as follows:

#### **Clinical studies**

- In 8 clinical studies, comprising 3635 patients treated with TachoSil, one patient (0.03 %) had immunological events (pyrexia and eosinophilia) that were considered to be related to TachoSil. A detailed description of the event was not available, but it was not reported as serious.
- No possible or probable immune-mediated adverse drug reactions have been reported after treatment with 830,000 fleeces of TachoSil.
- No allergic reactions were reported in 37 recent published studies on TachoSil.

The report concludes, “The presence of pre-formed antibodies against equine collagen or cross-reacting antibodies against equine collagen cannot be ruled out in the patients. Such antibodies could react with the equine collagen in the TachoSil sponge and induce a local inflammatory response in the sponge. Hypersensitivity reactions in form of pruritus and rash would require diffusion of soluble collagen from the sponge throughout the body to the skin. As the equine collagen in the TachoSil sponge is insoluble, such hypersensitivity reactions would not be expected. Thus, also from this point of view it seems unlikely that the described cutane manifestations in the 5 cases were due to hypersensitivity reactions against TachoSil.”

#### **Survey of the AER list**

The list is based on registered all serious adverse events and all adverse drug reactions reported during treatment with 900,000 fleeces of TachoComb, 385,000 fleeces of TachoComb H and 830,000 fleeces of TachoSil (TachoComb S).

The list includes 511 patients with adverse events/adverse drug reactions from clinical trials and post-marketing adverse drug reactions reported until June 8th 2008.

#### **Summary of the AER list**

A total of 111 patients of the 511 patients with adverse events/adverse drug reactions had symptoms that at first sight could suggest an immunological reaction (Appendix 1). 97 of these patients were treated with TachoComb and 14 were treated with TachoSil

The 97 patients treated with TachoComb could be grouped as follows:

- 5 patients received TachoComb twice or more, 4 of these patients developed anaphylactic shock after the second treatment. This suggested that TachoComb have (sic. *has*) the potential to induce immunological reactions in humans. These observations are in agreement with animal study number 4 that demonstrated that immunological reactions against TachoComb were induced in guinea pigs treated with TachoComb as under clinical conditions. Anaphylactic shock is induced by cross-linking of preformed specific IgE antibodies bound to FcεR at the surface of mast cells by soluble antigens. The most likely candidate antigens are the bovine thrombin and aprotinin in the case of TachoComb treatment.
- 31 patients developed prolonged eosinophilia 1-4 weeks after treatment with TachoComb. The eosinophilia was in some cases accompanied with fever and could be sign of an ongoing immune reaction.
- The rest of the patients had symptoms like fever. The relation between these symptoms and TachoComb was considered unlikely in the majority of the cases as other precipitating factors were identified (Please see Appendix 1) below.

AER number	Drug	Times treated	Reaction	Immunological reaction
CPV1999JPN0012	TachoComb	1	Fever, 40 C immediately after operation	Not assessable
CPV1999JPN0015	TachoComb	1	Fever, 40 C 4 d after operation, subsided after antibiotics	Unlikely
CPV1999JPN0038	TachoComb	1	Fever, 40 C x d after operation, subsided after antibiotics	Unlikely
CPV1999JPN0076	TachoComb	1	Fever, 39,9 C immediately after operation, subsided after antipyretic	Unlikely
CPV2001DEU0909	TachoComb S	1	Raise in CRP	Not related
CPV2001DNK1382	TachoComb S	1	Circulatory instability	Not related
CPV2003DEU3511	TachoComb S	1	Syncope	Not related
CPV1999JPN0117	TachoComb	1	Erythema multiforme	Unlikely
CPV1999JPN0189	TachoComb	1 ? Maybe treated previously with related compound	Fever, 39,2 C immediately after operation, gradually declined	Possible
CPV1999JPN0190	TachoComb	1	Fever and eosinophilia 1 week after operation	Possible
CPV1999JPN0385	TachoComb	1	Fever and eosinophilia 11 days after operation	Possible
CPV1999JPN0398	TachoComb	1	Subfebrile immediately after operation, duration 40 d	Unlikely
CPV2000JPN0451	TachoComb	1	Fever, intraabdominal abscess	Not related
CPV2000JPN0452	TachoComb	1	Fever 1 month after operation	Not related
CPV2000JPN0453	TachoComb	1	Fever 4 d after operation	Unlikely
CPV2000JPN0572	TachoComb	1	Fever immediately after operation	Unlikely
CPV2000JPN0574	TachoComb	1	Fever immediately after operation	Unlikely
CPV2000JPN0575	TachoComb	1	Fever immediately after operation	Unlikely
CPV2000JPN0580	TachoComb	1	Subfebrile immediately after operation, decline after antifungal treatment	Not related
CPV2000JPN0730	TachoComb	1	Fever immediately after operation	Unlikely
CPV2000JPN0731	TachoComb	1	Fever 4 d after operation	Possible
CPV2000JPN0732	TachoComb	1	Fever 2 d after operation	Unlikely

AER number	Drug	Times treated	Reaction	Immunological reaction
CPV2000JPN0733	TachoComb	1	Fever and exanthema X d after operation	Possible
CPV2000JPN0734	TachoComb	1	Eosinophilia 14 d after operation	Possible
CPV2000JPN0788	TachoComb	1	Fever 3 d after operation	Possible
CPV2000JPN0789	TachoComb	1	Circulatory instability	Unlikely
CPV2000JPN0791	TachoComb	1	Fever immediately after operation	Unlikely
CPV2000JPN0793	TachoComb	2 ?	Fever immediately after operation	Possible
CPV2000JPN0856	TachoComb	1	Fever 7 d after operation	Unlikely
CPV2000JPN0857	TachoComb	1	Fever immediately after operation	Unlikely
CPV2000JPN0864	TachoComb	2	Circulatory instability, rash (anaphylactic shock?)	Probable
CPV2001JPN0929	TachoComb	1	Rash	Unlikely
CPV2001JPN0932	TachoComb	1	Eosinophilia 21 d after operation	Possible
CPV2001JPN0936	TachoComb	1	Fever immediately after operation	Unlikely
CPV2001JPN0937	TachoComb	1	Fever immediately after operation	Unlikely
CPV2001JPN0929	TachoComb	1	Rash immediately after operation	Unlikely
CPV2001JPN1334	TachoComb	1	Fever immediately after operation	Unlikely
CPV2001JPN1335	TachoComb	1	Rash and fever 1 and 2 weeks after operation	Unlikely
CPV2001JPN1338	TachoComb	1	Fever 1 week after operation	Unlikely
CPV2001JPN1372	TachoComb	1	Fever immediately after operation	Unlikely
CPV2001JPN1419	TachoComb	1	Fever and eosinophilia 14 d after operation	Possible
CPV2001JPN1569	TachoComb	1	Fever immediately after operation	Unlikely
CPV2001JPN1715	TachoComb	1	Fever and eosinophilia 2-3 w after operation	Possible
CPV2001JPN1716	TachoComb	1	Eosinophilia 3-4 w after operation	Possible
CPV2001JPN1717	TachoComb	1	Fever 6 months after operation	Not related
CPV2001JPN1718	TachoComb	1	Fever 2 months after TachoComb	Not related
CPV2001JPN1719	TachoComb	1	Fever immediately after operation, staphylococcus detected	Not related
CPV2002JPN2034	TachoComb	1	Fever immediately after operation	Unlikely
CPV2002JPN2113	TachoComb	1	Fever 1 w after operation	Unlikely

AER number	Drug	Times treated	Reaction	Immunological reaction
CPV2002JPN2118	TachoComb	1	Eosinophilia 3-4 w after operation	Possible
CPV2002JPN2119	TachoComb	1	Eosinophilia 2-6 w after operation	Possible
CPV2002JPN2120	TachoComb	1	Eosinophilia 3-4 w after operation	Possible
CPV2002JPN2121	TachoComb	1	Eosinophilia and elevated CRP 2-3 w after operation	Possible
CPV2002JPN2122	TachoComb	1	Eosinophilia and fever 2-3 w after operation	Possible
CPV2002JPN2124	TachoComb	1	Eosinophilia 3-4 w after operation	Possible
CPV2002JPN2126	TachoComb	1	Eosinophilia 3-4 d after operation	Possible
CPV2002JPN2129	TachoComb	1	Eosinophilia 3-4 w after operation	Possible
CPV2002JPN2130	TachoComb	1	Fever 6 d after operation	Possible
CPV2002JPN2162	TachoComb	1	Eosinophilia 4-5 w after operation	Possible
CPV2002JPN2359	TachoComb	1	Elevated CRP ½-3 w after operation	Possible
CPV2002JPN2411	TachoComb	1	Elevated CRP immediately after operation	Unlikely
CPV2002JPN2412	TachoComb	1	Fever 1 w after operation, staphylococcus detected	Not related
CPV2002JPN2415	TachoComb	1	Eosinophilia and fever 2-4 w after operation	Possible
CPV2002JPN2416	TachoComb	1	Fever immediately after operation	Unlikely
CPV2002JPN2431	TachoComb	1	Fever and elevated CRP 1 w after operation	Possible
CPV2002JPN2433	TachoComb	1	Eosinophilia 1 w after operation	Possible
CPV2002JPN2434	TachoComb	1	Eosinophilia 3 w after operation	Possible
CPV2002JPN2435	TachoComb	2	Eosinophilia 3-5 w after operation	Possible
CPV2002JPN2436	TachoComb	1	Fever x? after operation	Not assessable
CPV2002JPN2437	TachoComb	1	Fever immediately and 5 d after operation	Unlikely
CPV2002JPN2465	TachoComb	1	Eosinophilia 1 w after operation	Possible
CPV2002JPN2470	TachoComb	1	Fever and elevated CRP x? after operation	Not assessable
CPV2002JPN2471	TachoComb	1	Eosinophilia 4 w after operation	Possible
CPV2002JPN2472	TachoComb	1	Fever immediately after operation	Not related

AER number	Drug	Times treated	Reaction	Immunological reaction
CPV2002JPN2481	TachoComb	1	Fever immediately after operation	Unlikely
CPV2002JPN2483	TachoComb	1	Eosinophilia x? after operation	Not assessable
CPV2002JPN2561	TachoComb	1	Fever immediately after operation	Unlikely
CPV2002JPN2672	TachoComb	1	Anaphylactic shock and rash	Probable
CPV2002JPN2683	TachoComb	1	Eosinophilia 4 w? after operation	Possible
CPV2002JPN2683	TachoComb	1	Eosinophilia 2 w after operation	Possible
CPV2002JPN2625	TachoComb	2	Anaphylactic shock and rash	Probable
CPV2002JPN2882	TachoComb	1	Eosinophilia 2 w after operation	Possible
CPV2002JPN2988	TachoComb	1	Elevated CRP 5 d after operation	Possible
CPV2002JPN2998	TachoComb	1	Fever and elevated CRP 2 w after operation	Possible
CPV2002JPN3001	TachoComb	1	Eosinophilia, fever and elevated CRP 2 w after operation	Possible
CPV2002JPN3362	TachoComb	1	Elevated CRP 2 w after operation	Possible
CPV2003JPN4058	TachoComb	1	Eosinophilia for several weeks after operation	Possible
CPV2003JPN4059	TachoComb	1	Eosinophilia 2-3 w after operation	Possible
CPV2003JPN4066	TachoComb	1	Fever immediately after operation	Unlikely
CPV2003JPN4068	TachoComb	1	Eosinophilia 2-4 w after operation	Possible
CPV2003JPN4085	TachoComb	1	Anaphylactic shock and rash	Possible
TAC934DEU0002	TachoComb	1	Allergic reaction	Not assessable
TAC982DEU0003	TachoComb	1	Hypersensitivity reaction, fever and eosinophilia in CFS	Possible
100182	TachoComb	1	Eosinophilia 3-6 w after operation	Possible
100183	TachoComb	2	Anaphylactic shock	Probable
100760	TachoSil	1	Anaphylactic reaction	Unlikely
100327	TachoComb	1	Rash 24 after operation. Positive patch test for TachoComb	Possible
101757	TachoComb	1	Fever and eosinophilia 1 w after operation	Unlikely
101884	TachoSil	1	Abscess 2 w after operation	Unlikely
102735	TachoSil	1	Local inflammatory syndrome ? w after operation	Not assessable
102736	TachoSil	1	Local inflammatory syndrome ? w after operation	Not assessable

AER number	Drug	Times treated	Reaction	Immunological reaction
102932	TachoSil	1	Rash and pruritus 6 months after operation	Not related
102968	TachoSil	1	Exanthem 2-5 w after operation	Unlikely
102978	TachoSil	1	Exanthem 5 days after operation	Unlikely
103037	TachoSil	1	Fever and eosinophilia 1 w after operation	Unlikely
103424	TachoComb	3	Anaphylactic shock	Probable
104115	TachoSil	1	Rash, exanthem and nausea 4 month after operation	Unlikely
104221	TachoComb	1?	Anaphylactic shock	Possible
104315	TachoComb	1	Anaphylactic shock	Unlikely
104476	TachoSil	1	Erythem in hands and neck	Unlikely
105316	TachoSil	1	Leucocytosis	Unlikely

Regarding the events reported for the 14 patients treated with TachoSil (TachoComb S), the report suggests that sufficient information existed to indicate that an immunological reaction against TachoSil was unlikely/not related in 12 of the cases. In 2 cases, data were insufficient to assess whether a specific immunological reaction against TachoSil was involved. In the legacy report the cases were distributed as follows:

1. *One case of rise in C-reactive protein levels.* A 69-year old male had a partial --(b)(4)-- ----- where TachoSil (TachoComb S) was used for -----(b)(4)----. Two days later he suffered from --(b)(4)---- with high blood levels of C-reactive protein. Antibiotic treatment was started and 17 days later he recovered.
2. *One case of circulatory instability.* A 68-years old man had a ----(b)(4)----- and TachoSil (TachoComb S) was used for --(b)(4)--. Three days later he developed atrial fibrillation and falling blood pressure. Echocardiography concluded that the reaction did not have a cardiac etiology. Explorative laparotomy was performed, and a stenosis on a level with porta was found. It was treated with a stent and a drain in ----(b)(4)----- . Cordarone, dopamine and noradrenalin was given but the patient died after the re-operation.
3. *One case of syncope.* A 37-year old female had a -----(b)(4)----- and TachoSil (TachoComb S) was used for hemostasis. The next day the patient developed syncope after vomiting for 5 minutes. The syncope deteriorated to cardiac and respiratory arrest lasting for 10 – 20 seconds. The patient recovered spontaneously. The patient had a medical history of recurrent syncopes.
4. *One case of anaphylaxis.* A 72-year old male was electively operated due to aortic aneurism. After three hours of operation, TachoSil was placed around the graft. The operation lasted for four hours. The patient bled four liters during the operation. On an unspecified moment the patient developed asystolia and was resuscitated. Three hours post-operatively, he received three bags of fresh frozen plasma. During transfusion of the third plasma, he developed hypotension, tachycardia, urticaria, and bronchospasm. He was diagnosed with anaphylaxis and treated with adrenalin and fluid. No sufficient documentation to assume specific immunological reaction against TachoSil was included. The patient developed anaphylaxis 4 hours after TachoSil was applied. The reaction happened in close connection to infusion of the third portion of fresh frozen plasma. The

patient had not previously been treated with TachoSil.

5. *Five cases of erythema.* The patients developed local erythema from 2 days to 6 months after the operation. For all cases, it seems unlikely that the reaction should have been induced by TachoSil.

6. *One case of eosinophilia and fever.* A 34-year old female underwent unspecified surgery. During surgery TachoSil was applied for hemostasis. Five days after surgery the patient developed fever and eosinophilia. In this case very sparse information was provided.

7. *One case of abscess.* A 4-year old girl underwent surgery due to volvulus. TachoSil was used to treat diffuse bleeding and to seal the anastomosis. 35 days after the initial operation the patient was operated again due to intense abdominal pain and intestinal invagination. During the operation it was discovered that TachoSil had not been resorbed and a collar of compact tissue had developed at the site where TachoSil was initially applied. According to reference information the collagen components of TachoSil are degraded by resorptive granulation tissue within 24 weeks after application.

8. *Two cases of local inflammatory syndrome.* In both cases description of the event is lacking. Local inflammatory syndrome is not defined in the literature. The information is insufficient and does not allow any conclusion to be drawn concerning immune-mediated reactions against TachoSil.

9. *One case of leucocytosis.* An increase in the leucocyte count was found in a 72-year old man one day after heart surgery where TachoSil was applied for haemostasis. The patient had chronic myelogenous leukemia and was treated with anti-leukemic drugs and recovered.

#### **Sponsor's conclusion on the AER list**

“Clinical use of 830,000 fleeces of TachoSil (TachoComb S) has resulted in 14 reported cases of events that at first sight could be suspected to be induced by immune-mediated reactions against TachoSil. However, other underlying factors were identified for the majority of the cases in the follow-up materials, and specific immune-mediated reactions against TachoSil could be excluded. Thus, no possible or probable immune mediated adverse events were reported for patients treated with TachoSil (TachoComb S).

Following clinical use of 900,000 fleeces of the predecessor TachoComb 4 cases of severe adverse events were reported with good reason and sufficient documentation to assume specific immunological reactions against TachoComb. All of these patients had previously been treated with TachoComb. The most likely candidate antigens were the TachoComb components bovine thrombin and aprotinin. For this review it is relevant to note that TachoSil does not contain bovine thrombin or aprotinin.”

#### *Reviewer comments:*

*The extensive use of the TachoSil pad through clinical studies and postmarketing studies does not suggest a safety signal with respect to immunogenicity. It is difficult to adjudicate the information in the legacy report. The conclusions may be plausible. However, it is important that the sponsor develop an assay to look for immunological responses to components of the TachoSil sponge in a controlled fashion. This is being planned and will be implemented in the US studies conducted under IND. One such study*

*has been allowed to proceed as a phase 3 study in---(b)(4)--- and this information is being evaluated in the study protocol. Viral safety markers will also be studied in controlled clinical trials. No data submitted to the BLA suggest that viral safety problems are a safety issue.*

**Special Populations:**

In the initial application amendment the sponsor did not specifically address PREA requirements for all indications in this license application. The observational study TC-19 conducted in pediatric liver patients is intended to provide evidence that TachoSil is efficacious and safe in the pediatric population. Furthermore, the sponsor states that the fact that TachoSil was able to achieve effective hemostasis in this pediatric liver transplantation population can------(b)(4)----- hemostatic efficacy in the pediatric population.

**Pediatrics Pediatric Research Equity Requirements (PREA):**

The sponsor conducted the following study for the purpose of obtaining a -----(b)(4)----- to hemostasis indication in the pediatric patient population:

**Study TC-019-IN Synopsis (Source: Sponsor)**

**Title of Trial:**

**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**

**Studied period (years):**

May 2006 – July 2007

**Trial Centers:**

Two centers in UK

Study period (years):

May 2006 – July 2007

**Phase of development:**

Therapeutic confirmatory

**Objectives:**

To collect data on efficacy, i.e. intra-operative hemostasis, and safety of TachoSil as treatment to control local bleeding in children undergoing surgical resection of the liver with or without segmental transplantation. The study was part of a post-authorization commitment required by CHMP as all previous trials were in adults.

**Methodology:**

Open, prospective, non-comparative

**Number of patients (total and for each treatment):**

Planned: 40. Study put on hold and abandoned after enrollment of 16 subjects as it proved very difficult to conduct a study in this population of severely ill children within the strict boundaries of GCP (delayed availability of hospital records and the complexities of multidisciplinary critical care).

**Diagnosis and main criteria for inclusion:**

Main inclusion criteria: at least segmental resection of the liver or resection followed by placement of a segmental liver graft; age: above 4 weeks and below 6 years; minor or moderate hemorrhage after primary surgical haemostatic procedures of major vessels.

Specifically:

Inclusion criteria

1. Has the parent(s)/legal guardian given informed consent according to local requirements before any trial related activities?
2. Is the child above 4 weeks and below 6 years of age?
3. Has at least segmental resection (anatomical/non-anatomical) of the liver and primary hemostatic treatment been performed?

or

Has resection of the liver and placement of a segmental liver graft and primary hemostatic treatment been performed?

4. Is only minor, i.e. oozing, or moderate hemorrhage persisting after primary surgical hemostatic procedures of the major vessels (no pulsating arterial hemorrhage and/or major venous bleeding)?

All inclusion criteria were to be answered “yes” for a child to participate in the study.

**Exclusion criteria:**

1. Was the child re-transplanted or had liver transplantation in combination with other organs?
2. Was there anamnestic or laboratory evidence of congenital coagulation disorders including Hemophilia A or B and von Willebrand disease?
3. Has the child a history of allergic reactions after application of human fibrinogen, human thrombin and/or collagen of any origin?
4. Has the child fulminant hepatic failure, portal vein thrombosis or anamnestic or clinical evidence of cirrhotic condition of the liver, including cirrhosis due to genetic deficiency of  $\alpha_1$  - Antitrypsin?
5. Did the child undergo an emergency operation?
6. Does the child participate in another clinical trial during the intra-operative phase?
7. Has any serious surgical complication occurred?
8. Has any fibrin glue haemostatic (including TachoSil) been used on the target wound before the planned application of TachoSil?

To participate in the study all exclusion criteria were to be answered “No” for a child having segmental resection. For a child having total hepatectomy and placement of a segmental liver transplant, Criteria 4 and 5 could be answered “Yes”.

**Test product, dose and mode of administration, batch number:**

Tachosil (equine collagen sponge with human fibrinogen and thrombin); number of

sponges as needed applied to the cut surface of the liver

**Duration of treatment:**

Intra-operative application with 6 months follow-up

**Treatment Regimen:**

For management of hemorrhagic sites as many sponges as needed were to be used. The sponge(s) were to cover the site(s) at least 1 cm beyond the immediate margins. If more than one sponge was required, the individual sponges were to overlap. If too large, the sponge could be cut to the correct size.

Escape treatment was any haemostatic treatment except TachoSil routinely used

**Criteria for evaluation:**

**Efficacy:**

Time to intra-operative hemostasis after the application of TachoSil

**Safety**

Adverse events

**Statistical methods:**

No statistical testing was performed; results presented on the basis of descriptive statistics

No study-specific procedures were performed except the use of TachoSil, assessment of time to hemostasis and 6-month follow-up. As these severely ill children spent most of their time in intensive care units at the hospitals strictly adherence to GCP (monitoring) was very difficult resulting in late reporting of AEs and SAEs. Due to this the sponsor had the study put on halt and a thorough investigation focusing on the reporting of AEs/SAEs was initiated. No safety concerns were raised, but at a meeting with the CHMP Rapporteur it was agreed to discontinue the study because most information collected is rather related to the underlying serious disease than the use of TachoSil. Sixteen children were enrolled in the study before it was discontinued, three had segmental liver resection and 13 resection followed by transplantation of a graft. Two discontinued during the study – one died from multi organ failure and the other one needed a re-transplantation after 4 months. In- and exclusion criteria were violated by three children, one both by being too old and having liver combined with kidney transplantation, one by being re-transplanted and one by having combined liver and kidney transplantation

Seven of the 16 children were male, median (range) age was 15 (2.5 – 147.5) months and BMI 17.4 (13.8 – 22.0) kg/m<sup>2</sup>.

**General protocol deviations:**

Protocol violation: Inclusion criterion no 1: physical examination and vital signs recorded one day before informed consent obtained (no.(b)(6)). These signs, however, were unchanged on the day the child was consented.

Protocol violation: Inclusion criterion no. 2: age above 6 years (no.(b)(6))

Protocol violation: Exclusion criterion no.1: one child re-transplanted (no.(b)(6)) and two had liver transplants combined with kidney transplantation (nos.---(b)(6)-----)  
 One month follow-up in four cases (nos. ----(b)(6)-----) was not performed exactly one month after surgery.  
 In three cases (nos.---(b)(6)-----), it was not possible to schedule visits exactly at 6-months (+/- 14 days)

*Reviewer comment: Protocol Deviations were quite frequent in this observational study. The sponsor comments on the protocol deviations noting the following: “Conducting a study in this population of severely ill children within the strict boundaries of GCP proved to be very difficult. The delayed availability of hospital records (child on ICU or other hospital units) and the complexities of multidisciplinary critical care i.e. multiple professionals managing patient at any one time and multiple interventions as part of the critical care, made comprehensive and consistent data recording in the CRF impractical and monitoring - including source data verification – fairly difficult. These circumstances along with the skewed perception of normality within the critical care environment i.e. critical clinical events are not necessarily perceived as abnormal, resulted in the late reporting of a serious adverse event. This event and the difficulty working to GCP led the sponsor to halt the study so that the issues and specifically the reporting of AEs/SAEs could be properly investigated.”*

No further safety concerns were identified, but the sponsor remained concerned regarding their ability to adequately ensure compliance with GCP going forward. Additionally, the sponsor claims that it became apparent during this review that the study, as performed, was mainly collating safety data related to the underlying disease/procedure rather than the use of TachoSil and so was not actually meeting its primary purpose. After a requested meeting between the sponsor and the Rapporteur it was agreed to discontinue the study and report the findings for the patients included to that point.

**Disposition of patients**

Number of patients	
Received TachoSil®	16
Completed 6-month follow-up	14
Discontinued due to adverse events	1
Discontinued for other reasons	1

The discontinuation due to an adverse event was a child (no. (b)(6)) who died following post operative complications.  
 The other discontinuation was the child (no. (b)(6)) who received a repeat transplantation after 4 months.  
 In one child (no. (b)(6)) satisfactory hemostasis was not achieved with TachoSil and required other hemostatic measures. The child was followed and completed the 6-month follow-up.

**Efficacy results:**

Thirteen – 81.3% (95% CI: 61.8 – 100%) subjects obtained hemostasis at 3 minutes; one after 8 minutes and two failed with TachoSil application and other hemostatic remedies had to be used.

**Safety results:**

A total of 64 adverse events were reported in 14 children. Further to these events information about post-operative infections (29 events), re-operations (9 events) and graft rejections (6 events) were collected so in total 108 events were reported.

Six events in five children were classified as serious and among these one died from overwhelming sepsis leading to multi organ failure.

None of the events reported were considered by the sponsor to be possibly or probably related to the use of TachoSil.

**Extent of Exposure**

A total of 27 TachoSil sponges were used (Table 13). The two patients where satisfactory hemostasis was not achieved (nos. ---(b)(6)---) accounted for three and four sponges, respectively

**Deaths, Other Serious Adverse Events and Other Significant Adverse Events**

A total of six adverse events in five children were reported as SAEs: cardiomyopathy (1); multiorgan failure (1); postoperative bleeding (1); pulmonary edema (2); bleeding (1)

**Adverse events:**

N = number of TachoSil patients n = number of patients with event % = number of patients with event by patients exposed E = number of events		TachoSil N = 16		
System Organ Class	Preferred term	n	%	E
CARDIAC DISORDERS	Bradycardia	2	13	2
GASTROINTESTINAL DISORDERS	Ascites	2	13	2
	Diarrhoea	2	13	2
	Gastrointestinal haemorrhage	2	13	2
METABOLISM AND NUTRITION DISORDERS	Hyperglycaemia	3	19	3
RENAL AND URINARY DISORDERS	Renal impairment	2	13	2
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Pleural effusion	3	19	4
	Pulmonary oedema	3	19	3
VASCULAR DISORDERS	Hypertension	5	31	5

### Post-Operative Infections

A total of 29 post-operative infections were reported in 12 children. In one case (no. (b)(6)) the infection (sepsis) contributed to the fatal outcome and in another child (no. (b)(6)) a reactivated cytomegalovirus infection was still present at the 6-month follow-up.

### Graft Rejections

Four children on 6 occasions showed symptoms of graft rejection (e.g. elevated transaminases) and in one case (no. (b)(6)) chronic rejection developed necessitating a repeat transplantation.

Five of the 16 children needed a total of nine re-operations. Four of these procedures were performed for one child (no.(b)(6)) with an eventual fatal outcome. The re-transplantation performed (no.(b)(6)) is related to the chronic rejection. Of the total number of 9 re-operations reported, none were considered to be possibly or probably related to the use of TachoSil.

### Reviewer comments

*Sponsor notes that according to the literature 2%-28% of the pediatric patients die subsequent to a liver transplantation.*

*It is unlikely that TachoSil had an influence on occurrence of postoperative infections, graft rejection, re-operation and patient death which are well known complications.*

**Sponsor's Conclusion:**

The study showed TachoSil to be effective in obtaining intra-operative hemostasis in the majority of children undergoing liver resection with or without segmental liver transplantation. Furthermore it was concluded from the safety data collected that TachoSil was not considered to be related to any of the AE/SAEs reported and has demonstrated an acceptable safety profile and is thus clinically appropriate for use in this population.

*Reviewer comments: Reviewer does not concur with sponsor that the study meets the standard for licensing the use of TachoSil as an adjunct to hemostasis in pediatric patients. The study had many trial conduct problems as noted in the protocol deviations and the BIMO report below. The study did not include all pediatric age groups. Furthermore, the study did not include an optimal trial design (uncontrolled study).*

**BIMO reporting (Source: Lillian Ortega, Consumer Safety Officer, Division of Inspections and Surveillance Bioresearch Monitoring Branch , FDA/CBER/Office of Compliance and Biologics Quality)**

TC-019: 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

Site TC019-IN-GBR013-01: Birmingham, United Kingdom (Major Deficiencies)

- Investigator failed to identify, document or report serious adverse events (SAE) within 24 hours as required per the protocol. The SAE (death) were reported to the sponsor during a monitor's visit approximately 4 months after the event occurred. No documentation to show that the sponsor was notified prior to the monitoring visit.
- Investigator randomized and enrolled three subjects that met the exclusion criteria.
  1. Subject (b)(6) was 12 years old Exclusion: protocol required age range 4weeks to 6 years old.
  2. Subject (b)(6) had a liver/kidney transplant and a serious surgical complication prior to application of Tachosil Exclusion: liver transplant
  3. Subject (b)(6) was a re transplant: Exclusion: re transplant
- Investigator failed to obtain informed consent prior to investigational drug administration for at least 2 subjects.
- Investigator did not maintain adequate case histories with respect to observations and data pertinent to the primary efficacy endpoint specifically seven out of 11 subjects did not have source documentation to support the data recorded in the " Application of Tachosil" and Haemostatic Efficacy" section of the case report form.

- Investigator provided Investigational Medical Product (test article) to non study subjects. Five packs of the Tachosil sponges were documented on the “Drug Accountability per Site” form as being used for patients not included in the study.

*Reviewer comments:*

*It was noted on BIMO inspections during the BLA review that there were significant problems in terms of data integrity and trial conduct at the 2 sites in the UK where this study was conducted. The study was also prematurely terminated. In this reviewer’s opinion, the results of this open label study are not sufficient for approval of TachoSil for pediatric use in liver surgery or------(b)(4)----- pediatric population as an adjunct to hemostasis.*

*In the information request letter dated November 25, 2009 FDA requested that the sponsor request a pediatric deferral. The sponsor did request a pediatric deferral and they plan to include pediatric patients in their US IND studies-----*

*------(b)(4)-----.*

*Pediatric review committee will review the plan on March 10, 2010 and provide the review division with feedback.*

*At this time it is not appropriate to include information on the TC 19 IN pediatric liver surgery study conducted in the United Kingdom in the labeling. Since the sought indication is for an adjunct to hemostasis in cardiovascular surgery in adults,-----*

*------(b)(4)-----. It is also noted that the sponsor did not include all pediatric age groups in the TC 19 liver study as required by PREA in this uncontrolled study. Only ages 2.5 months to 12 years were included in that 16 patient study.*

*------(b)(4)-----  
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**Labeling:** The sponsor submitted the SPL for the labeling.

Labeling review:

On February 5, 1010, Nycomed submitted the first revised prescribing information (PI) to the BLA under STN 125351,------(b)(4)-----

----- for TachoSil and to pursue approval only for the indication related to hemostasis in cardiovascular surgery. OBRR consulted with APLB to review the proposed PI. As a result, the assigned medical officer and APLB reviewer cooperatively reviewed and revised the proposed PI submitted by Nycomed on February 5, 2010. APLB offered comments and recommendations from a promotional and comprehension perspective.

On March 5, 2010, OBBR sent an annotated PI as an Information Request (IR) to Nycomed. In response, on March 10, 2010, Nycomed submitted a revised proposed PI. APLB and the medical officer reviewed this submission, and also incorporated comments from other Review Committee members. An annotated PI was sent to Nycomed on March 12, 2010. Nycomed responded to this IR by submitting a revised draft PI on March 17, 2010.

APLB offered comments and recommendations from a promotional and comprehension perspective on each of these draft labels, and has worked closely with the Medical Officer to resolve labeling issues. Working with the Medical Officer's most recent version of the PI (circulated to the team for further discussion on March 23, 2010), APLB included its comments and recommendations to OBBR for further consideration from a promotional and comprehension perspective.

A telecon was held with the sponsor on Monday March 29, 2010 after the Division received revisions of the package insert from the sponsor.

On March 30, 2010, Nisha Jain, MD (acting chief, Clinical Review Branch) provided minor additional revisions for the package insert. These revisions were reviewed by Basil Golding, MD, Director, Division of Hematology. The revisions were sent to the sponsor on March 31, 2010 and considered to be final upon the sponsor's acceptance of the revisions. The version of the package insert concurred upon by Drs. Jain and Golding is reproduced below.

Package insert: