Application Type	Efficacy Supplement
STN	125351/172
CBER Received Date	June 20, 2014
PDUFA Goal Date	April 20, 2015 extended to July 20, 2015 based on major amendment
Division / Office	DH /OBRR
Priority Review	No
Reviewer Name(s)	Charles M. Maplethorpe M.D., Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Takeda Pharma A/S
Established Name	Fibrin Sealant Patch
(Proposed) Trade Name	TachoSil
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	Human Thrombin and Human Fibrinogen on an Equine Collagen Patch
Dosage Form(s) and Route(s) of Administration	Patch applied topically to bleed site
Dosing Regimen	Patch cut to size of bleed site, apply topically, repeat use permitted by labeling
Indication(s) and Intended Population(s)	TachoSil is a fibrin sealant patch indicated for use with manual compression in adult and pediatric patients as an adjunct for hemostasis in cardiovascular and hepatic surgery when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical. Limitations for TachoSil Use Not for use in place of sutures or other forms of mechanical ligation in treatment of major arterial or venous bleeding.

	Not for use in children under one month of age.
Orphan Designated (Yes/No)	No

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GLOSSARY

AE:	adverse event
CI:	confidence interval
DSMB:	data safety monitoring board
eCRF:	electronic case report form
EMA:	European Medicines Agency
EU:	European Union
EXT	extension
FAS:	full analysis set
HBV:	hepatitis virus b
HCV:	hepatitis virus c
HIV:	human immunodeficiency virus
ICF:	informed consent form
IND:	investigational new drug
MELD:	model for end stage liver disease
NAT:	nucleic acid testing
OR:	odds ratio
PeRC	Pediatric Research Committee
PP:	per-protocol analysis set
PREA	Pediatric Research Equity Act
PV B19:	parvovirus B19
SAE:	serious adverse event
SAF:	safety analysis set
SAP:	statistical analysis plan
SD:	standard deviation
SOC:	system organ class
SOP:	standard operating procedure
TEAE:	treatment-emergent adverse event

STN125351/172
TachoSil (Fibrin Sealant Patch) (Takeda Pharma A/S)
as an adjunct to hemostasis for adult and pediatric hepatic resection surgery
Clinical Review Memo – Charles Maplethorpe, MD., Ph.D. CBER/OBRR/DHCR/HPRB

1. Executive Summary

Takeda Pharma A/S has submitted STN125351/172, containing the results of Study TC-2402-040-SP, titled, "A Randomized, Open-Label, Parallel Group, Multi-Center Trial to Compare the Efficacy and Safety of TachoSil® versus Surgicel® Original for the Secondary Treatment of Local Bleeding in Adult and Pediatric Patients Undergoing Hepatic Resection Surgery" for the following purposes:

- to expand the labeled TachoSil indication, and
- to fulfil the Pediatric Research Equity Act (PREA) requirement, as stated in the April 5, 2010, TachoSil approval letter.

The sought indication is the following:

> TachoSil is a fibrin sealant patch indicated for use with manual compression in adult and pediatric patients as an adjunct for hemostasis in cardiovascular and hepatic surgery when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical.
>
> Limitations for TachoSil Use
> Not for use in place of sutures or other forms of mechanical ligation in treatment of major arterial or venous bleeding.
> Not for use in children under one month of age.

The original action due date of April 20, 2015, was extended to July 20, 2015, after a major amendment (STN125351/172.2) containing immunogenicity data was submitted on November 13, 2014.

Pediatric Research Equity Act (PREA) Requirement.

The April 5, 2010, approval letter for TachoSil contained the following statement regarding the PREA requirement:

> We are deferring submission of your pediatric study until December 2010 because this product is ready for approval for use in adults and the pediatric study has not been completed.
>
> Your deferred pediatric study required under 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.70 and section

505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below:

1. Deferred pediatric study under PREA for use of TachoSil as an adjunct to hemostasis in pediatric patients 0-16 years undergoing hepatic resection surgery.
2. Final Report Submission: December 2012

The Pediatric Study Plan (PSP) was presented to the PeRC, and discussed with them on March 10 and March 31, 2010, in conjunction with the initial approval of TachoSil for the adjunct to surgical hemostasis in cardiovascular surgery indication. PeRC recommended that pediatric studies in cardiovascular surgery be conducted; however, the applicant stated that such studies would be problematic because of a low enrollment, and the heterogeneous nature of bleed sites that would be studied. The applicant proposed that the PREA requirement be satisfied by enrolling pediatric subjects into the planned liver surgery study TC-2402-040-SP (see below). CBER/OBRR agreed with this proposal.

When study TC-2402-040-SP was completed after enrolling 20 subjects into the TachoSil arm, there were no subjects in the neonate (0 to 28 days of age) category; therefore, the pediatric indication excludes neonates.

Study TC-2402-040-SP Design.
This was a randomized, open label, active-controlled, multicenter study comparing TachoSil (test) to Surgicel (control) as an adjunct to surgical hemostasis in adults and pediatric subjects undergoing liver resection surgery. The primary endpoint was the proportion of subjects achieving hemostasis at a pre-identified bleeding site with 3 minutes of study agent application. Secondary endpoints were the proportion of subjects achieving hemostasis within 5 or 10 minutes at the pre-identified bleeding site.

There were 244 adult subjects randomized (114 TachoSil, 110 Surgicel), and are referred to as the Full Analysis Set (FAS). Safety was evaluated in the exposed subjects (114 TachoSil, 109 Surgicel; one subject randomized to Surgicel did not receive the study agent), and are referred to as the Safety Analysis Set (SAF). The pediatric study randomized subjects 1:1 to TachoSil or Surgicel, until a total of 20 subjects were treated with TachoSil, or until the adult enrollment (244 subjects) was completed, at which point all pediatric subjects would be treated with TachoSil for a total of 20 TachoSil pediatric subjects.

In the adult study, a similar proportion of male subjects and female subjects were randomly assigned in the trial (53% and 47%, respectively). The mean (SD) age of subjects was 58.1 (13.95) years, and in both treatment groups approximately 30% of the subjects were above 65 years. The majority of subjects were White/Caucasian (80%), and the most common ethnicity was non-Hispanic/non-Latino (88%).

In the pediatric study, a similar proportion of male and female pediatric subjects were treated overall (48% and 52%, respectively). The majority of subjects were White/Caucasian (79%) and the most common ethnicity was non-Hispanic/non-Latino (69%). The mean age was slightly higher in the TachoSil group (4.58 years; range 0.4, 13.0 years) than in the comparator group (3.77 years; range 0.4, 16.0 years).

Study TC-2402-040-SP Efficacy.
There were 244 adult subjects randomized (114 TachoSil, 110 Surgicel; one subject randomized to Surgicel did not receive the study agent); this referred to as the Full Analysis Set (FAS). Safety was evaluated in the exposed subjects (114 TachoSil, 109 Surgicel); this referred to as the Safety Analysis Set (referenced as SAF). The pediatric study randomized subjects 1:1 to TachoSil or Surgicel, until a total of 20 subjects were treated with TachoSil, or until the adult enrollment (244 subjects) was completed, at which point all pediatric subjects would be treated with TachoSil for a total of 20 TachoSil pediatric subjects.

Study TC-2402-040-SP demonstrated efficacy for both adult and pediatric groups, as shown in Tables 1 and 2:

Table 1: Logistic Regression Models of Proportion of Adult Subjects with Hemostasis within 3 Minutes

Treatment	**n/N (%)**	**Exact Binomial 95% CI**	**Pairwise Comparison TachoSil - Surgicel Original**		
			Odds Ratio (SE)	**Wald 95% CI**	***P* value**
FAS					
TachoSil	92/114(80.7)	(72.3, 87.5)			
Surgicel Original	55/110 (50.0)	(40.3, 59.7)	4.87 (1.60)	(2.55, 9.29)	<0.001
PP					
TachoSil	81/99 (81.8)	(72.8, 88.9)			
Surgicel Original	52/99 (52.5)	(42.2, 62.7)	4.83 (1.75)	(2.37, 9.82)	<0.001
Sensitivity Analysis[1] (FAS)					

Treatment	n/N (%)	Exact Binomial 95% CI	Pairwise Comparison TachoSil - Surgicel Original		
			Odds Ratio (SE)	Wald 95% CI	*P* value
TachoSil	92/114 (80.7)	(72.3, 87.5)			
Surgicel Original	56/110 (50.9)	(41.2, 60.6)	4.73 (1.56)	(2.47, 9.03)	<0.001

CI, confidence interval; FAS, full analysis set; PP, per-protocol analysis set – subjects compliant with the protocol; SE, standard error.
Percentages are based on the number of subjects with time to hemostasis in the FAS.
The proportion of subjects with hemostasis within 3 minutes was analyzed by using a logistic regression model with treatment and pooled center as factors.
[1] Missing values in the Surgicel Original group were counted as having hemostasis within 3 minutes and those in TachoSil group were counted as not having hemostasis within 3 minutes.
P values are 2-sided.
Source: STN125352/172 Clinical Report page 117 of 186

Table 2: Difference in Proportion of Pediatric Subjects with Hemostasis within 3 Minutes

Treatment	%	Exact Binomial CI	Pairwise Comparison TachoSil - Surgical Original	
			(%)	Exact Binomial CI
Pediatric FAS				
TachoSil (n=8)	87.5	(47.3, 99.7)	43.1	(-4.9, 85.5)
Surgicel Original (n=9)	44.4	(13.7, 78.8)		
Pediatric SAF				
TachoSil (n=20)	85.0	(62.1, 96.8)	40.6	(0.4, 80.8)
Surgicel Original (n=9)	44.4	(13.7, 78.8)		
Pediatric EXT				
TachoSil (n=12)	83.3	(51.6, 97.9)	–	–

CI, confidence interval; EXT, extension set, FAS, full analysis set; SAF, safety analysis set.
Percentages are based on the number of subjects with time to hemostasis in the relevant population.

The proportion of subjects with hemostasis within 3 minutes (n) was analyzed by using an exact binomial method.
Source: STN125352/172 Clinical Report page 14of 186

In both adult and pediatric studies, the use of TachoSil resulted in more rapid hemostasis, as shown by the higher proportion of subjects who achieve hemostasis within three minutes at the target bleed site compared to the control group. In the adult study, 80 percent of subjects achieved hemostasis within three minutes, with the lower bound of the 95 percent confidence interval excluding the result for the control group, which was 50 percent achieving hemostasis within three minutes. In the pediatric study, a similar result was observed; however the small sample size limited the statistical analysis.

Study TC-2402-040-SP Safety.
The serious and non-serious adverse events for the adult population are shown in appendix 1, and for the pediatric population in appendix 2.

In the adult study, there were 4 (3.5%) deaths in the TachoSil arm and 7 (6.4%) in the Surgicel arm. In the pediatric study, there was 1(5%) death in the TachoSil arm and no deaths in the Surgicel arm. All deaths were attributed to the serious underlying medical condition that resulted in liver surgery, or to adverse events associated with liver surgery.

The following table shows the serious adverse events (SAEs) in the adult population that occurred in more than 2 percent of the SAF population:

Summary of Serious Adverse Events Other than Death in Adult Patients by Treatment (Reported in ≥2% of Patients in Either Treatment Group) (SAF)

System Organ Class Preferred Term	**TachoSil (N=114)**		**Surgicel Original (N=109)**	
	n (%)	**E**	**n (%)**	**E**
Total number of patients with at least 1 SAE other than death	**43 (37.7)**	**80**	**51 (46.8)**	**109**
Cardiac disorders				
Atrial fibrillation	2 (1.8)	2	5 (4.6)	5
Gastrointestinal disorders				
Localised intraabdominal fluid	3 (2.6)	3	4 (3.7)	4
Infections and infestations				
Abdominal abscess	3 (2.6)	3	2 (1.8)	2
Postoperative wound infection	3 (2.6)	3	0	0
Injury, poisoning, and procedural complications				
Postprocedural bile leak	4 (3.5)	4	7 (6.4)	7
Metabolism and nutrition disorders				

Dehydration	4 (3.5)	4	3 (2.8)	3

Source: STN125352/172 Clinical Report

In the pediatric component of study TC-2402-040-SP, there were 156 AEs reported in the 20 TachoSil-exposed pediatric subjects; 34 of these AEs were categorized a serious, and occurred in 12pediatric subjects. AE rates were similar in the TachoSil and control arms, although the small sample size of the pediatric cohorts does not allow a reliable estimation of event rates. The AEs appeared to be related to the underlying medical condition.

Immunogenicity.

TachoSil is comprised of two active substances – human fibrinogen and human thrombin – coated onto an equine collagen sponge. Study TC-2402-040-SP monitored the adult subjects for antibody formation to 1) equine collagen and 2) human fibrinogen. In the TachoSil arm, 27 of the 96 adult subjects assessed were found to have developed equine collagen antibodies, 25 (26%) of whom were considered truly immunized. One adult in the TachoSil group developed fibrinogen antibodies.

During the long-term safety follow-up, 7 of 14 (50%) available subjects were still positive for equine antibodies approximately 1.5 to 2 years after exposure. However, no cross-reactivity between equine collagen antibodies and human collagen was identified, and no new medical conditions that could have been potentially related to the development of antibodies were reported.

The single adult subject developing antibodies against fibrinogen still had antibody titers at long-term follow-up; however, no coagulation abnormalities or medical conditions potentially related to fibrinogen antibodies have been noted.

Although the antibodies to the equine collagen component of TachoSil were found to be common in this clinical study, they appear to have minimal to no clinical impact. The results of the extension trial confirm the conclusions of the main trial, and the benefit-to-risk ratio of TachoSil remains favorable.

The Pediatric Study Plan (PSP) was presented to the PeRC, and discussed with them on March 10 and March 31, 2010, in conjunction with the initial approval of TachoSil for the adjunct to surgical hemostasis in cardiovascular surgery indication. PeRC recommended that pediatric studies in cardiovascular surgery be conducted; however, the applicant stated that such studies would be problematic because of a low enrollment, and the heterogeneous nature of bleed sites that would be studied. The applicant proposed that the PREA requirement be satisfied by enrolling pediatric subjects into the planned liver surgery study TC-2402-040-SP. CBER/OBRR agreed with this proposal.

The results of study TC-4202-040-SP demonstrate the safety and efficacy of the use of TachoSil as an adjunct to hemostasis in hepatic surgery in adults and pediatric patients. The safety profiles of the adult cardiovascular study, which was used for product licensure, and the adult hepatic resection study in this submission are similar. Although the pediatric hepatic resection study was small, the safety profile was similar to that of the adult hepatic resection study. Therefore, we can extrapolate to conclude that pediatric use is also considered safe for the approved indication, as an adjunct to hemostasis in cardiovascular surgery.

When study TC-2402-040-SP was completed after enrolling 20 subjects into the TachoSil arm, there were no subjects in the neonate (0 to 28 days of age) category; therefore, the pediatric indication excludes neonates.

Benefit/Risk Assessment.

Potential risks base on previous observations or mode of action include 1) adverse effects from antibody formation to product components, and 2) potential thrombogenicity. Observed antibody formation has not been associated with adverse effects on safety or efficacy. The potential risk of thrombogenicity has not been observed. Therefore, the risk associated with the use of TachoSil as an adjunct to surgical hemostasis in adult and pediatric patients is small and is out-weighed by the hemostatic benefit.
Routine post-marketing surveillance should be sufficient for detection of risks associated with the use of TachoSil.

Recommendation.

STN125351/172 may be approved to add the adjunct to hemostasis indication for adult and pediatric hepatic resection surgery. The pediatric study under protocol TC-2402-040-SP satisfies the PREA requirement for all future adjunct to surgical hemostasis indications. There should be a limitation of use that excludes neonates (less than 30 days of age) because no subjects in this pediatric category were studied.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Subjects were undergoing liver resection for a variety of reasons, with bleeding requiring an adjunct to hemostasis.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Tisseel®, a fibrin sealant, has a general surgical indication. Pharmacologically-unrelated interventions would include Surgicel®, local pressure with gauze pads, and related surgical adjunct to hemostasis techniques.

2.3 Safety and Efficacy of Pharmacologically Related Products

Fibrin Sealant products have been recently reviewed in "Hemostats, Sealants, and Adhesives: A Practical Guide for the Surgeon" [*The American Surgeon* **78:**1305-1321 (2012)].

2.4 Previous Human Experience with the Product (Including Foreign Experience)

TachoComb S (TachoSil was approved for marketing in the European Union in June 2004.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Date	Regulatory Event
June 2004	European Commission approved marketing of TachoComb S (b) (4) TachoSil)
September 21, 2004	Type B Pre-BLA meeting (Nycomed, Inc.)
June 29, 2007	Telecon to discuss required nonclinical studies
April 1, 2008	Type C meeting to discuss CMC issues
May 14, 2008	Telecon follow-up to April 1, 2008, meeting
July 24, 2008	Telecon to discuss clinical development plan
November 21, 2008	Type B meeting to discuss clinical development plan
May 29, 2009	STN125351/0 submitted for TachoSil as an adjunct to hemostasis for cardiovascular surgery
March 10, 2010	Pediatric deferral plan for hepatic surgery (not cardiovascular surgery) submitted to PeRC; PeRC recommended pediatric studies in cardiovascular surgery
March 15, 2010	Applicant (Nycomed) submitted rationale for conducting hepatic

	surgery studies (rather than cardiovascular surgery studies) based on patient availability and confounding co-morbidities in cardiovascular surgery
March 31, 2010	PeRC rejected the applicant's rationale for not doing pediatric cardiovascular studies, but did not make this a requirement.
April 5, 2010	STN125352/0 approved with deferral of pediatric studies in hepatic surgery
November 17, 2011	Teleconference to discuss applicant's difficulties in recruiting pediatric subjects to the hepatic surgery study and a request for delayed time lines
June 14, 2013	FDA responses to CRMTS #8898 on plans for submitting results of pediatric hepatic surgery study
November 13, 2014	STN125351/172.2 submitted containing immunogenicity data; declared a major amendment; action due date extended to July 20, 2015
June 20, 2014	STN125352/172 submitted contain results for the hepatic surgery adjunct to hemostasis indication for adults and pediatric subjects
June 10, 2015	PeRC presentation for deferred pediatric studies in hepatic surgery
July 20, 2015	Action Due Date for STN125351/172

The original action due date of April 20, 2015, was extended to July 20, 2015, after a major amendment (STN125351/172.2) containing immunogenicity data was submitted on November 13, 2014.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission lacked basic information, such as narratives for deaths and serious adverse events, and incomplete information on the type of surgical procedures.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The submission appears to be compliant with Good Clinical Practices and Submission Integrity policies.

3.3 Financial Disclosures

Covered clinical study (name and/or number): Study TC-2402-040-SP		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 35		

Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable Significant payments of other sorts: Not applicable Proprietary interest in the product tested held by investigator: Not applicable Significant equity interest held by investigator in sponsor of covered study: Not applicable		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

Not applicable – licensed product

4.2 Assay Validation

Not applicable

4.3 Nonclinical Pharmacology/Toxicology

See nonclinical reviews for STN125351/0

4.4 Clinical Pharmacology

Not applicable.

4.4.1 Mechanism of Action

The thrombin/fibrinogen components on the pad form a clot on the matrix of the pad when it is applied to the wound surface.

4.4.2 Human Pharmacodynamics (PD)

Not applicable.

4.4.3 Human Pharmacokinetics (PK)

Not applicable.

4.5 Statistical

See the statistical review for STN125351/172.

4.6 Pharmacovigilance

Not applicable for the review of the submission.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This review is based on the adult and pediatric results from the IND study TC-2402-040-SP, conducted under IND 14210.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

- STN 125351/172
- IND 14210
- STN 125351/0 clinical review memo of Kimberly Lindsey, M.D.

5.3 Table of Studies/Clinical Trials

TABULAR LISTING OF ALL CLINICAL STUDIES

Type of Study	**Study Identifier**	**Location of Study Report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects (SAF)**	**Healthy Subjects or Diagnosis of Subjects**	**Duration of Treat-ment**	**Study Status; Type of Report**
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Type of Study	**Study Identifier**	**Location of Study Report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects (SAF)**	**Healthy Subjects or Diagnosis of Subjects**	**Duration of Treat-ment**	**Study Status; Type of Report**
Phase 3 2 arms Efficacy and safety	TC-014-IN	5.3.5.1	Comparison of efficacy and safety of TachoSil versus argon beam coagulator treatment	Open, randomized, prospective, multicenter, 2-arm, parallel-group study Control: Argon beam coagulator	TachoSil Intraoperative application	121	Subjects requiring elective liver resection for any reason, with minor or moderate hemorrhage persisting after primary surgical hemostatic	Single application	Completed Full report
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Type of Study	**Study Identifier**	**Location of Study Report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects (SAF)**	**Healthy Subjects or Diagnosis of Subjects**	**Duration of Treat-ment**	**Study Status; Type of Report**
Phase 3 2 arms Efficacy and safety	TC-016-IN	5.3.5.1	Comparison of efficacy and safety of TachoSil versus argon beam coagulator treatment	Open, randomized, prospective, multicenter, 2-arm, parallel-group study Control: Argon beam coagulator	TachoSil Intraoperative application	119	Subjects requiring elective liver resection for any reason, with only minor or moderate hemorrhage persisting after primary surgical hemostatic procedures of the major vessels	Single application	Completed Full report

Type of Study	**Study Identifier**	**Location of Study Report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects (SAF)**	**Healthy Subjects or Diagnosis of Subjects**	**Duration of Treat-ment**	**Study Status; Type of Report**
Phase 4 Safety trial	TC-018-IN	5.3.5.2	Collection of safety information on thromboembolic events, immunological events, and drug interactions leading to thromboembolic events or major bleeding	Prospective, multicenter, noninterventional, single-cohort study	TachoSil Intraoperative application	3098	Subjects prescribed TachoSil in accordance with European label who gave consent for collection of data	Not predefined	Completed Full report
Phase 3b Single arm Efficacy and safety	TC-019-IN	5.3.5.2	Collection of data on efficacy and safety TachoSil in children.	Prospective, noncomparative, multicenter study	TachoSil Intraoperative application	16	Children >4 weeks and <6 years of age undergoing liver resection with/without segmental liver transplantation	Single application	Completed Full report

Type of Study	**Study Identifier**	**Location of Study Report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s);** **Dosage Regimen;** **Route of Administration**	**Number of Subjects (SAF)**	**Healthy Subjects or Diagnosis of Subjects**	**Duration of Treat-ment**	**Study Status;** **Type of Report**
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Type of Study	**Study Identifier**	**Location of Study Report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects (SAF)**	**Healthy Subjects or Diagnosis of Subjects**	**Duration of Treat-ment**	**Study Status; Type of Report**
Phase 4 2 arms Efficacy and safety	TC-023-IM	5.3.5.1	Comparison of efficacy and safety of TachoSil versus hemostatic fleece material in cardiovascular surgery	Open, randomized, prospective, multicenter, 2-arm, parallel-group study	TachoSil Intraoperative application	119	Subjects having elective surgery on the heart, the ascending aorta or arch, requiring a cardiopulmonary by- pass procedure, and having bleeding from the heart muscle, pericardium, a major vessel or vascular bed that required supportive hemostatic treatment	Single application	Completed Full report

Type of Study	**Study Identifier**	**Location of Study Report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects (SAF)**	**Healthy Subjects or Diagnosis of Subjects**	**Duration of Treat-ment**	**Study Status; Type of Report**
Phase 3 Efficacy and Safety	TC-026-JP	5.3.5.1	Comparison of efficacy and safety of TachoSil versus TachoComb	Multicenter, double-blind, randomized, comparative, noninferiority study Control: TachoComb	TachoSil Intraoperative application	111	Subjects undergoing elective liver resection	Single application	Completed Full report
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Type of Study	**Study Identifier**	**Location of Study Report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s);** **Dosage Regimen;** **Route of Administration**	**Number of Subjects (SAF)**	**Healthy Subjects or Diagnosis of Subjects**	**Duration of Treat-ment**	**Study Status;** **Type of Report**
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Source: STN125351/172 Clinical Report Section 2.7.6

5.4 Consultations

None

5.4.1 Advisory Committee Meeting (if applicable)

Not applicable

5.4.2 External Consults/Collaborations

None

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1 Study TC-2402-040-SP "A randomized, open label, parallel-group, multi-center trial to compare the efficacy and safety of TachoSil® versus Surgicel® Original for the secondary treatment of local bleeding in adult and pediatric patients undergoing hepatic resection surgery."

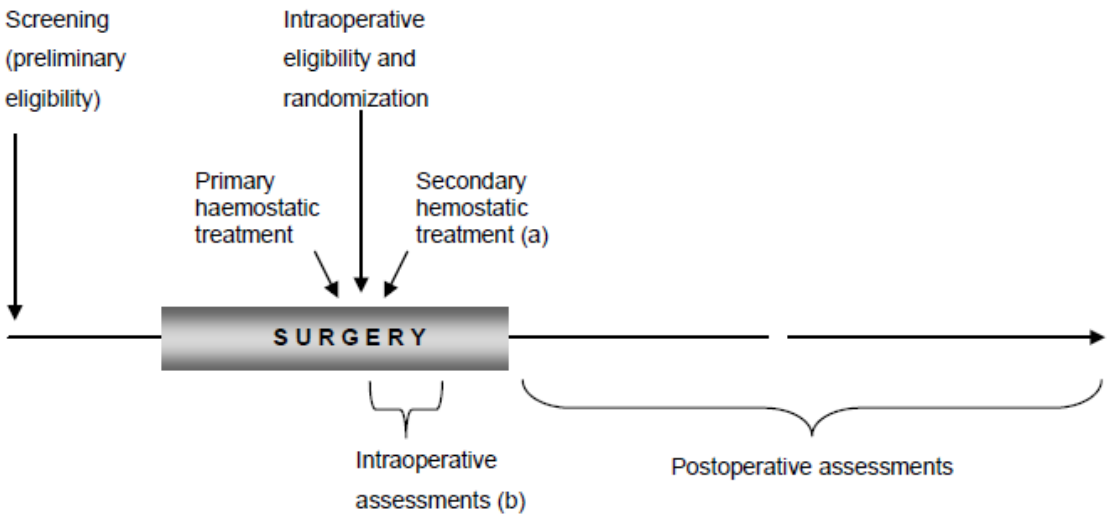
6.1.1 Objectives (Primary, Secondary, etc)

- to show that TachoSil was superior to Surgicel Original as secondary hemostatic treatment after hepatic resection surgery and primary hemostatic treatment in adult patients
- safety of TachoSil as secondary hemostatic treatment in hepatic resection surgery
- to explore the efficacy and safety of TachoSil as secondary hemostatic treatment in hepatic resection surgery in pediatric patients.

6.1.2 Design Overview

Randomized (1:1), open-label, parallel-group, multicenter in adults and pediatric subjects undergoing liver surgery

Figure 1 General Study Schema for TachoSil Hemostasis Studies



TachoSil or standard hemostatic (comparator) treatment. (b) Hemostasis in studies TC-014-IN, TC-016-IN, TC-2402-040-SP (adults and pediatric) and TC-019-IN was assessed at 3 to 10 minutes after the first application of test treatment (ie, the secondary hemostatic treatment). Hemostasis in study TC-023-IM was assessed at 3 and 6 minutes after the first application of test treatment (ie, the secondary hemostatic treatment).
Source: STN125352/172 module 2.6 Clinical Overview p. 14 of 47

Reviewer Comment: This is a standard design for fibrin sealant adjunct to surgical hemostasis studies, and is acceptable.

6.1.3 Population

The subjects were adults or pediatric patients (age 0 to 18 years of age) undergoing elective hepatectomy of at least one anatomical segment of the liver for any medical reason. Subjects needed to demonstrate mild to moderate (oozing/diffuse) bleeding from the resection area after primary control of arterial or venous bleeding by conventional measures. Subjects were excluded for coagulopathy (investigator's discretion), hypersensitivity to product components (human fibrinogen, human thrombin and/or collagen of any type), drug or alcohol abuse, or participation in another investigational study within 30 days of enrollment, among other conventional exclusions.

Reviewer Comment: The study population is acceptable.

6.1.4 Study Treatments or Agents Mandated by the Protocol

1. TachoSil, an equine collagen patch coated with the fibrin glue components: human fibrinogen and human thrombin
2. Surgicel Original absorbable hemostat (oxidized regenerated cellulose)

6.1.5 Directions for Use

The hemostatic patches are cut-to-size as needed.

6.1.6 Sites and Centers

Enrollment of Adult Patients		
Site No	**Principal Investigator**	**Site Address**
US-4001	William C. Chapman	Washington University School of Medicine 660 South Euclid Ave, Campus Box 8109 St Louis, MO 63110 Center for Advanced Medicine 4921 Parkview Place St Louis, MO 63110
US-4002	James D. Eason	James D. Eason, MD, FACS 1211 Union Ave, Ste 340 Memphis, TN 38104 Methodist University Hospital 1265 Union Ave Memphis, TN 38104
US-4003	Thomas Fishbein	Georgetown University Hospital 2 Main – Transplant Institute 3800 Reservoir Rd NW Washington, DC 20007
US-4004	David Anthony Iannitti	Carolinas Medical Center Department of General Surgery 1025 Morehead Medical Dr, Ste 300 Charlotte, NC 28204

Enrollment of Adult Patients		
Site No	**Principal Investigator**	**Site Address**
US-4005	David Imagawa	University of California Irvine Medical Center – 101 The City Drive Orange, CA 92868
US-4007	James John Pomposelli	Lahey Clinic 41 Mall Rd Burlington, MA 01805
US-4008	Charles Raben Scoggins	314 E. Broadway, #303 Louisville, KY 40202 University of Louisville Hospital 530 S. Jackson St Louisville, KY 40202
US-4009	Linda S. Sher	Division of Hepatobiliary Pancreatic Surgery and Abdominal Organ Transplantation Keck Medical Center of USC HCC 1, Ste 200 1510 San Pablo St Los Angeles, CA 90033
US-4010	Douglas Philip Slakey	Tulane University School of Medicine Department of Surgery 1430 Tulane Ave New Orleans, LA 70112

Enrollment of Adult Patients		
Site No	**Principal Investigator**	**Site Address**
US-4011	Gary S. Xiao	Drexel University College of Medicine Multi-Organ Transplant and Hepatobiliary Pancreato Surgery 216 N Broad St, 5th Floor, Feinstein Bldg Philadelphia, PA 19102
US-4012	Tomoaki Kato	Columbia University Medical Center (CUMC) 622 West 168th St, 14th Floor, Ste 105 New York, NY 10032 Center for Liver Disease and Transplantation, CUMC 622 W 168th St, PH-14 Clinic New York, NY 10032 CUMC 177 Fort Washington Ave New York, NY 10032 Children's Hospital of New York 3959 Broadway New York, NY 10032
US-4014	Ervin Steve Woodle	University of Cincinnati College of Medicine 231 Albert Sabin Way, ML 0558 Cincinnati, OH 45267
US-4015	Reid Barton Adams	University of Virginia Health System 1300 Jefferson Park Ave Charlottesville, VA 22903

Enrollment of Adult Patients		
Site No	**Principal Investigator**	**Site Address**
US-4016	Myron Eliot Schwartz	Mount Sinai School of Medicine 1425 Madison Ave, Suite L4-66, Box 1104 New York, NY 10029
US-4017	James Michael Millis	University of Chicago Medical Center Department of Transplantation 5841 South Maryland Ave, MC 5026 Chicago, IL 60637
US-4018	John Kelly Wright, Jr.	Vanderbilt University Medical Center 1211 Medical Center Dr Nashville, TN 37232
US-4019	Sharon Marie Weber	University of Wisconsin Hospital and Clinics 600 Highland Ave Madison, WI 53792
US-4020	Barburao Koneru	UMDNJ Division of Transplant Surgery 185 South Orange Ave, G 536 Newark, NJ 07101
US-4021	Kenneth David Chavin	Medical University of South Carolina Department of Transplant Surgery 96 Jonathan Lucas St, CSB 409 Charleston, SC 29425

Enrollment of Pediatric Patients		
Site No	**Principal Investigator**	**Site Address**
US-4003	Thomas Fishbein	Georgetown University Hospital 2 Main – Transplant Institute 3800 Reservoir Rd NW Washington, DC 20007
US-4012	Tomoaki Kato	Columbia University Medical Center (CUMC) 622 West 168th St, 14th Floor, Ste 105 New York, NY 10032 Center for Liver Disease and Transplantation, CUMC 622 W 168th St, PH-14 Clinic New York, NY 10032
US-4021	Kenneth David Chavin	Medical University of South Carolina Department of Transplant Surgery 96 Jonathan Lucas St, CSB 409 Charleston, SC 29425 Medical University of South Carolina Transplant Clinic 135 Rutledge Ave, 9th Floor Clinic Charleston, SC 29425
US-4022	Yuri Genyk	Children's Hospital Los Angeles 4650 Sunset Blvd Los Angeles, CA 90027 Division of Abdominal Organ Transplantation Health Care Consultation 1 1510 San Pablo St, Ste 200 Los Angeles, CA 90033

Enrollment of Pediatric Patients		
Site No	**Principal Investigator**	**Site Address**
US-4023	Riccardo Superina	Ann and Robert H. Lurie Children's Hospital of Chicago 225 East Chicago Ave Chicago, IL 60611

6.1.7 Surveillance/Monitoring

Trial Flow Chart

Procedures	**Screening** (Day -42 to Day 1)[1]	**Baseline** (Day -1 or Day 1 prior to randomi-zation/ TRIAL TREATMENT	**Day of Surgery** (Day 1)	**Daily assess-ments** until discharge	**Dis-charge** from surgical ward	**Follow - up** (1 month ± 10 days)	**Follow - up** (3 months ± 10 days)	**Follow - up** (6 months ± 10 days)[8]
Informed consent	X							
Inclusion and exclusion criteria	X	[2] X	X					
Demographics	X							
Medical	X							
Concomitant illness	X	X	[3] X		[3] X	[3] X	[3] X	X[3]
Planned procedures	X							
Physical examination	X	X		X	X	X	X	
Vital signs[4]	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X

Procedures	**Screening** (Day -42 to Day 1)[1]	**Baseline** (Day -1 or Day 1 prior to randomi-zation/ TRIAL TREATMENT	**Day of Surgery** (Day 1)	**Daily assess-ments** until discharge	**Dis-charge** from surgical ward	**Follow - up** (1 month ± 10 days)	**Follow - up** (3 months ± 10 days)	**Follow - up** (6 months ± 10 days)[8]
Pregnancy test (urine or blood)		X[2]						
Hematology and blood chemistry[5]		X			X	X		
Blood sampling for immunogenicity testing [6,7]		X				X	X	
Viral serology testing[6,7]		X					X	
Randomization [7]			X					
Efficacy endpoints			X					
Rescue treatment			X					
Intraoperative parameters			X					
Additional parameters					X	X	X	X
Drug accountability			X					
Adverse events	X	X	X	X	X	X	X	X
End of trial								X

[1] Screening and/or Baseline and/or Day of Surgery procedures were done on the same day, but all Screening and Baseline
procedures were done prior to randomization
[2] Pregnancy test was done at Baseline; exclusion criterion was considered

[3] After Baseline visit, only follow-up/resolution of documented concomitant illness
[4] Height/length without shoes and body weight were only recorded at Screening. On Day of Surgery, vital signs were recorded before surgery
[5] Hematology: blood hemoglobin, complete blood count, erythrocytes, leukocytes (lymphocytes, neutrophils, eosinophils, basophils, monocytes) and platelets; blood chemistry: prothrombin time, activated partial thromboplastin, international
Source: STN125351/172 Clinical Report page 59 or 186

Reviewer Comment: The monitoring plan is standard for fibrin sealants for use as an adjunct to surgical hemostasis, and is acceptable.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint was hemostasis at the target bleeding site (i.e. the bleed site identified during surgery for primary endpoint evaluation) within 3 minutes of application of the hemostatic study agent in the ITT population.
Secondary endpoints included the following:

- Hemostasis at the target bleed site within 5 minutes of application of the study agent
- Hemostasis at the target bleed site within 10 minutes of application of the study agent

6.1.9 Statistical Considerations & Statistical Analysis Plan

The following considerations entered into the statistical analysis plan:

- centers with small enrollment were pooled
  - if all or none of the subjects at the center achieved the primary endpoint
  - if the center enrolled fewer than 6 subjects
- center pooling fulfilled the following criteria:
  - geographic proximity
  - within same time zone and hospital type (public or private)
- For all logistic regression analyses, the Wald 95% confidence intervals is obtained from the model and presented for the odds ratios.
  - Exact binomial 95% confidence intervals are obtained for any raw proportions presented. P-values are based on the Wald test.
- Analysis sets are as follows:
  - 'Full Analysis Set' (FAS) is used to describe the analysis set which is as complete as possible and as close to the intent-to-treat ideal of including all randomized subjects
  - Per-protocol analysis set (PP) defines a subset of randomized patients who are considered compliant with the protocol.
  - Safety analysis set (SAF) will be defined as all patients who are randomized and exposed to trial treatment.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The outcomes were analyzed for the Intent-to-Treat population (the 'full analysis set' or subjects as randomized), the per-protocol population (protocol compliant subjects), and the safety analysis population (all subjects as treated). The following table shows subject disposition within these analysis populations:

Analysis Populations for Adult Patients at Baseline

	TachoSil (N=114)	**Surgicel Original (N=110)**
Analysis population	**n (%)**	**n (%)**
FAS	114 (100)	110 (100)
PP	99 (86.8)	99 (90.0)
SAF	114 (100)	109 (99.1)

FAS, full analysis set; N, total number of patients in group; n, the number of patients within the analysis set; PP, per-protocol analysis set; SAF, safety analysis set.
The enrolled total includes all patients enrolled in the trial, including those who were not randomly assigned. A patient was considered enrolled if they were given a patient ID number and had given informed consent.
Source: STN125352/172 Clinical Report p. 97 of 186

6.1.10.1.1 Demographics

The following table shows the adult and pediatric distribution of the enrollment across sex and race categories:

Study TC-2402-040-SP Demographic by Treatment and Age Group

RACE	**SEX**	**Surgicel Pediatric (< 18 y.o)**	**Surgicel Adult**	**TachoSil Pediatric (< 18 y.o)**	**TachoSil Adult**
Asian		**1**	**10**	**2**	**6**
	Female	1	2	2	4
	Male	0	8	0	2
Black or African American		**0**	**10**	**1**	**9**
	Female	0	5	1	6
	Male	0	5	0	3
Multiple		**0**	**0**	**0**	**2**
	Male	0	0	0	2
Other		**1**	**3**	**1**	**4**
	Female	1	0	1	1
	Male	0	3	0	3
White		**6**	**56**	**14**	**60**

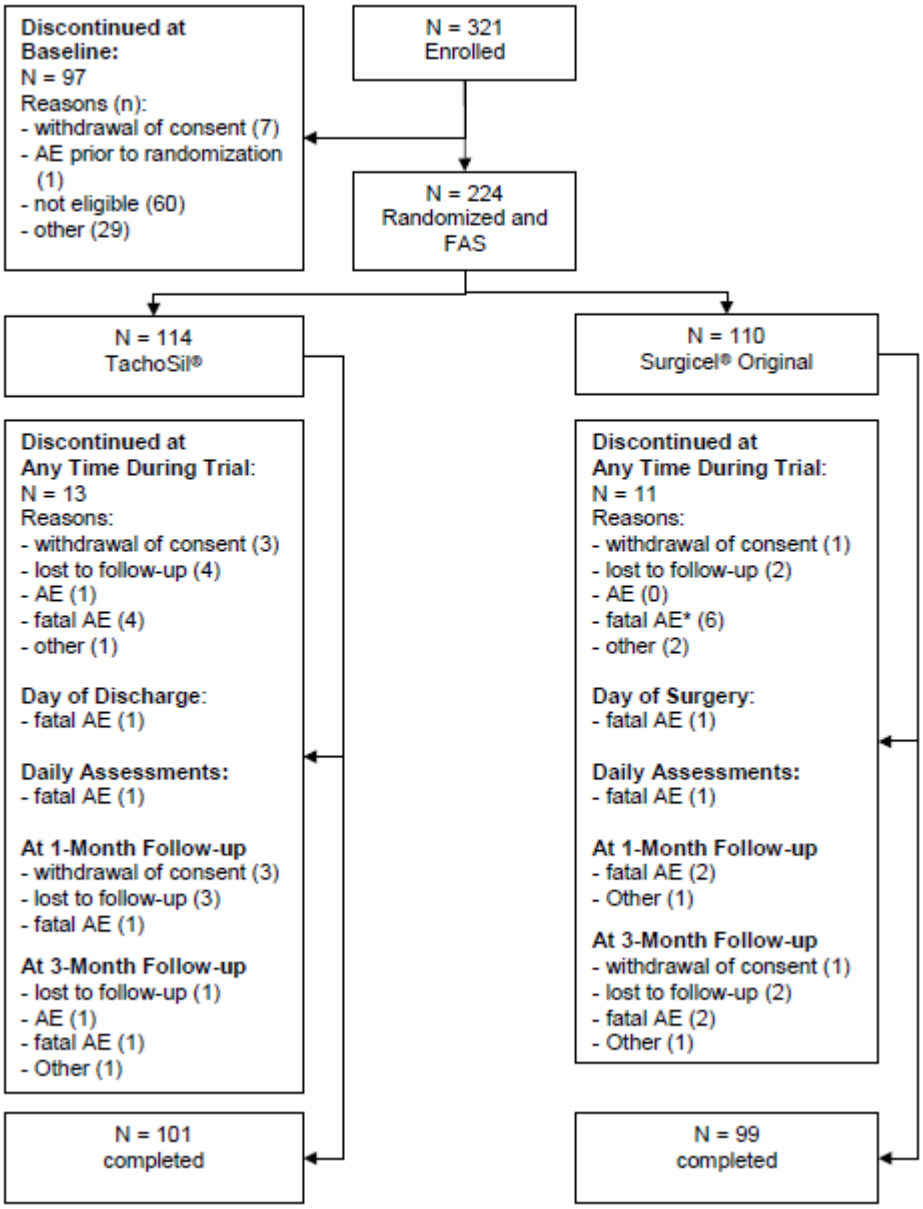
RACE	SEX	Surgicel Pediatric (< 18 y.o)	Surgicel Adult	TachoSil Pediatric (< 18 y.o)	TachoSil Adult
	Female	3	27	6	28
	Male	3	29	8	32

Source: Analysis of data in STN125351/172 database ADDM

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

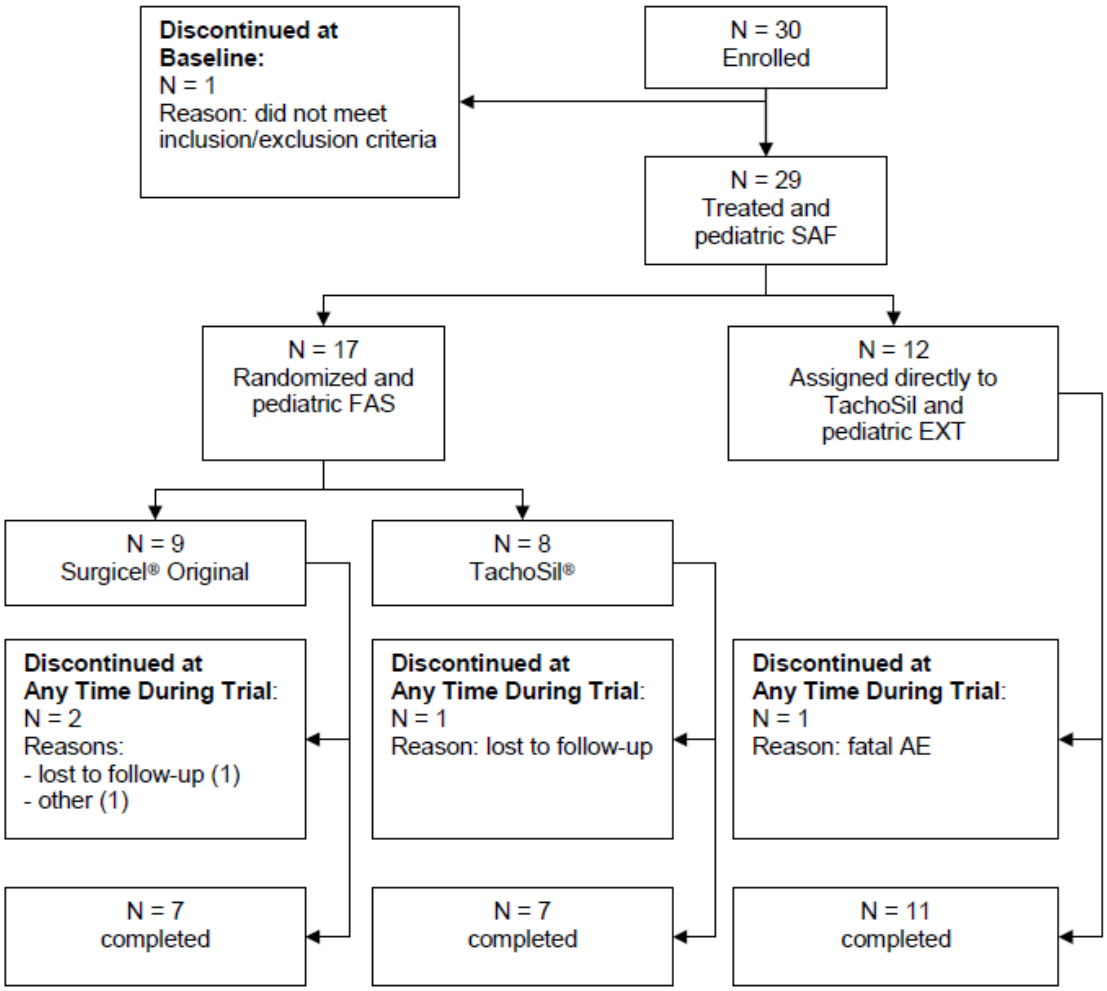
6.1.10.1.3 Subject Disposition

Figure 2 Disposition of Patients - All Adult Patients Enrolled



AE, adverse event; FAS, full analysis set.
* One additional patient in the Surgicel Original group (Patient 4007018) had a fatal AE but was not recorded as discontinuing due to this AE because the date of death ((b) (6)) was after the date the patient completed the trial (07 September 2012).
Source: STN125352/172 Clinical Report p. 91 of 186

Figure 3 Disposition of Patients - All Pediatric Patients Enrolled



AE, adverse event; EXT, extension analysis set, FAS, full analysis set; SAF, safety analysis set.
Source: STN125352/172 Clinical Report p. 93 of 186

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The full analysis set (FAS) consisted of 144 subjects in the TachoSil arm, and 110 subjects in the Surgicel control arm. All these subjects, except one subject in the Surgicel arm, were included in the safety analysis set (SAF). The per protocol (PP) set excluded 15 subjects from the TachoSil arm, and 11 subjects from the Surgicel arm, leaving 99 subjects in the TachoSil PP set, and 99 subjects in the Surgicel PP set.

Logistic Regression Models of Proportion of Adult Patients With Hemostasis Within 3 Minutes

Treatment	n/N (%)	Exact Binomial 95% CI	Pairwise Comparison		
			Odds Ratio (SE)	Wald 95% CI	*P* value
FAS					
TachoSil	92/114	(72.3, 87.5)			
Surgicel Original	55/110 (50.0)	(40.3, 59.7)	4.87 (1.60)	(2.55, 9.29)	<0.001
PP					
TachoSil	81/99 (81.8)	(72.8, 88.9)			
Surgicel Original	52/99 (52.5)	(42.2, 62.7)	4.83 (1.75)	(2.37, 9.82)	<0.001
Sensitivity Analysis[1] (FAS)					
TachoSil	92/114	(72.3, 87.5)			
Surgicel Original	56/110 (50.9)	(41.2, 60.6)	4.73 (1.56)	(2.47, 9.03)	<0.001

CI, confidence interval; FAS, full analysis set; PP, per-protocol analysis set; SE, standard error.
Percentages are based on the number of patients with time to hemostasis in the FAS.
The proportion of patients with hemostasis within 3 minutes was analyzed by using a logistic regression model with treatment and pooled center as factors.
1. Missing values in the Surgicel Original group were counted as having hemostasis within 3 minutes and those in TachoSil group were counted as not having hemostasis within 3 minutes.
P values are 2-sided.
Source: STN125352/172 Clinical Report page 117 of 186

6.1.11.2 Analyses of Secondary Endpoints

Logistic Regression Models of Proportion of Adult Patients with Hemostasis within 5 Minutes

Treatment	n/N (%)	Exact	Pairwise Comparison

		Binomial 95% CI	**Odds Ratio (SE)**	**Wald 95% CI**	***P* value**
FAS					
TachoSil	108/114	(88.9, 98.0)			
Surgicel Original	84/110 (76.4)	(67.3, 83.9)	6.24 (3.06)	(2.39, 16.30)	<0.001**1**
PP					
TachoSil	96/99 (97.0)	(91.4, 99.4)			
Surgicel Original	78/99 (78.8)	(69.4, 86.4)	10.03 (6.57)	(2.78, 36.19)	<0.001

CI, confidence interval; FAS, full analysis set; PP, per-protocol analysis set; SE, standard error.
Percentages are based on the number of patients with time to hemostasis in the FAS.
The proportion of patients with hemostasis within 5 minutes was analyzed by using a logistic regression model with treatment and pooled center as covariates.
1. *P* value was adjusted using Hochberg's adjustment for multiplicity (see Section 9.7.1.4.1.4 for details).
P values are 2-sided.
Source: STN125532/172 Clinical Report page 120 of 3301

6.1.11.4 Dropouts and/or Discontinuations

The primary efficacy analysis was repeated by imputing all missing values as having hemostasis at 3 minutes. A conservative sensitivity analysis for the primary efficacy analysis of the primary efficacy endpoint was conducted, where missing values in the Surgicel Original group were counted as having hemostasis within 3 minutes and those in the TachoSil group were counted as not having hemostasis within 3 minutes.

6.1.12 Safety Analyses

6.1.12.1 Methods

Treatment Exposure in Adult Patients: Number of Patches Applied by Treatment (SAF)

System Organ Class Preferred Term	**TachoSil (N=114)**		**Surgicel Original (N=109)**	
	n (%)	**E**	**n (%)**	**E**
Total number of patients with at least 1 adverse event of special interest	42 (36.8)	69	55 (50.5)	100
Adhesions (including bowel obstruction)	**33 (28.9)**	**42**	**37 (33.9)**	**54**
Serious	8 (7.0)	8	11 (10.1)	14
Nonserious	26 (22.8)	34	30 (27.5)	40
Hepatic abscess or other surgically related infections	**15 (13.2)**	**19**	**20 (18.3)**	**24**
Serious	11 (9.6)	12	7 (6.4)	8
Nonserious	7 (6.1)	7	14 (12.8)	16
Surgically related thromboembolic events	**4 (3.5)**	**8**	**14 (12.8)**	**22**
Serious	2 (1.8)	3	10 (9.2)	12
Nonserious	2 (1.8)	5	7 (6.4)	10

E, total number of events; N, number of patients in the SAF; n, number of patients with at least 1 event; %, number of patients with at least 1 event as % of the SAF; SAF, safety analysis set.
Adverse event terms were coded using the Medical Dictionary for Regulatory Activities, Version 15.1.
Source: STN125351/172 clinical report page 150 of 3301

Summary of Adverse Events of Special Interest in Pediatric Patients by Treatment (SAF)

System Organ Class Preferred Term	**TachoSil (N=20)**		**Surgicel Original (N=9)**	
	n (%)	**E**	**n (%)**	**E**
Total number of patients with at least 1 adverse event of special interest	6 (30.7)	12	4 (44.4)	6

System Organ Class Preferred Term	TachoSil (N=20)		Surgicel Original (N=9)	
	n (%)	E	n (%)	E
Adhesions (including bowel obstruction)	**5 (25.0)**	**6**	**2 (22.2)**	**3**
Serious	3 (15.0)	3	1 (11.1)	1
Nonserious	3 (15.0)	3	1 (11.1)	2
Hepatic abscess or other surgically related infections	**1 (5.0)**	**1**	**3 (33.3)**	**3**
Serious	0	0	1 (11.1)	1
Nonserious	1 (5.0)	1	2 (22.2)	2
Surgically related thromboembolic events	**2 (10.0)**	**5**	**0**	**0**
Serious	2 (10.0)	4	0	0
Nonserious	1 (5.0)	1	0	0

E, total number of events; N, number of patients in the SAF; n, number of patients with at least 1 event; %, number of patients with at least 1 event as % of the SAF; SAF, safety analysis set.
Adverse event terms were coded using the Medical Dictionary for Regulatory Activities, Version 15.1.
Source: STN125351/172 clinical report page 151 of 3301

6.1.12.2 Overview of Adverse Events

6.1.12.3 Deaths

There were 4 deaths in the TachoSil adult study arm, and 1 death in the TachoSil pediatric study arm. The adult deaths were from cardiorespiratory, gastrointestinal hemorrhage, multiorgan failure, and hepatic failure. The pediatric death was in a 6 month old female who experienced disseminated intravascular coagulopathy with exsanguination after septicemia.

Reviewer Comment: All deaths appear to be related to the underlying medical condition.

Study TC-2402-040-SP: Deaths of Adult Subjects – Narrative and Serious Adverse Events

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
4001015 57 y.o white female	**Surgicel**	This case concerns a 57 year old female subject who experienced a fatal serious adverse event of		

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
Biliary reconstruction with Roux En Y hepaticojejunostomy And Venovenous bypass		gastrointestinal hemorrhage. This subject underwent hepatic carcinoma surgery on (b) (6) (Study Day 1). The subject was randomized to the comparator treatment for secondary surgical hemostasis. On Study Day 16, the subject started feeling poorly; she had chills and feeling faint. Blood pressure was not measured and the subject was admitted to hospital. Upon admission antibiotic treatment was started. The subject presented with symptoms of dehydration and IV solution was started. The subject had a history of anemia and on Study Day 16, the subject's hemoglobin was 10.8 (units not provided). On Study Day 17, the subject's hemoglobin dropped to 6.8 (units not provided). A Blood transfusion was ordered. On Study Day 17, the subject experienced a bloody stool and a CT scan revealed a new mesenteric vein thrombus. No abscess or fluid collection was noted. On Study Day 20, the subject developed hematemesis and hematochezia. On Study Day 21, the subject vomited bright red blood, had several large bloody stools and became hypotensive. The subject was decompensated and transferred to Intensive Care Unit (ICU). She was hypotensive, tachycardic, hypoxic and was intubated. Massive transfusion was performed, however upper GI endoscopy revealed blood throughout the esophagus and gastric body with pulsatile bleeding noted in the second duodenum. Visceral angiography and embolization were performed. However the subject became unstable with drop in heart rate and blood pressure and died. The investigator considered cardiac arrest causing the death.		
4001015	Surgicel	-6	Granulomatous disease in spleen	Not Recovered
4001015	Surgicel	1	Periods of apnea	Recovered
4001015	Surgicel	1	Hyperglycemia	Recovered
4001015	Surgicel	2	Oliguria	Recovered

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
4001015	Surgicel	2	intermittent tacycardia	Recovered
4001015	Surgicel	3	post right liver trisectionectomy Bile duct leak	Not Recovered
4001015	Surgicel	4	Red rash on abdomen	Recovered
4001015	Surgicel	4	Red rash on left thigh	Recovered
4001015	Surgicel	5	Nausea	Recovered
4001015	Surgicel	6	bilateral pleural effusions	Not Recovered
4001015	Surgicel	8	Constipation	Recovered
4001015	Surgicel	10	left arm edema	Recovered
4001015	Surgicel	11	ecchymosis of left upper extremity	Not Recovered
4001015	Surgicel	15	Weakness	Not Recovered
4001015	Surgicel	15	Dizziness	Not Recovered
4001015	Surgicel	15	Chills	Not Recovered
4001015	Surgicel	15	Thrombocytopenia	Not Recovered
4001015	Surgicel	16	Hyponatremia	Recovered
4001015	Surgicel	16	Febrile	Recovered
4001015	Surgicel	16	Proteinurea	Not Recovered
4001015	Surgicel	16	Elevated BUN	Not Recovered
4001015	Surgicel	16	Hypoclacemia	Not Recovered
4001015	Surgicel	16	Left basilar atelectasis	Not Recovered
4001015	Surgicel	16	Hypotension	Not Recovered
4001015	Surgicel	16	intermittent Tachycardia	Not Recovered
4001015	Surgicel	16	worsening anemia	Not Recovered

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
4001015	Surgicel	16	massive Gastrointestinal bleed	FATAL
4001015	Surgicel	17	superior mesenteric vein thrombus	Not Recovered
4001015	Surgicel	17	Hematemesis	Not Recovered
4001015	Surgicel	18	Hypercoagulation	Not Recovered
4001015	Surgicel	20	Diffuse colitis	Not Recovered
4001015	Surgicel	20	Pelvic free fluid	Not Recovered
4001015	Surgicel	20	Melanic stool	Not Recovered
4001015	Surgicel	21	Partially contained dissection flap within the common hepatic artery	Recovered
4001015	Surgicel	21	Vascular procedure complication/	Recovered
4001015	Surgicel	21	Hyperkalemia	Recovered
4001015	Surgicel	21	Anxiety	Not Recovered
4001015	Surgicel	21	Shortness of breath	Not Recovered
4001015	Surgicel	21	Hypoxia	Not Recovered
4002005 53 y.o white female ECRP with stent placement	**Surgicel**	This case concerns a 54 year old female subject who experienced fatal serious adverse events of abdominal abscess and sepsis. This subject underwent resection for cell carcinoma of gallbladder and liver on (b) (6) (Study Day 1). The subject was randomized to the comparator treatment for secondary treatment of hemostasis. On Study Day 13, the subject was admitted from another hospital with abdominal abscess. Treatment with ciprofloxacin, doripenem, micafungin and vancomycin had been given for the abscess. Drainage revealed 1000 ml purulent fluid.		

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
		On Study Day 14, the subject developed sepsis and was too unstable to allow surgery to be performed. On Study Day 27, the subject passed away due to septic shock. The subject was not recovered from the abdominal abscess at time of death due to sepsis. An autopsy confirmed the diagnosis. The investigator considered the event to be not related to trial drug but due to operative complication.		
4002005	Surgicel	21	peripheral edema	Recovered
4002005	Surgicel	21	abdominal pain	Recovered
4002005	Surgicel	21	radiating right shoulder pain	Recovered
4002005	Surgicel	23	abdominal abscess	Not Recovered
4002005	Surgicel	24	sepsis	FATAL
4003001 77 y.o white male right hepatectomy for cancer	**Surgicel**	This case concerns a 77 year-old male subject who experienced a fatal serious adverse event of metastases to bone, and nonfatal serious adverse events of abdominal abscess, pleural effusion, and jaundice. This subject underwent a right hepatectomy on [redacted] (Study Day 1). The subject was randomized to the comparator treatment, Surgicel, for secondary treatment of hemostasis. The subject was re-admitted to the hospital due to weight loss and abnormal white blood count (WBC values), and was subsequently diagnosed with abdominal abscess on Study Day 35. On Study Day 49, the event of bilateral pleural effusion was diagnosed. On Study Day 49, new lesions were identified on CT scan and metastases to bone was reported. The subject recovered from abdominal abscess on Study Day 58. The subject was re-admitted on Study Day 64 for new onset of jaundice. The outcome for the events of pleural effusion and jaundice are unknown. Care was withdrawn on Study Day 80 when the subject died due to progression of cancer. The investigator considered the events to be not related		

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
		to study drug but due to progression of underlying disease		
4003001	Surgicel	1	atrial fibrillation	Recovered
4003001	Surgicel	1	dehydration	Recovered
4003001	Surgicel	1	elevated liver enzymes	Recovered
4003001	Surgicel	1	weight loss	Not Recovered
4003001	Surgicel	2	urticaria	Recovered
4003001	Surgicel	2	hypotension	Recovered
4003001	Surgicel	2	thrombocytopenia	Recovered
4003001	Surgicel	2	acute kidney injury	Recovered
4003001	Surgicel	2	bibasilar atelectasis	Recovered
4003001	Surgicel	2	hyperkalemia	Recovered
4003001	Surgicel	2	Dehydration	Recovered
4003001	Surgicel	2	bilateral pleural effusion	Not Recovered
4003001	Surgicel	3	hepatic steatosis	Not Recovered
4003001	Surgicel	7	melena	Recovered
4003001	Surgicel	20	fatigue	Not Recovered
4003001	Surgicel	35	abdominal abscess	Recovered
4003001	Surgicel	35	loss of appetite	Not Recovered
4003001	Surgicel	35	loss of mental acuity	Not Recovered
4003001	Surgicel	35	failure to thrive	Not Recovered
4003001	Surgicel	35	acute fatigue	Not Recovered
4003001	Surgicel	49	dehydration	Recovered
4003001	Surgicel	49	Carbohydrate antigen 19-9 increased/	Not Recovered
4003001	Surgicel	49	depression	Not Recovered
4003001	Surgicel	49	Elevated White Blood Cell Count	Not Recovered

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
4003001	Surgicel	49	Recurrant bilateral atelectasis	Not Recovered
4003001	Surgicel	49	pulmonary nodules	Not Recovered
4003001	Surgicel	49	renal cysts	Not Recovered
4003001	Surgicel	49	bowel wall thickening, terminal ileum	Not Recovered
4003001	Surgicel	50	hypokalemia	Recovered
4003001	Surgicel	57	progression of disease-metastasis to bone	FATAL
4003001	Surgicel	58	nausea	UNKNOWN
4003001	Surgicel	58	1.5 cm lucency t9 vertebral body on imaging	Not Recovered
4003001	Surgicel	64	Cough	Recovered
4003001	Surgicel	64	dehydration	Recovered
4003001	Surgicel	64	jaundice	Not Recovered
4003001	Surgicel	64	confusion	Not Recovered
4003001	Surgicel	64	Hyperbilirubinemia	Not Recovered
4003001	Surgicel	64	pedal edema	Not Recovered
4003001	Surgicel	64	joint pain	Not Recovered
4003001	Surgicel	64	abdominal pain	Not Recovered
4003001	Surgicel	68	atrial fibrillation	Not Recovered
4003001	Surgicel	72	Constipation	Recovered
4003001	Surgicel	76	Acute Respiratory Failure	Not Recovered
4003001	Surgicel	76	lower nephron nephrosis	Not Recovered
4003001	Surgicel	78	acidosis	Not Recovered

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
4003012 70 y.o. female Liver lobectomy for cancer	**Surgicel**	This case concerns a 70 year-old female subject who experienced a fatal serious adverse event of recurrent hepatic cancer, and nonfatal serious adverse events of wound infection staphylococcal and staphylococcus test positive. This subject underwent uncomplicated liver lobectomy due to hepatocellular carcinoma on [redacted] (Study Day 1). The subject was randomized to the comparator treatment, Surgicel, for secondary treatment of hemostasis. On Study Day 36, the subject was seen in the emergency department due to fatigue and fever. Blood cultures had returned positive for methicillin resistant staphylococcus aureus and a worsening of the wound infection was reported. The subject was considered stable and was discharged home with oral antibiotics (sulfamethoxazole/trimethoprim and cephalexin). The event of staphylococcus positive resolved on Study Day 40 and the wound infection resolved on Study Day 112. The subject died on Study Day 137 due to recurrence of hepatocellular carcinoma. The investigator considered the events as not related to Surgicel; an alternative etiology was not provided.		
4003012	Surgicel	1	Elevated White Blood Cell Count	Recovered
4003012	Surgicel	1	worsening anemia	Recovered
4003012	Surgicel	1	atelectasis	Recovered
4003012	Surgicel	1	bilateral pleural effusions	Recovered
4003012	Surgicel	2	fever	Recovered
4003012	Surgicel	3	Mild Confusion	Recovered
4003012	Surgicel	4	acidemia	Recovered
4003012	Surgicel	4	retaining oxygen	Recovered
4003012	Surgicel	5	Post Operative weakness	Recovered
4003012	Surgicel	20	Wound infection	Recovered
4003012	Surgicel	20	bilateral pedal edema	Recovered
4003012	Surgicel	34	fatigue	Recovered
4003012	Surgicel	36	Positive Blood Culture,	Recovered

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
			MRSA	
4003012	Surgicel	36	Recurrent wound infection, MRSA	Recovered
4003012	Surgicel	38	yeast infection	Recovered
4003012	Surgicel	63	nausea	Recovered
4003012	Surgicel	137	Hepatic neoplasm malignant recurrent	FATAL
4007018 75 y.o white male Radical Cholecystectomy	**Surgicel**	This case concerns a 75 year-old male subject who experienced a fatal serious adverse event of cholangitis, and nonfatal serious adverse events of bacteremia (twice), cholangitis, bile duct stenosis, and renal failure. This subject underwent liver surgery on [redacted] (Study Day 1). The patient was randomized to the comparator treatment, Surgicel, for secondary treatment of hemostasis. On Study Day 83, the subject developed bacteremia. Interventional antibiotic therapy was initiated and the subject recovered on Study Day 85. The investigator considered the event to be not related to study drug but due to bile duct stricture and cancer. On Study Day 97, the subject developed cholangitis. Following the scheduled Percutaneous Transhepatic Cholangigraphy, the subject was fully recovered on Study Day 98 and was discharged. The investigator considered the event to be not related to study drug but due to the underlying disease of stage IV gallbladder carcinoma. On Study Day 149, the subject once again developed bacteremia. Interventional therapy with antibiotics was initiated on Study Day 149. On Study Day 151, the subject was hospitalized and subjected to intravenous administration of vancomycin as interventional therapy. The event was considered recovered on Study Day 154. The investigator considered the event to be not related to study drug but an otherwise unspecified underlying disease of fevers. On Study Day 170, the subject developed recurrent		

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
		cholangitis. The subject was treated with intravenous antibiotics. The investigator considered the event to be not related to study drug but due to underlying diseases rigors, malaise, and abdominal pain (not further specified).On Study Day 190, the subject developed bile duct stenosis and, on Study Day 195, acute kidney injury leading to renal failure. Treatment with sodium chloride and albumin were initiated on Study Days 190 and 198, respectively. The subject was discharged to hospice on Study Day 203 and died on Study Day 204. The investigator reported that the subject had not recovered from the events of bile duct stenosis and renal failure at the time of death. The investigator considered the acute kidney injury leading to renal failure not related to study treatment and put forward atrial fibrillation as an alternative etiology.		
4007018	Surgicel	1	Dizziness	Recovered
4007018	Surgicel	2	Forgetfullness	Recovered
4007018	Surgicel	2	Agitated	Recovered
4007018	Surgicel	15	Bile Duct Stricture	Recovered
4007018	Surgicel	83	Bacteremia	Recovered
4007018	Surgicel	97	Cholangitis	Recovered
4007018	Surgicel	149	bacteremia	Recovered
4007018	Surgicel	170	recurrent cholangitis	FATAL
4007018	Surgicel	190	Malignant Biliary Stricture	Not Recovered
4007018	Surgicel	195	Acute Kidney Injury Leading to Renal Failure	Not Recovered
4021015 82 y.o. female Liver surgery for cancer	**Surgicel**	This case concerns an 82 year old female subject who experienced a fatal serious adverse event of acute myocardial infarction. This subject underwent liver surgery on (b) (6) (Study Day 1). The subject was randomized to the comparator treatment for secondary hemostasis. The subject had a normal post-operative recovery. On the same day of surgery, the subject developed acute myocardial infarction. Four hours after surgery		

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
		the subject developed cardiorespiratory arrest. Resuscitation with intubation, compression and defibrillation took place for 45 minutes. The subject went to the Intensive Care Unit (ICU) where it continued for additional 40 minutes. The subject was brought back to surgery for re-exploration and death was pronounced on Study Day one at 06:15 PM. According to the autopsy report, the probable death cause was acute myocardial infarction due to severe atherosclerotic coronary artery disease complicated by extensive pulmonary tumor embolic disease due to hepatocellular carcinoma. The autopsy also revealed that the subject had a medical history of coronary artery disease The subject died from the acute myocardial infarction on the same day. The subject's medical history of coronary artery disease presents a possible alternative etiology for acute myocardial infarction. The event of acute myocardial infarction is considered by the investigator to be not related to study treatment, and related to the postoperative course as a complication.	
4021015	Surgicel	-6	Granulomatous disease in spleen	Not Recovered
4021015	Surgicel	1	Periods of apnea	Recovered
4021015	Surgicel	1	Hyperglycemia	Recovered
4021015	Surgicel	2	intermittent tacycardia	Recovered
4021015	Surgicel	3	Bile duct leak	Not Recovered
4021015	Surgicel	4	Oliguria	Recovered
4021015	Surgicel	4	Red rash on abdomen	Recovered
4021015	Surgicel	4	Red rash on left thigh	Recovered
4021015	Surgicel	5	Nausea	Recovered
4021015	Surgicel	6	bilateral pleural effusions	Not Recovered
4021015	Surgicel	8	Constipation	Recovered
4021015	Surgicel	10	left arm edema	Recovered
4021015	Surgicel	11	ecchymosis of left upper extremity	Not Recovered

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
4021015	Surgicel	15	Weakness	Not Recovered
4021015	Surgicel	15	Dizziness	Not Recovered
4021015	Surgicel	15	Chills	Not Recovered
4021015	Surgicel	16	Hyponatremia	Recovered
4021015	Surgicel	16	Febrile	Recovered
4021015	Surgicel	16	Thrombocytopenia	Not Recovered
4021015	Surgicel	16	Proteinurea	Not Recovered
4021015	Surgicel	16	Elevated BUN	Not Recovered
4021015	Surgicel	16	Hypoclacemia	Not Recovered
4021015	Surgicel	16	Left basilar atelectasis	Not Recovered
4021015	Surgicel	16	Hypotension	Not Recovered
4021015	Surgicel	16	intermittent Tachycardia	Not Recovered
4021015	Surgicel	16	worsening anemia	Not Recovered
4021015	Surgicel	16	massive Gastrointestinal bleed	FATAL
4021015	Surgicel	17	superior mesenteric vein thrombus	Not Recovered
4021015	Surgicel	17	Hematemesis	Not Recovered
4021015	Surgicel	18	Hypercoagulation	Not Recovered
4021015	Surgicel	20	Diffuse colitis	Not Recovered
4021015	Surgicel	20	Pelvic free fluid	Not Recovered
4021015	Surgicel	20	Melanic stool	Not Recovered

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
4021015	Surgicel	21	Partially contained dissection flap within the common hepatic artery	Recovered
4021015	Surgicel	21	Hyperkalemia	Recovered
4021015	Surgicel	21	Anxiety	Not Recovered
4021015	Surgicel	21	Shortness of breath	Not Recovered
4021015	Surgicel	21	Hypoxia	Not Recovered
4015014 77 y.o. female Partial hepatectomy with bile duct reconstruction	**Surgicel**	This case concerns a 77 year old female subject who experienced a fatal serious adverse event of pulmonary artery thrombosis. This subject underwent partial hepatectomy with bile duct reconstruction on (b) (6) (Study Day 1). The subject was randomized to the comparator treatment for secondary treatment of hemostasis. Post-surgery, the subject presented with oliguria and creatinine values raised to 2.1 (normal range and units were not provided). On Study Day 3, two days after surgery had been performed; the subject became short of breath and was diagnosed with pulmonary artery embolism. Interventional intubation, administration of vasopressors, angio/ radiology procedure with right pulmonary artery thrombolysis, intravenous catheter filter and temporary dialysis catheter placement were performed. The subject died due to pulmonary artery embolism and multi organ failure on Study Day 11. The investigator attributed the event pulmonary artery embolism to the subject's underlying disease of cancer and the recent surgery. The subject's recent surgery represents a compelling alternative etiology, as pulmonary artery embolism is commonly observed post-operatively in immobilized subjects. In addition, the subject's medical history of transient ischemic attack is suggestive of an latent vascular disease with potential development of an embolism.	

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
4015014	Surgicel	3	hypocalcemia	Recovered
4015014	Surgicel	3	tachycardia	Recovered
4015014	Surgicel	3	Acute Kidney Injury	Not Recovered
4015014	Surgicel	3	pulmonary artery thrombus	FATAL
4015014	Surgicel	4	hypotension	Not Recovered
4015014	Surgicel	4	Atrial Fibrillation	Not Recovered
4015014	Surgicel	4	metabolic acidosis	Not Recovered
4015014	Surgicel	4	anemia	Not Recovered
4015014	Surgicel	5	hypoglycemia	Recovered
4015014	Surgicel	5	enterococcus bacteremia	Not Recovered
4015014	Surgicel	6	thrombocytopenia	Not Recovered
4015014	Surgicel	8	constipation	Not Recovered
4001043 73 y.o. male Hepatic lobectomy with diaphragm repair	**TachoSil**	This case concerns a 73 year old male subject who experienced a fatal serious adverse event of gastrointestinal hemorrhage and a nonfatal serious adverse event of cardiac arrest. This subject underwent surgery with hepatectomy, diaphragm repair and test tube placement on [redacted] (Study Day 1). The subject was randomized to TachoSil for secondary surgical hemostasis. Two patches of TachoSil were applied. On Study Day 5, four days after initial surgery, the subject was found unresponsive in the early evening with massive bloody emesis. Pulseless electric activity arrest was detected and resuscitative efforts were initiated. The subject's pulse was regained and the subject was transferred to the surgical intensive care unit. Packed red blood cells were administered for the massive hematemesis which was probably secondary to		

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
		esophageal varices. In the evening on Study Day 5, active massive bleeding was detected in the subject's esophagus, but visualization of the source of bleeding was not possible. An attempt to place bands blindly was unsuccessful. Massive transfusion protocol was applied. Some hours later, around midnight, asystole was observed, transfusion protocol was stopped and the subject died due to the massive gastrointestinal bleed on Study Day 6.		
4001043	TachoSil	1	Hypovolemia	Recovered
4001043	TachoSil	1	Right pneumothorax	Recovered
4001043	TachoSil	1	Intermittent sinus tachycardia	Not Recovered
4001043	TachoSil	1	Hypertension	Not Recovered
4001043	TachoSil	1	Coagulopathy	Not Recovered
4001043	TachoSil	1	Acute blood loss anemia	Not Recovered
4001043	TachoSil	1	Bibasilar atelectasis	Not Recovered
4001043	TachoSil	1	Hyperglycemia	Not Recovered
4001043	TachoSil	1	hepatic cirrhosis	Not Recovered
4001043	TachoSil	2	Methicillin-resistant staphylococcus aureus (MRSA)	Not Recovered
4001043	TachoSil	2	Oliguria	Recovered
4001043	TachoSil	3	Constipation	Not Recovered
4001043	TachoSil	4	Intermittent hiccups	Recovered
4001043	TachoSil	4	Hypokalemia	Recovered
4001043	TachoSil	4	Severe epigastric pain	Not Recovered
4001043	TachoSil	4	Post-op ileus	Not Recovered

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
4001043	TachoSil	5	Pulseless Electrical Activity Arrest	Recovered
4001043	TachoSil	5	Nausea	Recovered
4001043	TachoSil	5	Emesis	Recovered
4001043	TachoSil	5	Left pneumothorax	Not Recovered
4001043	TachoSil	5	Massive GI bleed	FATAL
4011005 48 y.o. male Hepatectomy with portal vein, vena cava, and bile duct reconstruction	**TachoSil**	This case concerns a 48 year-old male subject who experienced fatal serious adverse events of acute hepatic failure and cardiorespiratory arrest, and nonfatal serious adverse events of infectious peritonitis and hepatorenal syndrome. This subject underwent right hepatectomy with portal vein, inferior vena cava and bile duct resection and reconstruction on [redacted] (Study Day 1). The subject was randomized to TachoSil, for secondary treatment of hemostasis. Two and a half patches of TachoSil were applied. On Study Day 4, three days after surgery, acute hepatic failure was diagnosed White blood count (WBC) had decreased from 12.9 K/UL on Study Day 11 to 5.8 K/UL on Study Day 13. Platelet count had generally been low between 64-53 K/UL from Study Day 10 and 12, and decreased further to 42 K/UL on 28-AUG-2011. On Study Day 13, the subject developed ascites fluid infection with Enterobacter cloacae. No abscess was located. Additionally increased AST and ALT values had been noted in the full period. On Study Day 14, the subject was diagnosed with hepatorenal syndrome The subject had started therapy with vancomycin, octreotide, fluconazole and piperacillin/tazobactam. On Study Day 27, the subject developed acute ventilatory decompensation leading to cardiopulmonary arrest and death. The investigator considered the events as not related to study treatment, and put forward the underlying disease as alternative etiology and post-operative hepatic failure as the etiology for the hepatorenal		

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
		syndrome. In this case with a subject with a medical history of hypertension, insulin dependent diabetes, thrombocytopenia undergoing extended hepatic surgery due to intra hepatic cholangiocarcinoma, the development of the course of ascites fluid infection, hepatorenal syndrome and acute liver failure, the latter followed by complicating cardiopulmonary arrest and leading to a fatal outcome, is assessed as not related to study treatment but rather to the underlying disease and postoperative surgical complications.		
4011005	TachoSil	3	Sinus Tachycardia	Not Recovered
4011005	TachoSil	4	Acute Liver Failure	FATAL
4011005	TachoSil	13	Ascitis Fluid Infection	Recovered
4011005	TachoSil	14	Hepatorenal Syndrome	Not Recovered
4011005	TachoSil	17	Acute Respiratory Distress	Not Recovered
4011005	TachoSil	18	Artrial Fibrillation	Recovered
4011005	TachoSil	18	Worsening Anemia	Not Recovered
4011005	TachoSil	19	Hypothermia	Recovered
4011005	TachoSil	19	Acute Kidney Injury	Not Recovered
4011005	TachoSil	22	MSSA Pneumonia	Not Recovered
4011005	TachoSil	27	Death related to Cardiopulmonary Arrest	FATAL
4011011 75 y,o. male Right hepatectomy, cholecystectomy, left nephrectomy, left adrenalectomy for metastatic colon cancer	**TachoSil**	This case concerns a 75 year-old male subject who experienced a fatal serious adverse event of multi-organ failure. This subject underwent right hepatectomy, cholecystectomy, left nephrectomy and left adrenalectomy on (b) (6) (Study Day 1). The subject was randomized to TachoSil, for secondary treatment of hemostasis. Five patches were used during surgery. On Study Day 7, the subject		

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
		developed multiorgan failure (liver failure, acute respiratory distress syndrome, renal failure). The subject was placed on ventilator and continuous venovenous hemodialysis and sepsis/septic shock protocol was initiated for elevated white blood cell count (white blood cell count reported was 53.6 (no normal range was provided). Interventional therapy with intravenous vancomycin, piperacillin/tazobactam, metronidazole and fluconazole and general life supporting therapy was initiated. No cultures were returned as positive. During the post-operative course the subject's condition deteriorated and on (b) (6) Study Day 11, the subject died. Autopsy was declined by the subject's family. Death cause was reported to be multiorgan failure and metastatic colon cancer. The reporting investigator considers the event as not related to study treatment, but due to the subject's underlying disease of metastatic colon cancer and stress of extensive surgery. Confounding factors in this case is the subject's medical history of metastatic colon cancer, renal cell carcinoma who underwent right hepatectomy, cholecystectomy, left nephrectomy and left adrenalectomy, the development of multi organ failure with liver failure, acute respiratory distress syndrome, renal failure, is assessed as not related to study treatment but rather to the subject morbidity and postoperative surgical complications.		
4011011	TachoSil	1	Liver Steatosis	Not Recovered
4011011	TachoSil	4	Atrial Fibrillation	Not Recovered
4011011	TachoSil	6	cardiogenic shock	Not Recovered
4011011	TachoSil	6	Hyperkalemia	Not Recovered
4011011	TachoSil	7	Multiorgan Failure	FATAL

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
4021020 59 y.o. male Hepatic lobectomy	**TachoSil**	This case concerns a 59 year old male subject who experienced a fatal serious adverse event of hepatic failure and a nonfatal serious adverse event of abdominal infection. This subject underwent liver surgery on [redacted] (Study Day 1). The subject was randomized to TachoSil for secondary hemostasis. Three patches were applied during surgery. On Study Day 18, the subject developed liver failure cholestasis. The subject died due to the event liver failure on Study Day 126. No autopsy was performed. The investigator considered the relationship to study treatment as not related but attributed the event to the subject's underlying liver disease and recent liver lobectomy.		
4021020	TachoSil	1	Acute myocardial infarction	FATAL
4021020	TachoSil	2	Jaundice	Not Recovered
4021020	TachoSil	2	Elevated bilirubin	Not Recovered
4021020	TachoSil	8	Persistent night time agitation	Recovered
4021020	TachoSil	11	Biloma	Recovered with Sequelae
4021020	TachoSil	11	Head laceration	Recovered
4021020	TachoSil	11	Intra-abdominal infection	Recovered
4021020	TachoSil	13	Fever	Recovered
4021020	TachoSil	18	Liver failure	FATAL
4021020	TachoSil	22	VRE (vancomycin resistant enterococcus)	Recovered
4021020	TachoSil	75	Bile leak (x2)	Recovered
4021020	TachoSil	110	Fever	Recovered
4021020	TachoSil	110	Nausea	Recovered
4021020	TachoSil	110	abdominal pain	Recovered
4021020	TachoSil	110	intra-abdominal infection	Recovered
4021020	TachoSil	?	Fibrosis	UNKNOWN

Source: STN125352/172 data from listing 14.3.2.1.1; Narratives from STN125351/173 module 5.3.5.3 Integrated Summary of Safety

Study TC-2402-040-SP: Deaths of Pediatric Subjects – Narrative and Serious Adverse Events

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
4021021 6 month old African-American Female Liver transplantation	**TachoSil**	This case concerns a 6 month-old female subject who experienced a fatal serious adverse event of exsanguinations and nonfatal serious adverse events of disseminated intravascular coagulation, mycobacterium abscessus infection, portal vein thrombosis, hepatic necrosis, enterobacter infection, anastomotic complication, splenic rupture, septic shock, stenotrophomonas infection. This subject underwent liver surgery (b) (6) (Study Day 1). The subject had a medical history of liver transplantation, primary hyperoxaluria, and end stage kidney disease. The subject was randomized to TachoSil for secondary hemostasis. One patch of TachoSil was applied during surgery. On Study Day 12, the subject developed disseminated intravascular coagulopathy and a positive blood culture revealed Mycobacterium abcessus. The outcome of both of these events is unknown. The investigator considered the relationship to study drug as not related but provided alternative etiology as Mycobacterium abcessus. On Study Day 13, the subject developed liver failure. A portal vein thrombosis was diagnosed on Study Day 13 and a thrombectomy and liver biopsy was performed (artery flow was found normal) the same day. The liver biopsy revealed markedly increased amount of ischemia-induced hepatocytes necrosis. No portal inflammation, no bile duct damage, and no venulitis nor fibrosis was identified. The event of portal vein thrombosis and hepatic necrosis resolved on Study Day 13 and 16, respectively. The investigator considered the relationship to study drug as not related but attributed the event to the subject's status		

Patient ID	Study Arm	AE Onset Study Day	Adverse Event (AE)	Outcome
		Narrative		
		post liver transplantation, and underlying disease of hyperoxaluria and end stage renal disease. A second transplant was performed on Study Day 15. Due to failure of the graft following the second transplantation, the subject underwent repeated surgeries (washouts and explorative laparotomies). On Study Day 22, the subject was found to have a perforation of the previous Roux-en-Y anastomosis, splenic rupture in addition to necrotic liver. The subject had suffered from significant blood loss and was transferred to the pediatric intensive care unit where vasopressor treatment was initiated. Repeated washouts and in addition, a resection of the infarcted portion of the transplanted liver was performed. The subject's liver function declined further during the course of hospitalization. The subject developed profound septic shock and an infection with stenotrophomonas maltophilia and enterobacter cloacae on Study Day 29 as well as profound metabolic acidosis, lactic acidosis, thrombocytopenia, anemia and displayed signs of disseminated intravascular coagulopathy. The subject died due to exsanguination secondary to disseminated intravascular coagulopathy in the setting of septic shock on Study Day 43. None of the events of mycobacterium abscessus infection, enterobacter infection, anastomotic complication, splenic rupture, septic shock, and stenotrophomonas infection recovered before the subject's death.	
4021021	TachoSil	2	Gastrointestinal anastomotic leak/Roux-en-Y leak	Not Recovered
4021021	TachoSil	12	Disseminated intravascular coagulopathy	Not Recovered
4021021	TachoSil	13	Portal vein thrombosis	Recovered
4021021	TachoSil	22	Anastomotic complication/perforated roux en-y anastomosis	Not Recovered

Source: STN125352/172 data from listing 26.2.7.1.2; Narratives from STN125351/173 module 5.3.5.3 Integrated Summary of Safety

6.1.12.4 Nonfatal Serious Adverse Events

The following table shows the frequency of adverse events by body system in adults:

Study Study TC-2402-040-SP: Serious Adverse Events in Adults

Body System	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
Blood and lymphatic system disorders	5	5	3	3
Cardiac disorders	9	8	6	5
Congenital, familial and genetic disorders			1	1
Endocrine disorders			1	1
Gastrointestinal disorders	21	18	13	12
General disorders and administration site conditions	4	4	3	3
Hepatobiliary disorders	9	6	5	4
Infections and infestations	25	21	22	18
Injury, poisoning and procedural complications	12	11	6	6
Investigations	2	2		
Metabolism and nutrition disorders	5	5	6	6
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9	7	7	5
Nervous system disorders	2	2		
Psychiatric disorders	2	2	3	3
Renal and urinary disorders	2	2	2	2
Respiratory, thoracic and mediastinal disorders	7	7	7	4
Social circumstances			1	1
Vascular disorders	4	3		

Reviewer comment: Comparable numbers of adult subjects in both treatment arms experienced adverse events in all body system categories.

The following table shows the frequency of adverse events by body system in pediatric subjects:

Study Study TC-2402-040-SP: Serious Adverse Events in Pediatric Subjects

Body System	Surgicel Events	Surgicel Subjects N = 9	TachoSil Events	TachoSil Subjects N = 20
Blood and lymphatic system disorders	1	1	2	2
Congenital, familial and genetic disorders			1	1
Gastrointestinal disorders	1	1	5	5
General disorders and administration site conditions	2	2	3	3
Hepatobiliary disorders			5	3
Infections and infestations	4	3	12	4
Injury, poisoning and procedural complications			4	3
Metabolism and nutrition disorders			1	1
Nervous system disorders	1	1		
Vascular disorders			1	1

The body system category "Gastrointestinal disorders" for the pediatric subjects is shown in the following table by seriousness and treatment group:

Study Study TC-2402-040-SP: Serious and Non-serious Adverse Events in Pediatric Subjects for the Body System Category "Gastrointestinal disorders"

Seriousness	Reported Adverse Event Term	Surgicel Events	Surgicel Subjects N = 9	TachoSil Events	TachoSil Subjects N = 20
Serious	Diarrhea			2	2
Serious	Abdominal Pain			1	1
Serious	Acute Vomiting			1	1
Serious	GI Bleed			1	1
Serious	Fluid Collection At Cut Surface of The Liver	1	1		
Non-serious	Constipation			2	2
Non-serious	Emesis	1	1	2	2
Non-serious	Ascites			1	1
Non-serious	Bloody Stools			1	1
Non-serious	Chylous Ascites			1	1
Non-serious	Diarrhea			1	1
Non-serious	Distended Abdomen			1	1
Non-serious	Esophageal Ulcer			1	1
Non-serious	Gas	1	1	1	1
Non-serious	Hyperactive Bowel Sounds			1	1
Non-serious	Loose Stools			1	1

Seriousness	Reported Adverse Event Term	Surgicel Events	Surgicel Subjects N = 9	TachoSil Events	TachoSil Subjects N = 20
Non-serious	Mallory-Weiss Tear			1	1
Non-serious	Nausea			1	1
Non-serious	Right Upper Quadrant Fluid Collection			1	1
Non-serious	RLQ Pain			1	1
Non-serious	Abdominal Distention	2	1		
Non-serious	GI Upset	1	1		
Non-serious	Vomiting	1	1		

6.1.12.5 Adverse Events of Special Interest (AESI)

FDA requested monitoring of study TC-2402-040-SP for antibody formation against equine collagen and against human fibrinogen, based on earlier observations of antibody formation.

The following table summarizes the results of antibody monitoring:

Study TC-2402-040-SP: Immunogenicity and Cross-Reactivity Results for Patients Who Developed Equine Collagen Antibodies and Had a Positive Immunogenicity Result at the Long-Term Follow-Up Visit								
Patient No.	**Antigen**	**Visit**	**Date/Day of Sample**	**Sample Status**	**Immunogenicity**		**Cross-Reactivity**	
					Result	**Titer**	**Result**	**Titer**
US4001027	eqCollagen	Baseline	21 October 2011/1	Normal	Negative			
		1-Month follow-up	09 November 2011/20	Normal	Negative			
		3-Month follow-up	08 February 2012/111	Normal	Positive	188	Negative	
		24-Month follow-up (long-term)	18 March 2014/880	Normal	Positive	<50	Negative	
US4007008	eqCollagen	Baseline	28 February 2011/1	Normal	Negative			
		1-Month follow-up	31 March 2011/32	Normal	Positive	806	Negative	
		3-Month follow-up	27 May 2011/89	Normal	Positive	904	Negative	
		24-Month follow-up (long-term)	27 May 2014/1185	Normal	Positive	159	Negative	
US4007019	eqCollagen	Baseline	05 March 2012/1	Normal	Negative			
		1-Month follow-up	03 April 2012/30	Normal	Positive	440	Negative	
		3-Month follow-up	01 June 2012/89	Normal	Positive	1480	Negative	

Study TC-2402-040-SP: Immunogenicity and Cross-Reactivity Results for Patients Who Developed Equine Collagen Antibodies and Had a Positive Immunogenicity Result at the Long-Term Follow-Up Visit								
Patient No.	**Antigen**	**Visit**	**Date/Day of Sample**	**Sample Status**	**Immunogenicity**		**Cross-Reactivity**	
					Result	**Titer**	**Result**	**Titer**
		24-Month follow-up (long-term)	23 April 2014/780	Normal	Positive	222	Negative	
US4010003	eqCollagen	Baseline	14 March 2011/1	Normal	Negative			
		1-Month follow-up	28 April 2011/46	Normal	Positive	702	Negative	
		24-Month follow-up (long-term)	15 April 2014/1129	Normal	Positive	53	Negative	
US4012001	eqCollagen	Baseline	21 April 2011/1	Normal	Negative			
		1-Month follow-up	25 May 2011/35	Other: coordinator unable to properly assess	Negative			
		3-Month follow-up	29 July 2011/100	Other: coordinator unable to properly assess	Positive	127	Negative	
		24-Month follow-up (long-term)	02 June 2014/1139		Positive	116	Negative	

Study TC-2402-040-SP: Immunogenicity and Cross-Reactivity Results for Patients Who Developed Equine Collagen Antibodies and Had a Positive Immunogenicity Result at the Long-Term Follow-Up Visit								
Patient No.	**Antigen**	**Visit**	**Date/Day of Sample**	**Sample Status**	**Immunogenicity**		**Cross-Reactivity**	
					Result	**Titer**	**Result**	**Titer**
US4018013	eqCollagen	Baseline	26 July 2011/1	Other: Not specified	Negative			
		1-Month follow-up	24 August 2011/30	Other: Not specified	Negative			
		3-Month follow-up	02 November 2011/100	Other: Not specified	Positive	576	Negative	
		24-Month follow-up (long-term)	18 June 2014/1059		Positive	1279	Negative	
US4018016	eqCollagen	Baseline	27 September 2011/1	Other: Not specified	Negative			
		1-Month follow-up	19 October 2011/23	Other: Not specified	Negative			
		3-Month follow-up	04 January 2012/100	Other: Not specified	Positive	136	Negative	
		24-Month follow-up (long-term)	18 June 2014/996		Positive	463	Negative	

Day is relative to the day of surgery (Day 1).
Note: Cross-reactivity testing was only performed when the serum sample tested positive for equine collagen antibodies.

Reviewer comment: The single adult subject developing antibodies against fibrinogen still had antibody titers at long-term follow-up; however, no coagulation abnormalities or medical conditions potentially related to fibrinogen antibodies have been noted. Although the antibodies to the equine collagen component of TachoSil were found to be common in this clinical study, they appear to have minimal to no clinical impact. The results of the extension trial confirm the conclusions of the main trial, and the benefit-to-risk ratio of TachoSil remains favorable.

6.1.12.7 Dropouts and/or Discontinuations

From STN125351/172 clinical report page 94 of 186:

- A total of 26 patients (15 patients in the TachoSil group and 11 patients in the Surgicel Original group) were excluded from the PP based on events that occurred on the day of surgery.
    - The most common reason for exclusion from the PP was “randomized prior to primary hemostatic measures” (12 patients in the TachoSil group and 11 patients in the Surgicel Original group).
    - Two patients (Patients 4004001 and 4012006) in the Surgicel Original group who were excluded from the PP due to the reason of “randomized prior to primary hemostatic measures” also had other deviations that led to exclusion;
        - “radiofrequency pre-coagulation of the liver resection wound except focal radiofrequency ablation of vessels as primary hemostatic treatment” (Patient 4004001) and
        - “expected ability to lightly press the trial treatment to the liver resection wound for 3 minutes”, “minor to moderate bleeding from the resection area persisting after conventional resection procedure and primary control of arterial pulsating bleeding or major venous hemorrhage”, and “need for additional supportive hemostatic treatment” (Patient 4012006).
    - Other reasons for exclusion from the PP included:
        - “Time to hemostasis <8 minutes and 2nd treatment application recorded”. This was recorded for 2 patients in the TachoSil group (Patients 4016003 and 4021013). Patients who achieved hemostasis at 5 minutes or earlier but received a second treatment application were violating the treatment regimen and were therefore excluded from the PP (note that, after the 5-minute time point, the next time point for checking hemostasis was 8 minutes).
        - “Patient's age is invalid for the randomization schedule used”. This was recorded for 1 patient in the TachoSil group (Patient 4007014) who was allocated to the wrong age group due to an error in

entering the birth date in the IVRS. The patient was 64 years old and should therefore have been allocated to the adult group; however, he was allocated to the 0 to 23 months age group because the screening date was incorrectly entered as the date of birth.

- A total of 3 pediatric patients (1 patient in the TachoSil group and 2 patients in the Surgicel Original group) had protocol deviations recorded in Listing 26.2.2.1.1 (in the submission):
    - 1 patient in the TachoSil group (Patient 4021005) was randomized prior to primary hemostatic measures
    - 1 patient in the Surgicel Original group (Patient 4021014) received a hemostatic treatment other than the trial treatment between randomization and the time to hemostasis (or 10-minute evaluation), and had rescue medication applied less than 10 minutes after trial treatment application
    - 1 patient in the Surgicel Original group (Patient 4022004) had missing baseline immunogenicity data
    - No patients in the pediatric FAS group had actual treatment differing from randomized treatment (Appendix 16.2, Listing 26.2.2.1.3 in the submission).

Reviewer's Comment: The dropout rate and reasons for dropout are acceptable.

6.1.13 Study Summary and Conclusions

The results of study TC-4202-040-SP demonstrate the safety and efficacy of the use of TachoSil as an adjunct to hemostasis in hepatic surgery in adults and pediatric patients.

9. Additional Clinical Issues

9.1.3 Pediatric Use and PREA Considerations

The April 5, 2010, approval letter for TachoSil contained the following statement regarding the PREA requirement:

> We are deferring submission of your pediatric study until December 2010 because this product is ready for approval for use in adults and the pediatric study has not been completed.
>
> Your deferred pediatric study required under 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.70 and section

505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below:

1. Deferred pediatric study under PREA for use of TachoSil as an adjunct to hemostasis in pediatric patients 0-16 years undergoing hepatic resection surgery.
2. Final Report Submission: December 2012

The Pediatric Study Plan (PSP) was presented to the PeRC, and discussed with them on March 10 and March 31, 2010, in conjunction with the initial approval of TachoSil for the adjunct to surgical hemostasis in cardiovascular surgery indication. PeRC recommended that pediatric studies in cardiovascular surgery be conducted; however, the applicant stated that such studies would be problematic because of a low enrollment, and the heterogeneous nature of bleed sites that would be studied. The applicant proposed that the PREA requirement be satisfied by enrolling pediatric subjects into the planned liver surgery study TC-2402-040-SP (see below). CBER/OBRR agreed with this proposal.

When study TC-2402-040-SP was completed after enrolling 20 subjects into the TachoSil arm, there were no subjects in the neonate (0 to 28 days of age) category; therefore, the pediatric indication excludes neonates.

10. CONCLUSIONS

The risk associated with the use of TachoSil as an adjunct to surgical hemostasis in adult and pediatric patients is small and is out-weighed by the hemostatic benefit.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Decision Factor	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition	• Liver surgery creates large areas of parenchymal bleeding that must be addressed before surgical closure.	• TachoSil has demonstrated safety and efficacy for use as an adjunct to hemostasis in liver surgery.
Current Treatment Options	• There are several fibrin sealant products available for use as an adjunct to hemostasis	• There is no unmet medical need because the clinical studies have not demonstrated a more

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	in various surgical settings.	significant clinical benefit from the use of TachoSil compared to that of other adjunct to hemostasis products.
Clinical Benefit	• The indication for use as an adjunct to hemostasis in adult liver surgery is supported by the results of clinical study TC-2402-040-SP (TachoSil: 114 adults, 20 pediatric subjects; control Surgicel: 110 adults, 9 pediatric subjects) • Fibrin sealant products, when used as adjuncts to hemostasis, have not been able to demonstrate a traditional clinical benefit based on mortality or morbidity endpoints. For this reason, CBER decided to accept the surrogate endpoints of time-to-hemostasis or percent of subjects achieving hemostasis at a defined time point as acceptable primary endpoints for licensure. • Perhaps the major benefit from the licensure of these products has been the decreased use of the surgical practice of "home brew" fibrin	• TachoSil has demonstrated clinical benefit for use as an adjunct to hemostasis in adult liver surgery, according to the surrogate endpoint percent of subjects achieving hemostasis at 3 minutes.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	sealants made from fresh frozen plasma and licensed thrombin. These "home brew" products are thought to have a greater risk compared licensed fibrin sealant products that are validated to be virally safe.	
Risk	• TachoSil contains human thrombin and human fibrinogen on an equine collagen patch, and therefore, there is a theoretical risk for perturbation of the coagulation system. • The asborbable matrix pad delivery system is novel, and therefore, potential effects on immunogenicity have not been fully evaluated. Fifty percent of subjects form antibodies to equine collagen, however, these antibodies do not cross-react on human collage, and no immune-related adverse events have been observed.	• All the evidence indicates that the risk associated with the use of TachoSil as an adjunct to hemostasis is minor. There is no evidence of an increased risk for thrombogenicity. Immune-related clinical problems have not been observed.
Risk Management	• Potential for perturbation of the coagulation system (e.g. thrombogenicity)	• Routine pharmacovigilance should address the concern for potential perturbation of the coagulation system.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	• Potential for adverse events because of possibly increased immunogenicity.	• Routine pharmacovigilance should address the concern for potential for adverse events because of possibly increased immunogenicity. Immunogenicity monitoring of the hepatic surgery study TC-2402-040-SP has alleviated immediate concerns about immunogenicity.

11.2 Risk-Benefit Summary and Assessment

The risk associated with the use of TachoSil as an adjunct to surgical hemostasis in adult and pediatric patients is small and is out-weighed by the hemostatic benefit.

11.4 Recommendations on Regulatory Actions

The sought indication in STN 125351/172, for use with manual compression in adult and pediatric patients as an adjunct for hemostasis in cardiovascular and hepatic surgery when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical can be approve. There should be a limitation of use excluding neonates (less than 30 days of age) because this group was not studied.

11.5 Labeling Review and Recommendations

There were no disagreements with the applicant over changes to the submitted labeling recommended by FDA. The attached package insert can be approved.

11.6 Recommendations on Postmarketing Actions.

There are no recommended post-marketing requirements or commitments for clinical purposes. Routine post-marketing surveillance is recommended.

APPENDIX 1. ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
Y	Injury, poisoning and procedural complications	Post procedural bile leak	8	8	4	4
Y	Metabolism and nutrition disorders	Dehydration	3	3	4	4
Y	Gastrointestinal disorders	Localised intraabdominal fluid collection	4	4	3	3
Y	Infections and infestations	Abdominal abscess	2	2	3	3
Y	Infections and infestations	Postoperative wound infection			3	3
Y	Blood and lymphatic system disorders	Anaemia	2	2	2	2
Y	Cardiac disorders	Atrial fibrillation	5	5	2	2
Y	Gastrointestinal disorders	Impaired gastric emptying			2	2
Y	Infections and infestations	Infectious peritonitis			2	2
Y	Infections and infestations	Liver abscess	1	1	2	2
Y	Infections and infestations	Wound infection			2	2
Y	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hepatic neoplasm malignant recurrent	2	2	2	2
Y	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to liver	2	2	2	2
Y	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to lung	1	1	2	2
Y	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	1	1	2	2
Y	Blood and lymphatic system disorders	Leukocytosis			1	1
Y	Cardiac disorders	Bundle branch block right			1	1
Y	Cardiac disorders	Cardiac arrest			1	1
Y	Cardiac disorders	Cardio-respiratory arrest			1	1
Y	Cardiac disorders	Myocardial infarction			1	1
Y	Congenital, familial and genetic disorders	Syringomyelia			1	1

APPENDIX ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
Y	Endocrine disorders	Goitre			1	1
Y	Gastrointestinal disorders	Abdominal pain upper			1	1
Y	Gastrointestinal disorders	Ascites	2	2	1	1
Y	Gastrointestinal disorders	Colitis			1	1
Y	Gastrointestinal disorders	Gastrointestinal haemorrhage	2	2	1	1
Y	Gastrointestinal disorders	Gastrooesophageal reflux disease			1	1
Y	Gastrointestinal disorders	Intestinal perforation			1	1
Y	Gastrointestinal disorders	Oesophagitis	1	1	1	1
Y	Gastrointestinal disorders	Vomiting	1	1	1	1
Y	General disorders and administration site conditions	Multi-organ failure			1	1
Y	General disorders and administration site conditions	Non-cardiac chest pain			1	1
Y	General disorders and administration site conditions	Pyrexia	2	2	1	1
Y	Hepatobiliary disorders	Acute hepatic failure			1	1
Y	Hepatobiliary disorders	Bile duct obstruction			1	1
Y	Hepatobiliary disorders	Biloma			1	1
Y	Hepatobiliary disorders	Hepatic failure			1	1
Y	Hepatobiliary disorders	Hepatorenal syndrome			1	1
Y	Infections and infestations	Abdominal infection			1	1
Y	Infections and infestations	Bacteraemia	3	2	1	1
Y	Infections and infestations	Clostridial infection	1	1	1	1
Y	Infections and infestations	Clostridium difficile colitis	2	2	1	1
Y	Infections and infestations	Escherichia sepsis			1	1
Y	Infections and infestations	Haematoma infection			1	1

APPENDIX ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
Y	Infections and infestations	Lobar pneumonia			1	1
Y	Infections and infestations	Pneumonia	1	1	1	1
Y	Infections and infestations	Subdiaphragmatic abscess	1	1	1	1
Y	Infections and infestations	Viral infection			1	1
Y	Injury, poisoning and procedural complications	Postoperative adhesion			1	1
Y	Injury, poisoning and procedural complications	Seroma	1	1	1	1
Y	Metabolism and nutrition disorders	Fluid overload			1	1
Y	Metabolism and nutrition disorders	Hypophagia			1	1
Y	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to peritoneum			1	1
Y	Psychiatric disorders	Confusional state			1	1
Y	Psychiatric disorders	Delirium			1	1
Y	Psychiatric disorders	Mental status changes	2	2	1	1
Y	Renal and urinary disorders	Renal failure acute	1	1	1	1
Y	Renal and urinary disorders	Urethral haemorrhage			1	1
Y	Respiratory, thoracic and mediastinal disorders	Aspiration			1	1
Y	Respiratory, thoracic and mediastinal disorders	Pleural effusion	2	2	1	1
Y	Respiratory, thoracic and mediastinal disorders	Pneumothorax			1	1
Y	Respiratory, thoracic and mediastinal disorders	Pulmonary oedema			1	1
Y	Respiratory, thoracic and mediastinal disorders	Respiratory failure	1	1	1	1
Y	Social circumstances	Activities of daily living impaired			1	1
Y	Blood and lymphatic system disorders	Febrile neutropenia	2	2		
Y	Blood and lymphatic system disorders	Iron deficiency anaemia	1	1		
Y	Cardiac disorders	Acute myocardial infarction	1	1		
Y	Cardiac disorders	Cardiac tamponade	1	1		

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
Y	Cardiac disorders	Pericarditis	1	1		
Y	Cardiac disorders	Supraventricular tachycardia	1	1		
Y	Gastrointestinal disorders	Abdominal pain	2	2		
Y	Gastrointestinal disorders	Enterocutaneous fistula	1	1		
Y	Gastrointestinal disorders	Gastrointestinal disorder	1	1		
Y	Gastrointestinal disorders	Ileal fistula	1	1		
Y	Gastrointestinal disorders	Ileus	2	2		
Y	Gastrointestinal disorders	Nausea	1	1		
Y	Gastrointestinal disorders	Small intestinal obstruction	2	2		
Y	Gastrointestinal disorders	Small intestinal perforation	1	1		
Y	General disorders and administration site conditions	Device occlusion	1	1		
Y	General disorders and administration site conditions	Hernia obstructive	1	1		
Y	Hepatobiliary disorders	Bile duct stenosis	2	2		
Y	Hepatobiliary disorders	Cholangitis	2	1		
Y	Hepatobiliary disorders	Hepatic ischaemia	1	1		
Y	Hepatobiliary disorders	Hyperbilirubinaemia	1	1		
Y	Hepatobiliary disorders	Jaundice	1	1		
Y	Hepatobiliary disorders	Portal vein thrombosis	2	2		
Y	Infections and infestations	Appendicitis	1	1		
Y	Infections and infestations	Bacterial infection	1	1		
Y	Infections and infestations	Enterococcal bacteraemia	1	1		
Y	Infections and infestations	Klebsiella infection	1	1		
Y	Infections and infestations	Peritoneal abscess	1	1		
Y	Infections and infestations	Postoperative abscess	1	1		

APPENDIX ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
Y	Infections and infestations	Sepsis	2	2		
Y	Infections and infestations	Staphylococcal infection	1	1		
Y	Infections and infestations	Urosepsis	1	1		
Y	Infections and infestations	Wound abscess	2	1		
Y	Infections and infestations	Wound infection staphylococcal	2	2		
Y	Injury, poisoning and procedural complications	Post procedural haemorrhage	2	2		
Y	Injury, poisoning and procedural complications	Vascular graft thrombosis	1	1		
Y	Investigations	Antibiotic resistant Staphylococcus test positive	1	1		
Y	Investigations	False positive investigation result	1	1		
Y	Metabolism and nutrition disorders	Failure to thrive	1	1		
Y	Metabolism and nutrition disorders	Hyperglycaemic hyperosmolar nonketotic syndrome	1	1		
Y	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Colorectal cancer recurrent	1	1		
Y	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hepatic cancer metastatic	1	1		
Y	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to bone	1	1		
Y	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to lymph nodes	1	1		
Y	Nervous system disorders	Cerebral infarction	1	1		
Y	Nervous system disorders	Cerebrovascular accident	1	1		
Y	Renal and urinary disorders	Renal failure	1	1		
Y	Respiratory, thoracic and mediastinal disorders	Dyspnoea	1	1		
Y	Respiratory, thoracic and mediastinal disorders	Pneumonia aspiration	1	1		
Y	Respiratory, thoracic and mediastinal disorders	Pulmonary artery thrombosis	1	1		
Y	Vascular disorders	Deep vein thrombosis	2	2		

APPENDIX ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
Y	Vascular disorders	Shock	1	1		
Y	Vascular disorders	Thrombophlebitis superficial	1	1		
N	Gastrointestinal disorders	Nausea	36	29	45	34
N	Gastrointestinal disorders	Constipation	33	31	28	27
N	Blood and lymphatic system disorders	Anaemia	23	22	26	26
N	Respiratory, thoracic and mediastinal disorders	Atelectasis	16	13	23	22
N	Vascular disorders	Hypotension	18	18	22	20
N	Metabolism and nutrition disorders	Hypophosphataemia	8	8	21	18
N	General disorders and administration site conditions	Pyrexia	27	22	20	17
N	Respiratory, thoracic and mediastinal disorders	Pleural effusion	22	18	21	17
N	General disorders and administration site conditions	Oedema peripheral	16	16	17	16
N	Metabolism and nutrition disorders	Hypokalaemia	26	24	18	16
N	Gastrointestinal disorders	Vomiting	19	15	19	15
N	Metabolism and nutrition disorders	Decreased appetite	12	9	14	14
N	Gastrointestinal disorders	Abdominal pain	12	10	15	13
N	Gastrointestinal disorders	Diarrhoea	22	19	13	13
N	Vascular disorders	Hypertension	8	8	14	13
N	Gastrointestinal disorders	Ascites	4	4	14	12
N	Metabolism and nutrition disorders	Hypomagnesaemia	10	10	16	12
N	Renal and urinary disorders	Oliguria	5	5	13	12
N	Skin and subcutaneous tissue disorders	Pruritus	13	13	12	12
N	Cardiac disorders	Tachycardia	19	17	11	11
N	Gastrointestinal disorders	Abdominal distension	9	9	12	10
N	Infections and infestations	Urinary tract infection	4	4	9	9

APPENDIX ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
N	Renal and urinary disorders	Urinary retention	3	3	9	9
N	Blood and lymphatic system disorders	Leukocytosis	11	10	8	8
N	General disorders and administration site conditions	Fatigue	15	13	8	8
N	Metabolism and nutrition disorders	Hyperglycaemia	13	12	10	8
N	Cardiac disorders	Sinus tachycardia	8	8	7	7
N	Metabolism and nutrition disorders	Fluid overload	2	2	7	7
N	Musculoskeletal and connective tissue disorders	Back pain	5	5	7	7
N	Psychiatric disorders	Confusional state	6	6	7	7
N	Psychiatric disorders	Insomnia	7	7	7	7
N	Blood and lymphatic system disorders	Neutropenia	3	3	6	6
N	Gastrointestinal disorders	Dyspepsia	4	4	6	6
N	Injury, poisoning and procedural complications	Post procedural bile leak	6	6	6	6
N	Metabolism and nutrition disorders	Hypocalcaemia	6	6	6	6
N	Respiratory, thoracic and mediastinal disorders	Hypoxia	4	3	6	6
N	Hepatobiliary disorders	Hepatic steatosis	4	4	5	5
N	Metabolism and nutrition disorders	Dehydration	6	4	6	5
N	Metabolism and nutrition disorders	Hyperkalaemia	9	9	5	5
N	Metabolism and nutrition disorders	Hyponatraemia	3	3	5	5
N	Metabolism and nutrition disorders	Hypovolaemia	2	2	5	5
N	Nervous system disorders	Headache	5	5	5	5
N	Renal and urinary disorders	Renal failure acute	4	4	5	5
N	Respiratory, thoracic and mediastinal disorders	Dyspnoea	8	7	6	5
N	Respiratory, thoracic and mediastinal disorders	Pneumothorax	4	3	6	5
N	Gastrointestinal disorders	Localised intraabdominal fluid collection	10	10	4	4

APPENDIX ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
N	General disorders and administration site conditions	Asthenia	8	8	4	4
N	Injury, poisoning and procedural complications	Incision site pain	5	5	4	4
N	Investigations	Breath sounds abnormal	2	2	4	4
N	Investigations	International normalised ratio increased	2	2	4	4
N	Investigations	Transaminases increased	2	2	4	4
N	Investigations	Urine output decreased	2	2	5	4
N	Metabolism and nutrition disorders	Hypoalbuminaemia	5	5	4	4
N	Musculoskeletal and connective tissue disorders	Pain in extremity	1	1	4	4
N	Psychiatric disorders	Agitation	1	1	4	4
N	Psychiatric disorders	Hallucination			4	4
N	Respiratory, thoracic and mediastinal disorders	Hiccups	3	3	5	4
N	Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	7	6	4	4
N	Respiratory, thoracic and mediastinal disorders	Pulmonary oedema	1	1	4	4
N	Blood and lymphatic system disorders	Haemorrhagic anaemia	2	2	3	3
N	Blood and lymphatic system disorders	Thrombocytopenia	7	7	3	3
N	Cardiac disorders	Atrial fibrillation	6	5	3	3
N	Gastrointestinal disorders	Abdominal hernia			3	3
N	Gastrointestinal disorders	Abdominal pain upper	4	4	3	3
N	Gastrointestinal disorders	Flatulence	4	4	3	3
N	General disorders and administration site conditions	Chills	4	4	3	3
N	Hepatobiliary disorders	Jaundice	3	3	3	3
N	Infections and infestations	Enterococcal infection			3	3
N	Infections and infestations	Staphylococcal infection	1	1	3	3
N	Infections and infestations	Wound infection	4	4	3	3

APPENDIX ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
N	Injury, poisoning and procedural complications	Open wound	3	3	3	3
N	Injury, poisoning and procedural complications	Postoperative ileus			3	3
N	Injury, poisoning and procedural complications	Procedural pain			3	3
N	Injury, poisoning and procedural complications	Wound dehiscence	2	2	3	3
N	Metabolism and nutrition disorders	Hyperphosphataemia			3	3
N	Musculoskeletal and connective tissue disorders	Muscle spasms			3	3
N	Musculoskeletal and connective tissue disorders	Musculoskeletal chest pain	2	2	3	3
N	Nervous system disorders	Dizziness	6	5	5	3
N	Psychiatric disorders	Anxiety	3	3	3	3
N	Psychiatric disorders	Delirium	1	1	3	3
N	Psychiatric disorders	Depression	4	4	3	3
N	Psychiatric disorders	Mental status changes	2	2	3	3
N	Reproductive system and breast disorders	Benign prostatic hyperplasia	1	1	3	3
N	Respiratory, thoracic and mediastinal disorders	Bradypnoea			3	3
N	Respiratory, thoracic and mediastinal disorders	Cough	5	5	3	3
N	Respiratory, thoracic and mediastinal disorders	Respiratory failure	1	1	3	3
N	Respiratory, thoracic and mediastinal disorders	Rhinorrhoea			3	3
N	Respiratory, thoracic and mediastinal disorders	Wheezing	2	2	3	3
N	Blood and lymphatic system disorders	Leukopenia	1	1	2	2
N	Cardiac disorders	Sinus bradycardia			2	2
N	Gastrointestinal disorders	Abdominal discomfort	2	2	2	2
N	Gastrointestinal disorders	Faecaloma			2	2
N	Gastrointestinal disorders	Gastrooesophageal reflux disease	3	3	2	2
N	Gastrointestinal disorders	Ileus	7	7	2	2
N	General disorders and administration site	Granuloma			2	2

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
	conditions					
N	General disorders and administration site conditions	Temperature intolerance	3	3	2	2
N	Hepatobiliary disorders	Biloma			2	2
N	Infections and infestations	Bronchitis	1	1	2	2
N	Infections and infestations	Clostridial infection	1	1	2	2
N	Infections and infestations	Clostridium difficile colitis	1	1	2	2
N	Infections and infestations	Incision site cellulitis	2	2	2	2
N	Infections and infestations	Pneumonia			2	2
N	Infections and infestations	Upper respiratory tract infection	3	3	2	2
N	Injury, poisoning and procedural complications	Excoriation			2	2
N	Injury, poisoning and procedural complications	Fall	2	2	2	2
N	Injury, poisoning and procedural complications	Hepatic haematoma			2	2
N	Injury, poisoning and procedural complications	Incisional hernia	2	2	3	2
N	Injury, poisoning and procedural complications	Suture related complication			2	2
N	Investigations	Blood bilirubin increased			2	2
N	Investigations	Chest X-ray abnormal			2	2
N	Investigations	Heart rate decreased			3	2
N	Investigations	Liver function test abnormal	2	2	2	2
N	Investigations	Respiratory rate increased	1	1	4	2
N	Investigations	Weight decreased	4	4	2	2
N	Metabolism and nutrition disorders	Hypoglycaemia	2	2	2	2
N	Musculoskeletal and connective tissue disorders	Arthralgia	4	4	2	2
N	Musculoskeletal and connective tissue disorders	Musculoskeletal pain	4	4	2	2
N	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hepatic neoplasm			2	2

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
N	Nervous system disorders	Paraesthesia	3	3	3	2
N	Renal and urinary disorders	Dysuria	1	1	2	2
N	Renal and urinary disorders	Haematuria	2	2	3	2
N	Renal and urinary disorders	Incontinence			2	2
N	Renal and urinary disorders	Nephrolithiasis	1	1	2	2
N	Renal and urinary disorders	Renal impairment			2	2
N	Reproductive system and breast disorders	Pelvic pain			2	2
N	Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome			2	2
N	Respiratory, thoracic and mediastinal disorders	Nasal congestion			2	2
N	Skin and subcutaneous tissue disorders	Alopecia			2	2
N	Skin and subcutaneous tissue disorders	Night sweats			2	2
N	Blood and lymphatic system disorders	Coagulopathy			1	1
N	Blood and lymphatic system disorders	Hypocoagulable state			1	1
N	Blood and lymphatic system disorders	Iron deficiency anaemia			1	1
N	Blood and lymphatic system disorders	Splenic infarction			1	1
N	Blood and lymphatic system disorders	Splenic vein thrombosis			1	1
N	Blood and lymphatic system disorders	Thrombocytosis	1	1	1	1
N	Cardiac disorders	Bradycardia	1	1	1	1
N	Cardiac disorders	Bundle branch block left			1	1
N	Cardiac disorders	Cardiogenic shock			1	1
N	Cardiac disorders	Cardiomegaly	1	1	1	1
N	Cardiac disorders	Cardiopulmonary failure			1	1
N	Cardiac disorders	Left ventricular dysfunction			1	1
N	Cardiac disorders	Mitral valve calcification			1	1
N	Cardiac disorders	Palpitations			1	1

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
N	Cardiac disorders	Pericardial effusion	1	1	1	1
N	Cardiac disorders	Supraventricular extrasystoles			1	1
N	Cardiac disorders	Ventricular extrasystoles			1	1
N	Ear and labyrinth disorders	Deafness			1	1
N	Ear and labyrinth disorders	Ear pain			1	1
N	Eye disorders	Vision blurred	2	2	1	1
N	Eye disorders	Visual impairment			1	1
N	Gastrointestinal disorders	Abdominal tenderness	2	2	1	1
N	Gastrointestinal disorders	Anorectal discomfort			1	1
N	Gastrointestinal disorders	Crohn's disease			1	1
N	Gastrointestinal disorders	Dry mouth			1	1
N	Gastrointestinal disorders	Dysphagia			1	1
N	Gastrointestinal disorders	Gastric disorder			1	1
N	Gastrointestinal disorders	Gastrointestinal sounds abnormal			1	1
N	Gastrointestinal disorders	Haemorrhoids			1	1
N	Gastrointestinal disorders	Hiatus hernia			1	1
N	Gastrointestinal disorders	Intestinal dilatation	2	1	1	1
N	Gastrointestinal disorders	Intra-abdominal haemorrhage			1	1
N	Gastrointestinal disorders	Lip blister	1	1	1	1
N	Gastrointestinal disorders	Mesenteric vein thrombosis	1	1	1	1
N	Gastrointestinal disorders	Oesophagitis			1	1
N	Gastrointestinal disorders	Pancreatitis			1	1
N	Gastrointestinal disorders	Pneumoperitoneum			1	1
N	Gastrointestinal disorders	Stomatitis	1	1	1	1
N	General disorders and administration site	Catheter site pain	2	1	1	1

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
	conditions					
N	General disorders and administration site conditions	Device leakage			2	1
N	General disorders and administration site conditions	Fat necrosis			1	1
N	General disorders and administration site conditions	Generalised oedema	1	1	1	1
N	General disorders and administration site conditions	Hypothermia			1	1
N	General disorders and administration site conditions	Implant site effusion			1	1
N	General disorders and administration site conditions	Localised oedema	2	2	1	1
N	General disorders and administration site conditions	Medical device complication	2	2	1	1
N	General disorders and administration site conditions	Mucosal inflammation	4	4	1	1
N	General disorders and administration site conditions	Pain			1	1
N	General disorders and administration site conditions	Secretion discharge	1	1	1	1
N	Hepatobiliary disorders	Biliary fistula			1	1
N	Hepatobiliary disorders	Hepatic cirrhosis	1	1	1	1
N	Hepatobiliary disorders	Hepatic cyst			1	1
N	Hepatobiliary disorders	Hepatic fibrosis			1	1
N	Hepatobiliary disorders	Hepatic ischaemia			1	1
N	Hepatobiliary disorders	Hepatic lesion			1	1
N	Hepatobiliary disorders	Hyperbilirubinaemia	3	3	1	1
N	Hepatobiliary disorders	Portal vein thrombosis			1	1
N	Infections and infestations	Abdominal infection	3	3	1	1

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
N	Infections and infestations	Abdominal sepsis			1	1
N	Infections and infestations	Bacteraemia			1	1
N	Infections and infestations	Bacteroides bacteraemia			1	1
N	Infections and infestations	Cellulitis	4	4	1	1
N	Infections and infestations	Escherichia infection			1	1
N	Infections and infestations	Fungal infection	1	1	1	1
N	Infections and infestations	Localised infection			1	1
N	Infections and infestations	Nasopharyngitis	1	1	1	1
N	Infections and infestations	Oral infection			1	1
N	Infections and infestations	Pneumonia staphylococcal	1	1	1	1
N	Infections and infestations	Postoperative abscess			1	1
N	Infections and infestations	Postoperative wound infection	4	4	1	1
N	Infections and infestations	Sepsis	1	1	1	1
N	Infections and infestations	Sinusitis			1	1
N	Infections and infestations	Skin infection			1	1
N	Infections and infestations	Tooth abscess			1	1
N	Infections and infestations	Tracheobronchitis			1	1
N	Infections and infestations	Urinary tract infection bacterial	1	1	1	1
N	Injury, poisoning and procedural complications	Corneal abrasion			1	1
N	Injury, poisoning and procedural complications	Endotracheal intubation complication			1	1
N	Injury, poisoning and procedural complications	Fibula fracture			1	1
N	Injury, poisoning and procedural complications	Incision site complication	4	3	1	1
N	Injury, poisoning and procedural complications	Incision site pruritus			1	1
N	Injury, poisoning and procedural complications	Laceration			1	1
N	Injury, poisoning and procedural complications	Post procedural constipation			1	1

APPENDIX ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
N	Injury, poisoning and procedural complications	Postoperative fever			1	1
N	Injury, poisoning and procedural complications	Procedural haemorrhage	1	1	1	1
N	Injury, poisoning and procedural complications	Procedural hypertension	1	1	1	1
N	Injury, poisoning and procedural complications	Procedural hypotension			1	1
N	Injury, poisoning and procedural complications	Procedural nausea			1	1
N	Injury, poisoning and procedural complications	Seroma	2	2	1	1
N	Injury, poisoning and procedural complications	Wound			1	1
N	Injury, poisoning and procedural complications	Wound secretion			1	1
N	Investigations	Alpha 1 foetoprotein increased			1	1
N	Investigations	Blood creatinine decreased			1	1
N	Investigations	Blood creatinine increased	4	4	1	1
N	Investigations	Blood lactic acid increased	1	1	1	1
N	Investigations	Blood urea increased	1	1	1	1
N	Investigations	Body temperature decreased			2	1
N	Investigations	Body temperature increased			3	1
N	Investigations	Coagulation time prolonged			1	1
N	Investigations	Haematocrit decreased	1	1	1	1
N	Investigations	Hepatic enzyme increased	5	5	1	1
N	Investigations	Lipase increased			1	1
N	Investigations	Mean arterial pressure decreased			1	1
N	Investigations	Prothrombin time prolonged	1	1	1	1
N	Investigations	Respiratory rate decreased			1	1
N	Investigations	Total lung capacity decreased			1	1
N	Investigations	Troponin increased	1	1	1	1
N	Investigations	Weight increased	1	1	1	1

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
N	Investigations	White blood cell count increased	6	6	1	1
N	Metabolism and nutrition disorders	Acidosis	2	2	1	1
N	Metabolism and nutrition disorders	Cachexia	1	1	1	1
N	Metabolism and nutrition disorders	Diabetes mellitus			2	1
N	Metabolism and nutrition disorders	Failure to thrive	1	1	1	1
N	Metabolism and nutrition disorders	Hypernatraemia	1	1	1	1
N	Metabolism and nutrition disorders	Lactic acidosis			1	1
N	Metabolism and nutrition disorders	Malnutrition	2	1	1	1
N	Metabolism and nutrition disorders	Type 2 diabetes mellitus			1	1
N	Metabolism and nutrition disorders	Vitamin B1 deficiency			1	1
N	Musculoskeletal and connective tissue disorders	Mobility decreased	1	1	1	1
N	Musculoskeletal and connective tissue disorders	Muscular weakness			1	1
N	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	2	1	1	1
N	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Colon adenoma			1	1
N	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Colorectal cancer metastatic	1	1	1	1
N	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung neoplasm	4	4	1	1
N	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to adrenals			1	1
N	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to bone			1	1
N	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Peritoneal neoplasm			1	1
N	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Recurrent cancer			1	1
N	Nervous system disorders	Hypoaesthesia	6	5	1	1

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
N	Nervous system disorders	Lethargy	2	2	1	1
N	Nervous system disorders	Neuropathy peripheral	2	2	1	1
N	Nervous system disorders	Restless legs syndrome			1	1
N	Nervous system disorders	Sciatica			1	1
N	Nervous system disorders	Sedation			1	1
N	Nervous system disorders	Somnolence			1	1
N	Nervous system disorders	Tremor	2	2	2	1
N	Psychiatric disorders	Mental disorder			1	1
N	Psychiatric disorders	Panic attack			1	1
N	Renal and urinary disorders	Anuria	1	1	1	1
N	Renal and urinary disorders	Neurogenic bladder			1	1
N	Renal and urinary disorders	Pyuria			1	1
N	Reproductive system and breast disorders	Dysmenorrhoea			1	1
N	Reproductive system and breast disorders	Penile oedema			1	1
N	Respiratory, thoracic and mediastinal disorders	Aspiration			1	1
N	Respiratory, thoracic and mediastinal disorders	Asthma			1	1
N	Respiratory, thoracic and mediastinal disorders	Bronchospasm			1	1
N	Respiratory, thoracic and mediastinal disorders	Dry throat			1	1
N	Respiratory, thoracic and mediastinal disorders	Dysphonia	2	2	1	1
N	Respiratory, thoracic and mediastinal disorders	Dyspnoea exertional	3	3	1	1
N	Respiratory, thoracic and mediastinal disorders	Epistaxis			1	1
N	Respiratory, thoracic and mediastinal disorders	Haemoptysis			1	1
N	Respiratory, thoracic and mediastinal disorders	Hydropneumothorax			1	1
N	Respiratory, thoracic and mediastinal disorders	Hypoventilation			1	1
N	Respiratory, thoracic and mediastinal disorders	Orthopnoea			1	1

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
N	Respiratory, thoracic and mediastinal disorders	Pulmonary congestion	1	1	1	1
N	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	1	1	1	1
N	Respiratory, thoracic and mediastinal disorders	Pulmonary hypertension	1	1	1	1
N	Respiratory, thoracic and mediastinal disorders	Respiratory acidosis			1	1
N	Respiratory, thoracic and mediastinal disorders	Respiratory depression			1	1
N	Respiratory, thoracic and mediastinal disorders	Rhonchi			1	1
N	Respiratory, thoracic and mediastinal disorders	Tachypnoea	4	3	1	1
N	Skin and subcutaneous tissue disorders	Blister			1	1
N	Skin and subcutaneous tissue disorders	Dermal cyst			1	1
N	Skin and subcutaneous tissue disorders	Dermatitis			1	1
N	Skin and subcutaneous tissue disorders	Dermatitis contact			1	1
N	Skin and subcutaneous tissue disorders	Dry skin	1	1	1	1
N	Skin and subcutaneous tissue disorders	Erythema			1	1
N	Skin and subcutaneous tissue disorders	Hyperhidrosis	1	1	1	1
N	Skin and subcutaneous tissue disorders	Intertrigo			1	1
N	Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome			1	1
N	Skin and subcutaneous tissue disorders	Petechiae			1	1
N	Skin and subcutaneous tissue disorders	Rash	10	8	1	1
N	Skin and subcutaneous tissue disorders	Rash generalised			1	1
N	Skin and subcutaneous tissue disorders	Rash papular			1	1
N	Skin and subcutaneous tissue disorders	Skin disorder			1	1
N	Skin and subcutaneous tissue disorders	Skin fissures	1	1	1	1
N	Skin and subcutaneous tissue disorders	Skin irritation	1	1	1	1
N	Skin and subcutaneous tissue disorders	Skin lesion			1	1
N	Surgical and medical procedures	Incisional drainage			1	1

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
N	Surgical and medical procedures	Wound drainage			1	1
N	Vascular disorders	Vascular calcification			1	1
N	Blood and lymphatic system disorders	Eosinophilia	1	1		
N	Blood and lymphatic system disorders	Heparin-induced thrombocytopenia	1	1		
N	Blood and lymphatic system disorders	Hypercoagulation	2	2		
N	Blood and lymphatic system disorders	Lymphadenopathy	1	1		
N	Blood and lymphatic system disorders	Neutrophilia	1	1		
N	Cardiac disorders	Diastolic dysfunction	1	1		
N	Cardiac disorders	Pericardial haemorrhage	1	1		
N	Ear and labyrinth disorders	Vertigo	1	1		
N	Endocrine disorders	Hypothyroidism	1	1		
N	Endocrine disorders	Thyroid disorder	1	1		
N	Eye disorders	Conjunctivitis	1	1		
N	Eye disorders	Dry eye	1	1		
N	Eye disorders	Lacrimation increased	1	1		
N	Eye disorders	Ocular icterus	2	2		
N	Gastrointestinal disorders	Colitis	1	1		
N	Gastrointestinal disorders	Colonic polyp	1	1		
N	Gastrointestinal disorders	Faeces pale	1	1		
N	Gastrointestinal disorders	Gastric dilatation	1	1		
N	Gastrointestinal disorders	Gastritis	1	1		
N	Gastrointestinal disorders	Gastrointestinal disorder	1	1		
N	Gastrointestinal disorders	Gingival pain	1	1		
N	Gastrointestinal disorders	Haematemesis	1	1		
N	Gastrointestinal disorders	Haematochezia	3	3		

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
N	Gastrointestinal disorders	Impaired gastric emptying	1	1		
N	Gastrointestinal disorders	Inguinal hernia	1	1		
N	Gastrointestinal disorders	Intestinal mucosal hypertrophy	1	1		
N	Gastrointestinal disorders	Lip dry	1	1		
N	Gastrointestinal disorders	Malabsorption	1	1		
N	Gastrointestinal disorders	Melaena	4	4		
N	Gastrointestinal disorders	Mesenteric occlusion	1	1		
N	Gastrointestinal disorders	Oesophageal ulcer	1	1		
N	Gastrointestinal disorders	Oral pain	1	1		
N	Gastrointestinal disorders	Peritoneal disorder	1	1		
N	Gastrointestinal disorders	Retroperitoneal oedema	1	1		
N	Gastrointestinal disorders	Small intestinal obstruction	2	2		
N	General disorders and administration site conditions	Chest discomfort	2	2		
N	General disorders and administration site conditions	Chest pain	3	3		
N	General disorders and administration site conditions	Impaired healing	1	1		
N	General disorders and administration site conditions	Influenza like illness	1	1		
N	General disorders and administration site conditions	Infusion site swelling	1	1		
N	General disorders and administration site conditions	Malaise	3	3		
N	General disorders and administration site conditions	Non-cardiac chest pain	2	2		
N	General disorders and administration site conditions	Oedema	4	4		
N	Hepatobiliary disorders	Bile duct stenosis	3	3		

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
N	Hepatobiliary disorders	Dilatation intrahepatic duct acquired	1	1		
N	Hepatobiliary disorders	Hepatic infarction	1	1		
N	Hepatobiliary disorders	Periportal oedema	1	1		
N	Hepatobiliary disorders	Portal vein occlusion	1	1		
N	Infections and infestations	Bacterascites	1	1		
N	Infections and infestations	Candidiasis	1	1		
N	Infections and infestations	Catheter site infection	1	1		
N	Infections and infestations	Clostridium colitis	1	1		
N	Infections and infestations	Cystitis	1	1		
N	Infections and infestations	Device related infection	1	1		
N	Infections and infestations	Diverticulitis	1	1		
N	Infections and infestations	Enterococcal bacteraemia	1	1		
N	Infections and infestations	Fungaemia	1	1		
N	Infections and infestations	Fungal skin infection	1	1		
N	Infections and infestations	Implant site pustules	1	1		
N	Infections and infestations	Infectious peritonitis	1	1		
N	Infections and infestations	Intertrigo candida	1	1		
N	Infections and infestations	Liver abscess	1	1		
N	Infections and infestations	Perihepatic abscess	1	1		
N	Infections and infestations	Pharyngitis	1	1		
N	Injury, poisoning and procedural complications	Anaemia postoperative	1	1		
N	Injury, poisoning and procedural complications	Arteriovenous fistula site complication	1	1		
N	Injury, poisoning and procedural complications	Head injury	1	1		
N	Injury, poisoning and procedural complications	Incision site erythema	1	1		
N	Injury, poisoning and procedural complications	Incision site haemorrhage	1	1		

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
N	Injury, poisoning and procedural complications	Incision site oedema	1	1		
N	Injury, poisoning and procedural complications	Post procedural haemorrhage	1	1		
N	Injury, poisoning and procedural complications	Postoperative wound complication	2	2		
N	Injury, poisoning and procedural complications	Toxicity to various agents	2	2		
N	Injury, poisoning and procedural complications	Urinary retention postoperative	1	1		
N	Injury, poisoning and procedural complications	Vascular procedure complication	1	1		
N	Investigations	Ammonia increased	1	1		
N	Investigations	Antibiotic resistant Staphylococcus test positive	2	1		
N	Investigations	Blood albumin decreased	1	1		
N	Investigations	Blood alkaline phosphatase increased	1	1		
N	Investigations	Blood magnesium decreased	1	1		
N	Investigations	Blood pressure increased	1	1		
N	Investigations	Carbohydrate antigen 19-9 increased	1	1		
N	Investigations	Cardiac enzymes increased	1	1		
N	Investigations	Neutrophil count increased	1	1		
N	Investigations	Oxygen consumption increased	1	1		
N	Investigations	Spinal X-ray abnormal	1	1		
N	Metabolism and nutrition disorders	Electrolyte imbalance	1	1		
N	Metabolism and nutrition disorders	Gout	2	2		
N	Metabolism and nutrition disorders	Hypoproteinaemia	1	1		
N	Metabolism and nutrition disorders	Metabolic acidosis	1	1		
N	Musculoskeletal and connective tissue disorders	Flank pain	1	1		
N	Musculoskeletal and connective tissue disorders	Hypercreatinaemia	1	1		
N	Musculoskeletal and connective tissue disorders	Neck pain	1	1		

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
N	Musculoskeletal and connective tissue disorders	Rhabdomyolysis	1	1		
N	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to retroperitoneum	1	1		
N	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Rectal cancer metastatic	1	1		
N	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Tumour invasion	2	1		
N	Nervous system disorders	Cerebrovascular accident	1	1		
N	Nervous system disorders	Dysgeusia	1	1		
N	Nervous system disorders	Encephalopathy	1	1		
N	Nervous system disorders	Memory impairment	1	1		
N	Nervous system disorders	Mental impairment	1	1		
N	Nervous system disorders	Nerve compression	1	1		
N	Nervous system disorders	Sensory loss	1	1		
N	Nervous system disorders	Sinus headache	1	1		
N	Nervous system disorders	Toxic neuropathy	1	1		
N	Psychiatric disorders	Disorientation	1	1		
N	Renal and urinary disorders	Pollakiuria	2	1		
N	Renal and urinary disorders	Polyuria	1	1		
N	Renal and urinary disorders	Proteinuria	1	1		
N	Renal and urinary disorders	Renal cyst	1	1		
N	Renal and urinary disorders	Renal failure	2	1		
N	Renal and urinary disorders	Renal tubular necrosis	1	1		
N	Renal and urinary disorders	Urinary hesitation	1	1		
N	Renal and urinary disorders	Urine flow decreased	1	1		
N	Reproductive system and breast disorders	Dyspareunia	1	1		

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
N	Reproductive system and breast disorders	Pelvic fluid collection	1	1		
N	Reproductive system and breast disorders	Prostatitis	1	1		
N	Reproductive system and breast disorders	Scrotal swelling	1	1		
N	Reproductive system and breast disorders	Uterine mass	1	1		
N	Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	1	1		
N	Respiratory, thoracic and mediastinal disorders	Allergic respiratory symptom	2	1		
N	Respiratory, thoracic and mediastinal disorders	Apnoea	1	1		
N	Respiratory, thoracic and mediastinal disorders	Bronchial secretion retention	3	3		
N	Respiratory, thoracic and mediastinal disorders	Hypercapnia	1	1		
N	Respiratory, thoracic and mediastinal disorders	Hyperoxia	1	1		
N	Respiratory, thoracic and mediastinal disorders	Increased viscosity of bronchial secretion	1	1		
N	Respiratory, thoracic and mediastinal disorders	Painful respiration	1	1		
N	Respiratory, thoracic and mediastinal disorders	Productive cough	1	1		
N	Respiratory, thoracic and mediastinal disorders	Rales	1	1		
N	Respiratory, thoracic and mediastinal disorders	Respiratory distress	1	1		
N	Skin and subcutaneous tissue disorders	Ecchymosis	2	2		
N	Skin and subcutaneous tissue disorders	Lichen planus	1	1		
N	Skin and subcutaneous tissue disorders	Purpura	1	1		
N	Skin and subcutaneous tissue disorders	Rash erythematous	2	1		
N	Skin and subcutaneous tissue disorders	Skin exfoliation	1	1		
N	Skin and subcutaneous tissue disorders	Urticaria	2	2		
N	Social circumstances	Treatment noncompliance	1	1		
N	Surgical and medical procedures	Colostomy closure	1	1		
N	Vascular disorders	Bloody discharge	1	1		
N	Vascular disorders	Deep vein thrombosis	1	1		

APPENDIX ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 109	TachoSil Events	TachoSil Subjects N = 114
N	Vascular disorders	Flushing	1	1		
N	Vascular disorders	Haemodynamic instability	1	1		
N	Vascular disorders	Hypovolaemic shock	1	1		
N	Vascular disorders	Thrombophlebitis superficial	1	1		
N	Vascular disorders	Vena cava thrombosis	1	1		

APPENDIX 2. PEDIATRIC ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 9	TachoSil Events	TachoSil Subjects N = 20
Y	Gastrointestinal disorders	Diarrhoea			2	2
Y	General disorders and administration site conditions	Pyrexia	2	2	2	2
Y	Infections and infestations	Clostridium difficile colitis	1	1	3	2
Y	Blood and lymphatic system disorders	Disseminated intravascular coagulation			1	1
Y	Blood and lymphatic system disorders	Febrile neutropenia	1	1	1	1
Y	Congenital, familial and genetic disorders	Hydrocele			1	1
Y	Gastrointestinal disorders	Abdominal pain			1	1
Y	Gastrointestinal disorders	Gastrointestinal haemorrhage			1	1
Y	Gastrointestinal disorders	Vomiting			1	1
Y	General disorders and administration site conditions	Catheter site swelling			1	1

APPENDIX ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 9	TachoSil Events	TachoSil Subjects N = 20
Y	Hepatobiliary disorders	Cholangitis			1	1
Y	Hepatobiliary disorders	Hepatic artery thrombosis			2	1
Y	Hepatobiliary disorders	Hepatic necrosis			1	1
Y	Hepatobiliary disorders	Portal vein thrombosis			1	1
Y	Infections and infestations	Alpha haemolytic streptococcal infection			1	1
Y	Infections and infestations	Enterobacter infection			1	1
Y	Infections and infestations	Enterococcal infection			1	1
Y	Infections and infestations	Klebsiella infection			1	1
Y	Infections and infestations	Mycobacterium abscessus infection			1	1
Y	Infections and infestations	Septic shock			1	1
Y	Infections and infestations	Stenotrophomonas infection			1	1
Y	Infections and infestations	Urinary tract infection			1	1
Y	Infections and infestations	Viraemia	1	1	1	1
Y	Injury, poisoning and procedural complications	Anastomotic complication			1	1
Y	Injury, poisoning and procedural complications	Incision site haematoma			1	1
Y	Injury, poisoning and procedural complications	Post procedural bile leak			1	1
Y	Injury, poisoning and procedural complications	Splenic rupture			1	1
Y	Metabolism and nutrition disorders	Hypophagia			1	1
Y	Vascular disorders	Exsanguination			1	1
Y	Gastrointestinal disorders	Localised intraabdominal fluid collection	1	1		
Y	Infections and infestations	Gastroenteritis	1	1		
Y	Infections and infestations	Pneumonia klebsiella	1	1		
Y	Nervous system disorders	Convulsion	1	1		
N	General disorders and administration site conditions	Pyrexia	4	3	8	7
N	Blood and lymphatic system disorders	Anaemia	3	2	5	5

APPENDIX ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 9	TachoSil Events	TachoSil Subjects N = 20
N	Cardiac disorders	Tachycardia	2	2	3	3
N	Vascular disorders	Hypertension	1	1	3	3
N	Vascular disorders	Hypotension	1	1	3	3
N	Gastrointestinal disorders	Ascites			2	2
N	Gastrointestinal disorders	Constipation			2	2
N	Gastrointestinal disorders	Diarrhoea			2	2
N	Gastrointestinal disorders	Vomiting	2	2	2	2
N	Infections and infestations	Human herpesvirus 6 infection			2	2
N	Investigations	Transaminases increased			2	2
N	Metabolism and nutrition disorders	Hypomagnesaemia			2	2
N	Respiratory, thoracic and mediastinal disorders	Pleural effusion	1	1	2	2
N	Respiratory, thoracic and mediastinal disorders	Tachypnoea	1	1	2	2
N	Blood and lymphatic system disorders	Neutropenia	3	2	1	1
N	Cardiac disorders	Ventricular extrasystoles			1	1
N	Eye disorders	Eyelid ptosis			1	1
N	Gastrointestinal disorders	Abdominal distension	2	1	1	1
N	Gastrointestinal disorders	Abdominal pain lower			1	1
N	Gastrointestinal disorders	Flatulence	1	1	1	1
N	Gastrointestinal disorders	Gastrointestinal sounds abnormal			1	1
N	Gastrointestinal disorders	Haematochezia			1	1
N	Gastrointestinal disorders	Localised intraabdominal fluid collection			1	1
N	Gastrointestinal disorders	Mallory-Weiss syndrome			1	1
N	Gastrointestinal disorders	Nausea			1	1
N	Gastrointestinal disorders	Oesophageal ulcer			1	1
N	General disorders and administration site conditions	Catheter site haematoma			1	1

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 9	TachoSil Events	TachoSil Subjects N = 20
N	General disorders and administration site conditions	Oedema			1	1
N	General disorders and administration site conditions	Oedema peripheral			1	1
N	Hepatobiliary disorders	Hepatic vein stenosis			1	1
N	Hepatobiliary disorders	Portal vein stenosis			1	1
N	Hepatobiliary disorders	Venoocclusive liver disease			1	1
N	Immune system disorders	Drug hypersensitivity			1	1
N	Immune system disorders	Liver transplant rejection			1	1
N	Immune system disorders	Transplant rejection			2	1
N	Infections and infestations	Clostridial infection			1	1
N	Infections and infestations	Epstein-Barr viraemia			1	1
N	Infections and infestations	Influenza			1	1
N	Infections and infestations	Nasopharyngitis			1	1
N	Infections and infestations	Parainfluenzae virus infection			1	1
N	Infections and infestations	Peritonitis			1	1
N	Infections and infestations	Pharyngitis			1	1
N	Injury, poisoning and procedural complications	Accidental overdose			1	1
N	Injury, poisoning and procedural complications	Gastrointestinal anastomotic leak			1	1
N	Injury, poisoning and procedural complications	Inadequate analgesia	1	1	1	1
N	Injury, poisoning and procedural complications	Lower limb fracture			1	1
N	Injury, poisoning and procedural complications	Post procedural bile leak			1	1
N	Injury, poisoning and procedural complications	Toxicity to various agents			1	1
N	Investigations	Blood glucose decreased			1	1
N	Investigations	Blood potassium decreased			2	1
N	Investigations	Coagulation time prolonged			1	1
N	Investigations	International normalised ratio increased			1	1

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 9	TachoSil Events	TachoSil Subjects N = 20
N	Investigations	Lipase increased			1	1
N	Investigations	Urine output decreased			1	1
N	Investigations	White blood cell count increased			1	1
N	Metabolism and nutrition disorders	Acidosis	1	1	1	1
N	Metabolism and nutrition disorders	Fluid imbalance			1	1
N	Metabolism and nutrition disorders	Hyperglycaemia			1	1
N	Metabolism and nutrition disorders	Hypokalaemia			1	1
N	Metabolism and nutrition disorders	Hyponatraemia			1	1
N	Metabolism and nutrition disorders	Hypophagia			1	1
N	Metabolism and nutrition disorders	Hypophosphataemia			1	1
N	Metabolism and nutrition disorders	Iron deficiency			1	1
N	Metabolism and nutrition disorders	Metabolic acidosis			1	1
N	Metabolism and nutrition disorders	Vitamin D deficiency			1	1
N	Musculoskeletal and connective tissue disorders	Neck pain			1	1
N	Nervous system disorders	Dizziness			1	1
N	Nervous system disorders	Somnolence			1	1
N	Psychiatric disorders	Anxiety			1	1
N	Psychiatric disorders	Emotional distress			1	1
N	Psychiatric disorders	Emotional poverty			1	1
N	Psychiatric disorders	Insomnia			1	1
N	Psychiatric disorders	Suicidal ideation			1	1
N	Renal and urinary disorders	Dysuria			1	1
N	Renal and urinary disorders	Renal failure acute			1	1
N	Reproductive system and breast disorders	Scrotal swelling			1	1
N	Respiratory, thoracic and mediastinal disorders	Atelectasis	1	1	1	1

APPENDIX ADULT ADVERSE EVENTS BY SERIOUSNESS AND DECREASING FREQUENCY BY NUMBER OF TACHOSIL SUBJECTS

Seriousness	Body System	Adverse Event Decoded Term	Surgicel Events	Surgicel Subjects N = 9	TachoSil Events	TachoSil Subjects N = 20
N	Respiratory, thoracic and mediastinal disorders	Hypercapnia			1	1
N	Respiratory, thoracic and mediastinal disorders	Pneumothorax			1	1
N	Respiratory, thoracic and mediastinal disorders	Respiratory distress			1	1
N	Respiratory, thoracic and mediastinal disorders	Wheezing			1	1
N	Skin and subcutaneous tissue disorders	Dermatitis diaper			1	1
N	Skin and subcutaneous tissue disorders	Pruritus			1	1
N	Skin and subcutaneous tissue disorders	Skin disorder			1	1
N	Blood and lymphatic system disorders	Febrile neutropenia	1	1		
N	Blood and lymphatic system disorders	Leukocytosis	1	1		
N	Gastrointestinal disorders	Abdominal discomfort	1	1		
N	General disorders and administration site conditions	Generalised oedema	1	1		
N	Infections and infestations	Device related infection	1	1		
N	Infections and infestations	Febrile infection	1	1		
N	Injury, poisoning and procedural complications	Hepatic haematoma	1	1		
N	Injury, poisoning and procedural complications	Procedural hypertension	2	1		
N	Metabolism and nutrition disorders	Dehydration	1	1		
N	Metabolism and nutrition disorders	Hypoglycaemia	1	1		
N	Psychiatric disorders	Restlessness	1	1		
N	Renal and urinary disorders	Ketonuria	1	1		
N	Reproductive system and breast disorders	Menorrhagia	1	1		
N	Respiratory, thoracic and mediastinal disorders	Epistaxis	1	1		
N	Respiratory, thoracic and mediastinal disorders	Nasal congestion	1	1		
N	Skin and subcutaneous tissue disorders	Rash	1	1		
N	Vascular disorders	Vena cava thrombosis	1	1		