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(Proposed) Trade Name	TachoSil
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	<No Formulations>
Dosage Form(s) and Route(s) of Administration	< No Dosage Forms >
Dosing Regimen	< No Dosing Regimen >
Indication(s) and Intended Population(s)	For use in adult and pediatric patients as an adjunct for hemostasis in cardiovascular and hepatic surgery when control of bleeding by standard surgical techniques is ineffective or impractical

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GLOSSARY

ABC	argon beam coagulator
AE	adverse event
BLA	biologics license application
CI	confidence interval
FAS	full analysis set
ISD	individual subject data
ISE	integrated summary of efficacy
ISS	integrated summary of safety
ITT	intent-to-treat
MELD	model for end stage liver disease
OR	odds ratio
PP	per-protocol analysis set
SAE	serious adverse event
SAF	safety analysis set
sBLA	supplemental Biologics License Application

1. EXECUTIVE SUMMARY

TachoSil is an FDA approved product for use in cardiovascular surgery. This supplemental Biologics License Application (sBLA) proposes to expand the indication for use in adult and pediatric patients as an adjunct for hemostasis in cardiovascular and hepatic surgery when control of bleeding by standard surgical techniques is ineffective or impractical.

The primary evidences are based on the pivotal Study TC-2402-040-SP: a Phase 3, randomized, open-label, controlled, parallel-group, multi-center trial to compare TachoSil to an approved product as a secondary hemostatic treatment after hepatic resection surgery and primary hemostatic treatment in adult and pediatric patients. The primary efficacy endpoint is hemostasis within 3 minutes of application of the trial treatment. For the adult subjects, a higher proportion of subjects achieving hemostasis within 3 minutes was observed in the TachoSil group with an estimated odds ratio (OR) of 4.87 (95% CI: 2.55, 9.29, $P < 0.001$). Consistent efficacy results existed among subgroups regarding sex, age (below or above 65 years), race, and study site. No formal hypothesis testing was performed on the pediatric subjects but a similar treatment effect was observed as well. The results are reproducible.

The integrated summary of efficacy (ISE) is considered post-hoc. This reviewer suggests reporting only the descriptive analysis results for informational purposes, and no statistical inference should be drawn.

One comment was sent to the applicant regarding the larger odds ratio (OR) observed in the US pivotal study compared to the two European studies in ISE. The applicant attributed the difference to the comparator treatments used, potential changes in surgical practice over the years, geographical region, and the inherent sensitivity of OR to random variation in studies of small sample size. The explanations are acceptable. The applicant hypothesized that if argon beam coagulator (ABC) treatment (comparator in the European studies) had been used in the US Study, the OR may have been lower than that

obtained against Surgicel (comparator in the US study) because the hemostatic effect of ABC treatment is known to be superior to Surgicel. This reviewer recommends that all these ORs be included in the labeling.

2. CLINICAL AND REGULATORY BACKGROUND

TachoSil is a ready-to-use sterilized, degradable surgical collagen patch, consisting of an equine collagen patch coated with the fibrin glue components, human fibrinogen and human thrombin. TachoSil is currently approved in more than 50 countries. TachoSil was granted market approval from the FDA on April 5, 2010 (BLA 125351) as an adjunct to hemostasis for use in cardiovascular surgery when standard surgical techniques for the control of bleeding are ineffective or impractical.

This sBLA proposes to expand the indication of TachoSil for use in adult and pediatric subjects as an adjunct for hemostasis in cardiovascular and hepatic surgery. The pivotal Study TC-2402-040-SP has two portions: adult subjects aged 17 years or older and pediatric subjects under 17 years old. The pediatric portion fulfills the commitment of the Pediatric Research Equity Act Requirement as stated in the April 5, 2010 Approval Letter. Study TC-2402-040-SP was conducted under IND 14210.

A pre-sBLA meeting was held on June 14, 2013. The following agreement regarding the ISE/ISS SAP was made.

Nycomed Question 1:

As outlined and described in the ISE/ISS SAP:

- a) Does the Agency agree with Takeda's approach of integrating the clinical data of the 3 hepatic studies to support the Efficacy Supplement?
- b) Does the Agency agree that using all hemostasis studies as supportive data as part of the integrated analyses is acceptable?
- c) Does the Agency agree that using all TachoSil studies as part of the integrated safety analyses is acceptable?
- d) Does the Agency agree that the statistical methodology (including key efficacy endpoints and statistical modelling) described in the SAP for the ISS/ISE are adequate to support the review of the Efficacy Supplement?
- e) Does the Agency agree that the data presentation as described in the SAP for the ISS/ISE is adequate to support the review of the Efficacy Supplement?

FDA Response to Question 1:

General Comment:

The answers provided are based on our understanding that the phase 3 hepatic resection surgery study conducted under IND 14210 is the primary study being submitted to support expansion of the indication for TachoSil. The additional hepatic resection surgery studies and other subspecialty surgical studies may be submitted as supportive data.

- a) FDA agrees that this approach is acceptable.
- b) FDA agrees that this approach is acceptable.
- c) FDA agrees that this approach is acceptable.
- d) Key efficacy endpoints are acceptable.
- e) FDA agrees that this approach is acceptable.

The applicant submitted a major amendment on November 13, 2014 to include a safety study to understand the clinical impact of the immunogenicity findings. An additional three months review time was added; thus the action due date became July 20, 2015.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

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

The source of data is submitted in the final study report.

5.1 Review Strategy

- The adult and pediatric portions of Study TC-2402-040-SP will be covered in Sections 6.1 and 6.2 respectively. Section 6.1 is the main focus of this review.
- The ISE for adult and pediatric populations will be covered in Sections 7.1 and 7.2 respectively.
- This reviewer defers to the clinical reviewer for the evaluation of integrated summary of safety (ISS).

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

All the documents are submitted under sBLA 125351/172:

- Module 5.3.5.1 Study TC-2402-040-SP Clinical Trial Report
- Module 5.3.5.3 Reports of Analyses of Data from More than One Study (ISE)

5.3 Table of Studies/Clinical Trials

The studies to be included in this review are presented in Tables 1 and 2 for adult and pediatric subjects respectively.

Table 1. Clinical studies for efficacy of TachoSil in adult subjects

Surgical indication	Study Code	Treatments	N	Study Period
Liver resection	TC-014-IN	TS vs argon beam coagulator	121	2001-2002
Liver resection	TC-016-IN	TS vs argon beam coagulator	119	2003-2003
Liver resection	TC-2402-040-SP	TS vs Surgicel	224 (a)	2010-2012

TS=TachoSil; (a) adult subjects

Source: Original sBLA 125351/172; ise-report, Table 1, p.17

Table 2. Clinical studies for efficacy of TachoSil in pediatric subjects

Surgical indication	Study Code	Treatments	N	Study Period
Liver resection	TC-019-IN (a)	TS	16	2006-2007
Liver resection	TC-2402-040-SP	TS vs Surgicel	29 (b)	2010-2013

TS=TachoSil; (a) Single arm study, all treated with TachoSil; (b) Pediatric subjects

Source: Original sBLA 125351/172; ise-report, Table 2, p.18

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: TC-2402-040-SP (Adult Portion)

6.1.1 Objective (Primary)

To evaluate whether TachoSil is superior to Surgicel Original as a secondary hemostatic treatment after hepatic resection surgery and primary hemostatic treatment in adult subjects

6.1.2 Design Overview

It was a randomized, open-label, controlled, parallel-group, multi-center trial. During surgery, eligible subjects were randomly assigned to TachoSil or Surgicel Original in a 1:1 ratio. Randomization was stratified by center, using the method of randomly permuted blocks of size 2, 4, or 6 with a respective probability of 20%, 40%, and 40%. Treatment was applied immediately after randomization. Efficacy was evaluated as hemostasis obtained at the “target bleeding site” of the liver resection wound, which was defined as the area with the most prominent hemorrhage. Hemostasis was evaluated at 3, 4, 5, 8, 9, and 10 minutes after the first trial treatment application.

6.1.3 Population

Adults aged 17 years or older underwent liver surgery and needed supportive treatment to control the bleeding. Subjects were evaluated for eligibility at Screening and Baseline visits before surgery. Final eligibility was dependent on the fulfillment of intraoperative eligibility criteria.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Dosing (number of patches) for both TachoSil and Surgicel Original was according to the wound size.

6.1.6 Sites and Centers

All nineteen trial centers were in the United States.

6.1.8 Endpoints and Criteria for Study Success

- Primary efficacy endpoint: intraoperative hemostasis at target bleeding site within 3 minutes of application of allocated trial treatment.
- Secondary efficacy endpoints: intraoperative hemostasis at target bleeding site within 5 minutes of application of allocated trial treatment, and time to intraoperative hemostasis at target bleeding site within 10 minutes.

6.1.9 Statistical Considerations & Statistical Analysis Plan

It was planned to enroll 224 adult subjects in a 1:1 ratio to achieve 95% power for obtaining a significant result at the 5% significance level when assuming that 55% of the subjects in the TachoSil group and 30% of the subjects in the Surgicel Original group achieved hemostasis within 3 minutes.

The primary efficacy endpoint of hemostasis within 3 minutes of application of the trial treatment was analyzed using a logistic regression model with treatment group and pooled center as categorical variables. Subjects with missing time to hemostasis were counted as not having hemostasis within 3 minutes.

A center would be pooled if

1. either all or none of the subjects within a center had achieved hemostasis within 3 minutes, or
2. the center included fewer than 6 subjects.

Centers were pooled based on two criteria:

1. Geographical proximity preferably within standard federal region
2. Secondarily as possible within time zone and with same type of hospital, where “type” was defined as either private or public.

For all logistic regression analyses, the Wald 95% confidence intervals (CIs) were obtained from the model and presented for the odds ratios (ORs). Exact binomial 95% CIs were obtained for any raw proportions presented.

The following analysis sets were defined:

- Full analysis set (FAS): all randomly assigned subjects, analyzed as randomized. This was the primary analysis set for efficacy analyses.
- Per-protocol analysis set (PP): all randomly assigned subjects, analyzed as treated, who had no major protocol violations.

- Safety analysis set (SAF): all randomly assigned subjects who were exposed to trial treatment, analyzed as treated. This was the analysis set used for the majority of safety related variables.

The supportive analyses included the following:

- The primary analysis was repeated for the PP set.
- The homogeneity of the treatment effect across (pooled) centers was evaluated by a treatment-center interaction test.
- A worst scenario sensitivity analysis of missing data was performed: missing values in the Surgicel Original group were imputed as having hemostasis at 3 minutes and those in the TachoSil group imputed as not having hemostasis at 3 minutes.
- The effect of treatment and predictive variables (coagulation function, anticoagulative treatment, central venous pressure, liver condition, and Model for End Stage Liver Disease [MELD] score) were evaluated in a logistic regression model.

The secondary efficacy endpoint of hemostasis within 5 minutes of application of the trial treatment was analyzed in a similar way to the primary endpoint. The secondary efficacy endpoint, time to intraoperative hemostasis at the target bleeding site, was analyzed using survival analysis.

Two-sided testing was performed at the 5% significance level. The two secondary endpoints were adjusted using Hochberg's adjustment for multiplicity.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 3 reports the sample size for each analysis set. The FAS and SAF were almost the same.

Table 3. Analysis populations for adult subjects 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)

Source: Original sBLA 125351/172; TC-2402-040-SP Clinical Trial Report, Table 2, p.97

6.1.10.1.1 Demographics

Demographic characteristics were very similar across both treatment groups, thus they were reported on the overall population. A similar proportion of male subjects and female subjects were randomly assigned in the trial (53.1% and 46.9%, respectively). The mean (SD) age of subjects was 58.1 (13.95) years and approximately 30% of the subjects were

above 65 years. Eighty percent of subjects were White/Caucasian and the most common ethnicity was non-Hispanic/non-Latino (87.5%).

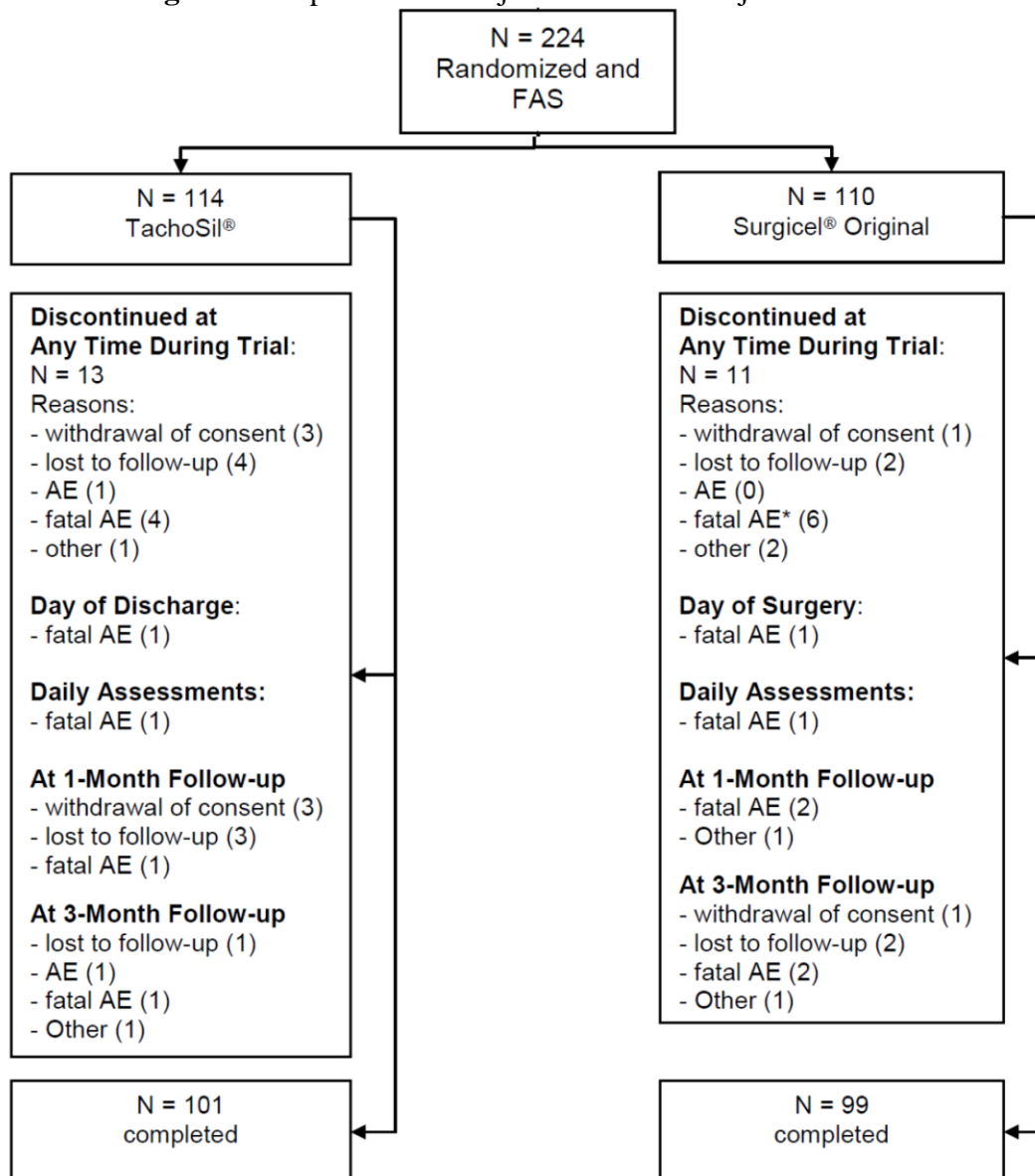
6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The two treatment groups had a similar distribution of disease indications. The most common indications for liver resection were malignant tumor (77.6%), organ donation (9.0%), and benign lesion (8.5%).

6.1.10.1.3 Subject Disposition

Subject disposition is presented in Figure 1 below. Ninety percent of the subjects completed the study.

Figure 1. Disposition of subjects - all adult subjects enrolled



Source: Original sBLA 125351/172; TC-2402-040-SP Clinical Trial Report, Figure 2, p.91

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Efficacy Endpoint

The primary analysis of the primary efficacy endpoint (FAS) showed an estimated OR of 4.87 (95% CI: 2.55, 9.29, $P < 0.001$). The only missing value in the Surgicel Original group was treated as a success in the sensitivity analysis, and the statistical significance was still achieved, as shown in the last two rows of Table 4.

Table 4. Logistic regression models of primary efficacy endpoint

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)					
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

¹. Subject US4012006 in the Surgicel Original group was randomized but did not receive any treatment, thus resulted in one missing outcome value.

“n/N”: the number of subjects with hemostasis at 3 minutes among the number of subjects in each arm.

Source: Original sBLA 125351/172; TC-2402-040-SP Clinical Trial Report, Table 11, p.117

The treatment by (pooled) center interaction term from the logistic regression model was not significant ($P = 0.925$). None of the predictive variables for the primary endpoint were significant in the logistic regression model with the p-value ranging from 0.373-0.793.

Centers involved in pooling are presented in Table 5 below. The number in the parentheses represents the sample size in that center. The two centers with a same underscore line were pooled together (e.g. centers 2 and 18). Detail on the choice of which smaller centers would be pooled with which larger centers was not explained in the submission.

Table 5. Center pooling

Region	Center (sample size)	Reason for pooling
IV	<u>center 2(8), center 18(10)</u> ,	Center 2 was pooled as all the subjects achieved hemostasis within 3 minutes.
	<u>center 4(5), center 21(10)</u>	Center 4 was pooled as it had <6 subjects.
V	<u>center 17(5), center 19(9)</u>	Center 17 was pooled as it had <6 subjects.
IX	<u>center 5(1), center 9(41)</u>	Center 5 was pooled as it only had one subject.

6.1.11.2 Analyses of Secondary Endpoints

The proportion of subjects with hemostasis at 5 minutes was statistically significantly higher in the TachoSil group (94.7% of subjects) than the Surgicel Original group (76.4% of subjects) with an estimated OR of 6.24 (95% CI: 2.39, 16.30, $P < 0.001$). The time to hemostasis was statistically significantly shorter for the TachoSil group compared with the Surgicel Original group ($P < 0.001$, log-rank test).

6.1.11.3 Subpopulation Analyses

As shown in Table 6 below, the subgroup analyses conducted by this reviewer demonstrated a consistent efficacy among demographic subpopulations, including sex, age (below or above 65 years old), race, and study site.

Table 6. Subpopulation analyses of primary efficacy endpoint TC-2402-040-SP (FAS)

		TachoSil		Surgicel Original	
		n/N ¹	Percentage	n/N ¹	Percentage
Sex	Male	48/60	80%	29/59	49.15%
	Female	44/54	81.48%	26/51	50.95%
Age	> 65 years old	24/33	72.73%	15/34	44.12%
	< 65 years old	68/81	83.95%	40/76	52.63%
Race	White	74/93	79.57%	42/87	48.28%
	Black	8/9	88.89%	6/10	60%
	Asian	5/6	83.33%	6/10	60%
	Multiracial	1/2	50%	0/0	
	Other	4/4	100%	1/3	33.33%
Site ²	ID=01	9/16	56.25%	6/15	40%
	ID=07	9/10	90%	7/10	70%
	ID=08	2/5	40%	2/5	40%
	ID=10	4/5	80%	4/5	80%
	ID=12	6/6	100%	3/6	50%
	ID=17 & 19	13/15	86.67%	9/14	64.29%
	ID=4 & 21	9/9	100%	4/6	66.67%
	ID=5 & 9	17/20	85.00%	8/22	36.36%

¹: n/N stands for the number of subjects with hemostasis at 3 minutes among the number of subjects in a certain subgroup in each arm.

²: only sites with total number of subject ≥ 10 are listed in the table

6.1.12 Safety Analyses

A summary of AEs in adult subjects is presented in Table 7. The safety profile was generally similar across both treatment groups.

Table 7. Summary of adverse events (SAF)

	TachoSil (# of subjects=114)		Surgicel Original (# of subjects=109)		Total (# of subjects=223)	
	n (%)	Events	n (%)	Events	n (%)	Events
Adverse events	107 (93.9)	1051	102 (93.6)	1096	209 (93.7)	2147
Related adverse events	5 (4.4)	7	4 (3.7)	7	9 (4.0)	14
Not related adverse events	106 (93.0)	1044	102 (93.6)	1089	208 (93.3)	2133
Mild adverse events	97 (85.1)	742	95 (87.2)	774	192 (86.1)	1516
Moderate adverse events	78 (68.4)	244	60 (55.0)	253	138 (61.9)	497
Severe adverse events	28 (24.6)	65	34 (31.2)	66	62 (27.8)	131
Serious adverse events	44 (38.6)	85	54 (49.5)	116	98 (43.9)	201
Serious related adverse events	3 (2.6)	3	2 (1.8)	2	5 (2.2)	5
Serious adverse events other than death	43 (37.7)	80	51 (46.8)	109	94 (42.2)	189
Adverse events leading to death	4 (3.5)	5	7 (6.4)	7	11 (4.9)	12
Adverse events leading to withdrawal	5 (4.4)	7	6 (5.5)	7	11 (4.9)	14

Source: Original sBLA 125351/172; TC-2402-040-SP Clinical Trial Report, Table 20, p.135

Three subjects in the TachoSil group and two subjects in the Surgicel Original group experienced SAEs considered by the investigator to be related to trial treatment. No AE leading to death was considered by the investigator to be related to treatment.

6.2 Trial #2 TC-2402-040-SP (Pediatric Portion)

6.2.1 Objective

To explore the efficacy and safety of TachoSil as a secondary hemostatic treatment in hepatic resection surgery in pediatric subjects. This is one of the two secondary objectives of Study TC-2402-040-SP.

6.2.2 Design Overview

Similarly to the adult portion, the pediatric portion was a randomized, open-label, controlled, parallel-group, multi-center trial. Randomization was stratified by age group, using an undisclosed block size.

At the time of completion of adult enrollment, 8 pediatric subjects had been treated with TachoSil and 9 pediatric subjects had been treated with Surgicel Original. An additional 12 pediatric subjects were therefore enrolled in an extensional part of the trial and treated with TachoSil in order to achieve a total of 20 pediatric subjects treated with TachoSil.

6.2.3 Population

Pediatric subjects 0 to 16 years old underwent liver surgery and needed supportive treatment to control the bleeding. The youngest subject enrolled was 5 months old.

6.2.6 Sites and Centers

Five centers in the United States.

6.2.8 Endpoints and Criteria for Study Success

The efficacy endpoints were the same as those of the adult portion.

6.2.9 Statistical Considerations & Statistical Analysis Plan

No formal hypothesis testing for treatment effect in the pediatric population was planned. Descriptive statistics were used for the efficacy analyses. The efficacy endpoints were presented for the following three groups stratified by treatment groups as applicable:

1. Pediatric FAS: 17 randomized subjects (8 subjects in TachoSil group and 9 subjects in Surgicel Original group), analyzed as randomized.
2. Pediatric EXT: 12 subjects from the extensional part of the trial
3. Pediatric SAF: 17 randomized subjects and 12 subjects from the extensional part of the trial, analyzed as treated. It can also be viewed as the total population.

Subsidiary analysis of pediatric data was also performed on 3 age groups: infants aged 5 months to 23 months (inclusive), children aged 2 to 11 years (inclusive), and adolescents aged 12 to 16 years (all months/years included).

6.2.10.1.1 Demographics

Demographic characteristics were generally similar across both treatment groups.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint

There were no missing outcome data for the primary efficacy endpoint. Results for the primary efficacy endpoint are presented in Table 8 below. The treatment effect was similar in adult subjects and pediatric subjects.

Table 8. 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)		
Surgicel Original (n=9)	44.4	(13.7, 78.8)	43.1	(-4.9, 85.5)
Pediatric EXT				
TachoSil (n=12)	83.3	(51.6, 97.9)	–	–
Pediatric SAF				
TachoSil (n=20)	85.0	(62.1, 96.8)		
Surgicel Original (n=9)	44.4	(13.7, 78.8)	40.6	(0.4, 80.8)

Source: Original sBLA 125351/172; TC-2402-040-SP Clinical Trial Report, Table 15, p.124

6.2.11.3 Subpopulation Analyses

The number of subjects with hemostasis achieved within 3 minutes by treatment and age group is presented in Table 9 below. This table also stratifies on analysis set.

Table 9. Subgroup analysis on age category by analysis set

Age category	FAS		EXT	SAF (total)	
	TachoSil	Surgicel Original	TachoSil	TachoSil	Surgicel Original
5 to 23 months	2/3	2/5	5/6	7/9	2/5
2 to 11 years	4/4	2/3	4/4	8/8	2/3
12 to 16 years	1/1	0/1	1/2	2/3	0/1
Total	7/8	4/9	10/12	17/20	4/9

Source: Original sBLA 125351/172; TC-2402-040-SP Clinical Trial Report, adapted from Table 24.2.1.1, p.608

6.2.12 Safety Analyses

In the SAF, serious AEs were reported for 12 (60.0%) subjects in the TachoSil group and 4 (44.4%) subjects in the Surgicel Original group. AEs leading to death were reported for one subject in the TachoSil group and no subject in the Surgicel Original group. No AE in either treatment group was considered by the investigator to be related to trial treatment.

7. INTEGRATED OVERVIEW OF EFFICACY

The ISE is based on three study pools: a Hepatic Study Pool and a Pediatric Study Pool that are pivotal for this application, and a Hemostasis Study Pool that provides supportive evidence for the hepatic surgery indication. Table 10 lists the studies included in each pool. Section 7.1 in this review will focus on the Hepatic Study Pool and Section 7.2 will focus on the Pediatric Study Pool. The Hemostasis Study Pool is not covered in this review as it included two non-liver studies.

Table 10. Study pools for ISE

Study	Organ	Comparator treatment	Hepatic	Hemostasis	Pediatric
TC-014-IN	Liver	Argon beam coagulator	x	x	
TC-016-IN	Liver	Argon beam coagulator	x	x	
TC-2402-040-SP	Liver	Surgicel	x (a)	x (a)	x (b)
TC-019-IN	Liver	No control			x
TC-023-IM	Heart	Standard surgical treatment		x	
(b) (4)					

(a) Adult subjects.

(b) Pediatric subjects.

Source: Original sBLA 125351/172; Integrated Summary of Efficacy, Table 3, p.19

7.1 ISE based on Hepatic Study Pool

7.1.1 Methods of Integration

Three liver studies forming the Hepatic Study Pool are described in Table 11 below. The major differences between TC-2402-040-SP and the other two studies were comparator, sites, and primary endpoint.

Table 11. Studies in Hepatic Study Pool

	TC-014-IN	TC-016-IN	TC-2402-040-SP (adult portion)
Study design	A phase 3 open label, randomized, prospective, multi-center, controlled study	A phase 3 open label, randomized, prospective, multi-center, controlled study	A phase 3 open label, randomized, prospective, multi-center, controlled study
Comparator	ABC	ABC	Surgicel
Inclusion criteria	Adult subjects undergoing liver resection	Adult subjects undergoing liver resection	Adult subjects undergoing liver resection
N (treatment /control)	121 (59/62)	119 (60/59)	224 (114/110)
Site	Europe	Europe	United States
Study period	2001-2002	2003-2003	2010-2012
Primary endpoint	Time to hemostasis	Time to hemostasis	Hemostasis within 3 minutes after treatment.

Source: Original sBLA 125351/172; Integrated Summary of Efficacy, adapted from Table 4, p.22-25

In ISE, the primary endpoints were 1) proportion of subjects with hemostasis at 3 minutes and 2) time to hemostasis. All efficacy endpoints were analyzed and/or summarized on an ITT principle using an integrated Full Analysis Set (FAS). The analyses are considered post hoc analyses. Multiplicity was not taken into account for the integrated analyses.

- **Hemostasis at 3 minutes**

It was analyzed using a logistic regression model including treatment group and study. Additionally, a model including treatment group, study, and the interaction between treatment group and study was computed to assess the homogeneity across

studies. As a sensitivity analysis, another model included treatment group, study and region. To avoid problems with sparse data occurrence due to a small region, Firth's penalized maximum likelihood estimation to reduce bias in the parameter estimates was applied.

- **Time to Hemostasis**

Time from first application of test treatment to hemostasis was recorded as 0-3, >3-4, >4-5, >5-8, >8-9, >9-10, or after 10 minutes, i.e., interval censored. Subjects with time to hemostasis greater than 10 minutes were censored at 10 minutes. Subjects with missing time to hemostasis were imputed with time censored at 10 minutes.

This endpoint was analyzed using a proportional hazard model stratifying by study and adjusting for treatment group. In addition a model also included the interaction between treatment group and study assessing the homogeneity across studies. As a sensitivity analysis, another model included treatment group and region still stratifying for study. A log-rank test stratifying by study was also computed as sensitivity analysis.

- **Meta-analysis of primary endpoints**

Fixed-effect meta-analyses using individual subject data (ISD) were conducted, weighting on the study size. The heterogeneity assessment was done by including an interaction term between treatment group and study (at alpha=0.10 significance level). Forest plots were generated for each of the primary endpoints for the Hepatic Study Pool.

Secondary endpoints analyses and subgroup analyses are not covered in this review.

7.1.2 Demographics and Baseline Characteristics

Demographic characteristics were generally similar across both treatment groups.

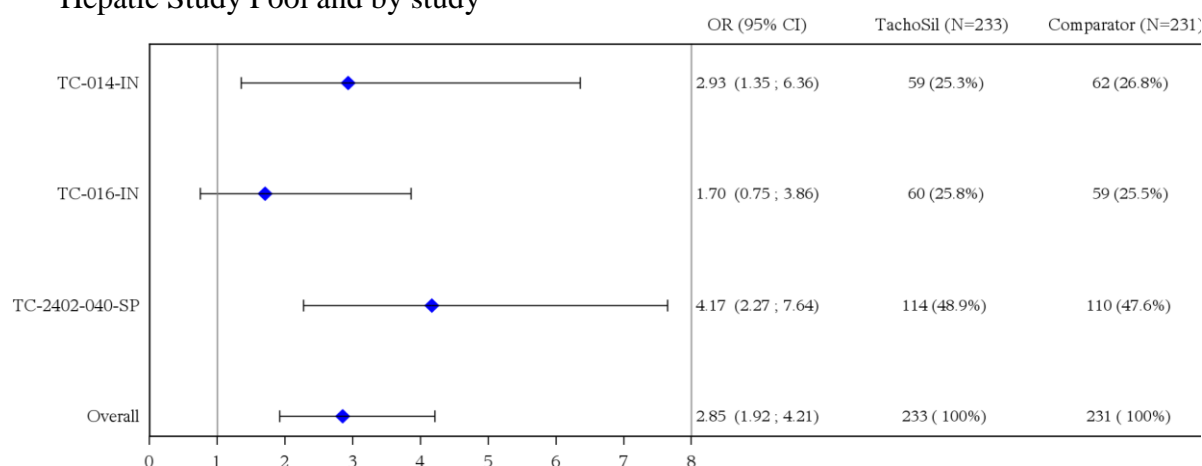
7.1.4 Analysis of Primary Endpoint(s)

- **Hemostasis at 3 minutes**

In the integrated analysis, 174 of 233 subjects (74.7%) in the TachoSil treatment group achieved hemostasis at 3 minutes compared with 117 of 231 subjects (50.6%) in the comparator treatment group achieved this goal ($P<0.0001$). The adjusted OR (95% CI) was 2.85 (1.92, 4.21).

The interaction term between treatment groups and studies (i.e., heterogeneity) had a p-value of 0.1277. The forest plot in the Hepatic Study Pool and by study was presented in Figure 2 below.

Figure 2. Forest plot of the proportion of subjects with hemostasis at 3 minutes in the Hepatic Study Pool and by study



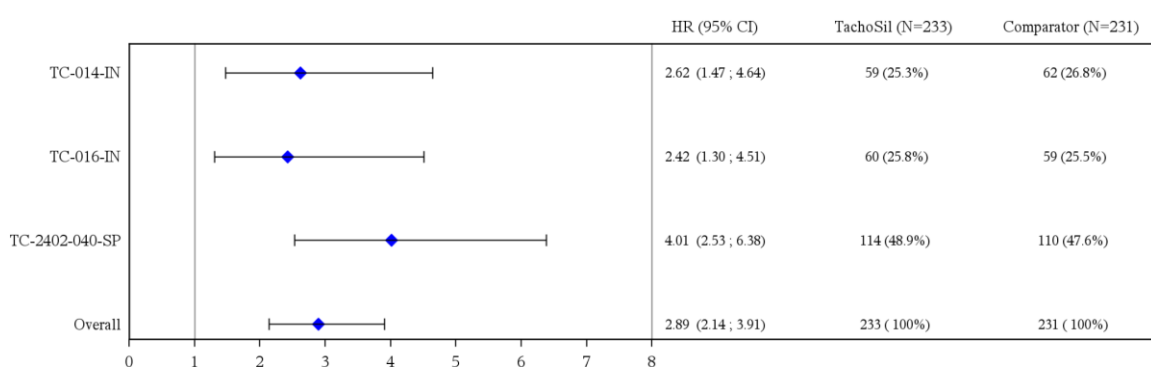
Source: Original sBLA 125351/172; Integrated Summary of Efficacy, Figure 2, p.54

Regarding the difference in the OR in Study TC-2402-040-SP (OR=4.17) compared with Studies TC-014-IN (OR=2.93) and TC-016-IN (OR=1.70), the sponsor assumed it was likely due to the different comparators used, since ABC has been demonstrated to be superior to Surgicel.

- **Time to Hemostasis**

In the Hepatic Study Pool, the median time to hemostasis was 3.0 minutes for both the TachoSil and comparator treatment groups. The log-rank test revealed a significant difference ($p < 0.0001$) for time to hemostasis between treatment groups. Based on the stratified proportional hazard model, the hazard ratio (95% CI) was 2.89 (2.14, 3.91). The interaction between treatment groups and studies had a p-value of 0.6444.

Figure 3. Forest plot of the time to hemostasis in the Hepatic Study Pool and by study



Source: Original sBLA 125351/172; Integrated Summary of Efficacy, Figure 7, p.60

7.2 ISE based on Pediatric Study Pool

The integrated analysis of the Pediatric Study Pool included subjects from Study TC-019-IN and the pediatric portion of Study TC-2402-040-SP.

- Study TC-019-IN was a prospective, open label, single arm, multi-center study, with the primary and only efficacy endpoint being time to hemostasis. It was conducted outside of the US. This study included 16 children under 6 years old.

- For the pediatric portion of Study TC-2402-040-SP, all the 17 randomized subjects and 12 subjects from the extensional part were included in the Pediatric Study Pool.

The efficacy endpoints for the Pediatric Study Pool were similar to those described for the Hepatic Study Pool. All efficacy endpoints were analyzed and/or summarized on an ITT principle using the integrated FAS. The efficacy endpoints for proportion of subjects with hemostasis at 3, 5, and 10 minutes are presented by an estimated proportion and a 95% exact binomial CI. For the time to hemostasis endpoint, simple descriptive summary statistics of the distribution of events are presented. No hypothesis testing was performed for the Pediatric Study Pool.

A total of 45 pediatric subjects were enrolled and treated in the Pediatric Study Pool: 36 in the TachoSil group and 9 in the comparator group. Subject disposition and demographic information were generally similar between the TachoSil and comparator treatment groups. The results are not presented here, as the number of subjects in both treatment groups was small, especially in the comparator group.

In Study TC-019-IN, 13 of 16 subjects (81.3%) in the ITT population obtained hemostasis at 3 minutes after application of TachoSil. In the integrated analysis, 30 subjects (83.3%) in the TachoSil treatment group achieved hemostasis at 3 minutes compared with 4 subjects (44.4%) in the comparator treatment group (Table 12).

Table 12. Hemostasis at 3 minutes –Pediatric Study Pool

Treatment	n/N (%)	Exact binomial 95% CI of proportion of subjects with hemostasis
Hemostasis within 3 minutes		
TachoSil	30/36 (83.3)	0.672, 0.936
Comparator	4/9 (44.4)	0.137, 0.788

Source: Original sBLA 125351/172; Integrated Summary of Efficacy, Table 44, p.103

In the Pediatric Study Pool, the median time to hemostasis for subjects in the TachoSil treatment group was 3.0 minutes and 4.0 minutes in the comparator treatment group.

9. COMMENTS TO THE APPLICANT

The following information request (IR) was sent to the applicant on March 4, 2015:

“For hemostasis in 3 minutes, a larger odds ratio (OR) of 4.17 was observed in Study TC-2402-040-SP, compared with Studies TC-014-IN (OR=2.93) and TC-016-IN (OR=1.70). You assumed it was likely due to the different comparators used. However, the percentage of subjects with hemostasis obtained at 3 minutes was actually very similar in all the control groups, while the difference only existed in the TachoSil groups. Please provide any other explanations for the treatment effect difference.”

The response was received on March 20, 2015. The applicant explained that:

- a) The comparator treatments were different between Studies TC-014-IN, TC-016-IN, and TC-2402-040-SP.

- b) The 2 European Studies TC-014-IN and TC-016-IN were completed in 2002 and 2003, respectively, whereas the US Study TC-2402-040-SP was completed in 2012. Surgical practice has developed over the past decade.
- c) The geographic difference (Europe vs. the US) might itself contribute to the variability in OR results.

In addition, the applicant stated that the OR value is inherently sensitive to the natural (random) variability in response rate due to the small number of subjects in each treatment arm.

Reviewer's comment: the above explanations are acceptable.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Adult studies:

1. The pivotal study, the adult portion of Study TC-2402-040-SP, achieved statistical significance for both the primary efficacy and secondary endpoints. The proportion of subjects with hemostasis within 3 minutes was approximately 80.7% in the TachoSil group and 50.0% in the Surgicel Original group.
2. Most of the study results are reproducible: this reviewer got either exactly the same or roughly the same results as provided in the study report.
3. The subgroup analyses showed consistent efficacy results among subgroups, regarding sex, age (below or above 65 years), race, and study site.
4. In the submitted datasets, there is no variable indicating center pooling. For Study TC-2402-040-SP, this reviewer created such a variable based on the information provided in Table 14.2.2.5: primary efficacy endpoint analysis by pooled center. However, this table is not available for the secondary efficacy endpoints, thus this reviewer is not able to reproduce the analyses exactly. This is not a concern as the results are very similar.
5. Regarding the integrated summary of efficacy (ISE), this reviewer suggests only reporting the descriptive analysis results for informational purposes only, and no statistical inference should be drawn. The reasons are as follows:
 - a) The other two liver studies in the Hepatic Study Pool (Studies TC-014-IN and TC-016-IN) used a different comparator than that of Study TC-2402-040-SP.
 - b) The SAP for the ISE was generated after the completion of the above two liver studies. The analyses were considered as post-hoc.
 - c) Time to hemostasis was the primary efficacy endpoint in the above two liver studies, however, it was the secondary efficacy endpoint in Study TC-2402-040-SP. It was chosen as one of the two primary efficacy endpoints in the ISE. As time to hemostasis was interval-censored, which resulted in too many ties between the treatment groups, the analysis was very sensitive to

the method of handling ties. This reviewer does not consider time to hemostasis a sensitive and informative endpoint in this setting.

6. In the ISE, for hemostasis in 3 minutes, a larger odds ratio (OR) of 4.17 was observed in Study TC-2402-040-SP, compared with Studies TC-014-IN (OR=2.93) and TC-016-IN (OR=1.70). The applicant assumed it was due to different comparator treatment used. However, as shown in Table 13, the results of the control arm in all the three studies were comparable. Therefore, an IR was sent to ask for further clarification. The applicant still attributed the difference primarily to the comparator treatments, but considered more factors such as potential changes in surgical practice over the years, geographical region, and the inherent sensitivity of OR to random variation in studies of small sample size. The explanations are acceptable. The applicant hypothesized that if ABC treatment (comparator in the European studies) had been used in the US Study, the OR may have been lower than that obtained against Surgicel (comparator in the US study) because the hemostatic effect of ABC treatment is known to be superior to Surgicel. It may be necessary to include the ORs of all the three studies in the labeling.

Table 13. Hemostasis at 3 minutes in the Hepatic Study Pool (FAS)

	TachoSil	Comparator	OR (CI)¹
TC-014-IN	72.9% (43/59)	48.4% (30/62)	2.87 (1.34, 6.13)
TC-016-IN	65.0% (39/60)	54.2% (32/59)	1.57 (0.75, 3.28)
TC-2402-040-SP (adult portion)	80.7 (92/114)	50.0% (55/110)	4.18 (2.30, 7.59)
Hepatic Study Pool	74.7 (174/233)	50.6 (117/231)	2.88 (1.94, 4.26)

¹: This table was created by this reviewer. The ORs were calculated without adjusting for study center.

Pediatric studies:

7. Descriptive statistics were used for the efficacy analyses. The proportion of pediatric subjects with hemostasis within 3 minutes was approximately 85% in the TachoSil group and 44% in the Surgicel Original group. The efficacy results were similar to the adult studies.

10.2 Conclusions and Recommendations

- Study TC-2402-040-SP showed better efficacy regarding hemostasis for TachoSil over Surgicel Original, in both adult and pediatric populations for hepatic surgery. The results are reproducible.
- The integrated summary of efficacy (ISE) is considered post-hoc. This reviewer suggests only reporting the descriptive analysis results for informational purposes only, and no statistical inference should be drawn.
- For hemostasis in 3 minutes, the OR of Studies TC-2402-040-SP, TC-014-IN and TC-016-IN should be included in the labeling.