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Division of Biostatistics

Mid-Cycle Statistical Review and Evaluation - BLA

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Product Name: Thrombin, Fibrinogen, patch

Indication(s): -----(b)(4)-----
an adjunct to hemostasis in cardiovascular surgery

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The major analyses results were reproducible. The results were in favor of TachoSil over the standard treatment with statistical significance regarding the efficacy of -----(b)(4)-----
----- and hemostasis in cardiovascular surgery (Study TC-023-IM). This statistical review memo serves the mid-cycle review commitment for BLA 125351/0.

1. -----(b)(4)-----

2. Study TC-023-IM reached statistical significance for both the primary and secondary efficacy endpoints, proportion of patients with hemostasis at 3 and 6 minutes. There were 59 subjects in the TachoSil group and 60 subjects in the Standard group in the ITT population. The proportion (95% CI) of subjects with haemostasis at 3 min was 0.75 (0.64 – 0.86) for TachoSil and 0.33 (0.21 – 0.45) for standard treatment ($p < 0.0001$). The proportion (95% CI) of subjects with haemostasis at 6 min was 0.95 (0.89 – 1.0) for TachoSil and 0.72 (0.60 – 0.83) for standard treatment ($p = 0.0006$). There was no evidence of heterogeneity in the odds ratios across centers. I have no objection to approving this product for the indication of haemostasis in cardiovascular surgery.
3. There seemed no major statistical issue in the safety analyses.

1.2 Major Statistical Issues and Findings

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(b)(4)

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

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

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

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

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

Haemostasis efficacy findings

1. In Study TC-023-IM, the proportion (95% CI) of subjects with haemostasis at 3 min was 0.75 (0.64 – 0.86) for TachoSil and 0.33 (0.21 – 0.45) for standard treatment ($p < 0.0001$) in the ITT population. The proportion (95% CI) of subjects with haemostasis at 6 min was 0.95 (0.89 – 1.0) for TachoSil and 0.72 (0.60 – 0.83) for standard treatment ($p = 0.0006$).
2. In the integrated analysis of three non-cardiovascular studies (----- (b)(4) -----), the primary efficacy endpoint, median time to hemostasis for patients in the TachoSil group was shorter (3.0 min) than that for patients in the Standard group (5.0 min). The p-value for the log-rank test was <0.001 .
3. In the integrated analysis of the 4 studies (----- (b)(4) -----), and TC-023-IM), a greater percentage of patients (174 patients [64.4%]) in the TachoSil group achieved hemostasis at 3 min (primary efficacy endpoint for integrated analysis) than in the Standard group (92 patients [33.6%]).
4. For the secondary efficacy endpoints in the integrated analysis of three non-cardiovascular studies, a greater proportion of patients in the TachoSil group (182

patients [86.3%]) achieved hemostasis at 5 min than in the Standard group (112 patients [52.3%]). The proportion of patients with hemostasis at 10 min was also greater in the TachoSil group (201 patients [95.3%]) than in the Standard group (174 patients [81.3%]). Both endpoints were statistically significant with p-value <0.001.

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There were no major statistical issues with the hemostasis studies.

2. INTRODUCTION

2.1 Overview

2.1.1 Product Information

TachoSil is a ready-to-use degradable surgical patch developed for topical use to support intraoperative hemostasis ----- (b)(4) ----- . The TachoSil patch consists of a dry --(b)(4)- collagen carrier of equine origin, coated with human fibrinogen and human thrombin. Upon contact with blood, body fluids or normal saline, the components of the coating dissolve, diffuse partly into the wound surface, and are activated. The components of TachoSil are degraded enzymatically and by phagocytosis in about -(b)(4)- months after application.

TachoSil was first approved by the European Commission on 08 June 2004 for supportive treatment in surgery for improvement of hemostasis where standard techniques are insufficient. Later variation applications based on further clinical studies led to the current European indication issued by the European Commission, February 2009: for supportive treatment in surgery for improvement of hemostasis, to promote tissue sealing, and for suture support in vascular surgery where standard techniques are insufficient. The product has obtained marketing authorizations in 42 countries and is marketed in 30 countries outside the United States.

The present Biologics License Application (BLA 125351) to the FDA represents the first regulatory submission for marketing approval of TachoSil in the United States. This BLA provides clinical data in support of the following intended indications:

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

These indications were discussed with FDA at a pre-BLA meeting on 21 November 2008.

2.1.2 Clinical Studies Reviewed

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

TC-023-IM was a Phase 3, multicenter, open-label, randomized, controlled trial comparing TachoSil and standard hemostatic fleece to evaluate the efficacy of TachoSil as an adjunct to hemostasis in cardiovascular surgery.

The supportive data from -----(b)(4)----- surgery (studies -----(b)(4)-----
-----) were used to provide further clinical evidence for TachoSil as an adjunct treatment of hemorrhage in -----(b)(4)-----.

Safety data were primarily based on above 6 randomized, controlled clinical studies.

Table 1. Completed Clinical Studies on TachoSil

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

2.2 Data Source

This is an eCTD submission. The data are stored in E-Room. The primary datasets used are: “adhe.xpt” for study TC-023-IM; “adal48.xpt” for study --(b)(4)--, and “adalsum.xpt” for study --(b)(4)--.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy in -(b)(4)-

3.1.1 Study --(b)(4)--

3.1.1.1 Study Design and Endpoints

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

22 Pages Determined to be Non-Releasable: (b)(4)

3.2 Evaluation of Efficacy in Hemostasis

3.2.1 Study TC-023-IM

3.2.1.1 Study Design and Endpoints

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

3.2.1.2 Patient Disposition, Demographic and Baseline Characteristics

One subject (subject 2034) was randomized to standard treatment but received no trial treatment since bleeding was no longer present when allocation to trial treatment was known. This subject was excluded from the ITT population. Three subjects (subject 1025, 3064, and 6157) randomized to standard treatment received TachoSil instead and therefore both an ITT and an “as treated” (AT) analysis set existed.

Table 1. Patient disposition (TC-023-IM)

Number of subjects		
Screened	326	
Screening failures	206	
Trial treatment	TachoSil	Standard
Randomised	59	61
Received no trial treatment	0	1
Intention-to-treat (ITT) analysis set	59	60
Safety analysis set (“as treated”)	62	57
Per-protocol (PP) analysis set	59	52
Completed the trial, i.e. had Visit 2	55	54
Discontinued due to adverse events	2	1
Discontinued for other reasons	2	5

The demographic variables and primary haemostatic treatment were comparable between the TachoSil group and the Standard group.

Table 2. Demographic and baseline characteristic by treatment (TC-023-IM)

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

Variable	Unit	TachoSil	Standard	All subjects
Sex				
Male	%	76	72	74
Female		24	28	26
Age	years	65 (23 - 82)	68 (36 - 86)	67 (23 - 86)
Age > 65 years	%	59	65	62
Height	cm	170 (150 - 196)	170 (155 - 186)	170 (150 - 196)
Weight	kg	77 (46 - 145)	79 (45 - 118)	78 (45 - 145)
Body Mass Index	kg/m ²	26.8 (18.3 – 50.2)	27.4 (16.5 - 37.2)	27.1 (16.5 – 50.2)
Blood pressure*				
Systolic	mmHg	128 (100 - 170)	128 (90 – 183)	128 (90 - 183)
Diastolic		74 (40 - 102)	73 (50 - 93)	73 (40 - 102)
Heart rate*	beats/min	71 (50 - 114)	73 (46 - 96)	72 (46 – 114)

However, there were some difference for the surgical variables between the TachoSil group and the Standard group listed in Tables 31 and 32.

Table 3. Surgical variables by treatment (TC-023-IM)

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

Table 4. Other variables by treatment (TC-023-IM)

	Tachosil	Standard
Blood transfusion	17 (27%)	21 (37%)
Inhibitor of Fibrinolysis	27 (46%)	35 (58%)
Treatment failures	3 (5%)	17 (28%)

Reviewer's comment: Clinical reviewer's input is needed to decide whether these differences in surgical variables were clinically meaningful.

3.2.1.3 Statistical Methodologies

All statistical tests were two-sided at a significance level of 5% unless stated otherwise.

Primary Efficacy Endpoints

The proportion of patients achieving hemostasis at 3 minutes after first application of the test treatment, was analyzed using the CMH test controlling for center (data from small study centers were pooled). The Breslow-Day tests for homogeneity of the odds ratios across centers were omitted from the sub-group analysis due to small cell counts in many of the strata.

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

The proportion of patients with hemostasis at 3 minutes was displayed graphically by treatment, with 95% CI.

Secondary Efficacy Endpoints

The secondary efficacy endpoint was the proportion of subjects achieving haemostasis after 6 minutes. This analysis was only done on the ITT population since only eight subjects were excluded from the PP analysis set.

Exploratory Efficacy Endpoints

Descriptive statistics was used for several exploratory efficacy endpoints.

Subgroup analysis

Subgroup analysis was performed for subjects whom treatment was applied before infusion of protamine, and for those where treatment was applied during or after infusion of protamine. Subgroup analyses by sex and age subgroups were not specified in the SAP.

3.2.1.4 Results and Conclusions

Primary Efficacy Endpoints

In the ITT population, the proportion (95% CI) of subjects with haemostasis at 3 min was 0.75 (0.64 – 0.86) for TachoSil and 0.33 (0.21 – 0.45) for standard treatment; the difference was statistically significant ($p < 0.0001$). There was no evidence of heterogeneity in the odds ratios across centers.

In the PP population, the proportion (95% CI) of subjects with haemostasis at 3 min was 0.75 (0.64 – 0.86) for TachoSil and 0.35 (0.22 – 0.48) for standard treatment; the difference was statistically significant ($p < 0.0001$). There was no evidence of heterogeneity in the odds ratios across centers.

Secondary Efficacy Endpoints

The proportion (95% CI) of subjects with haemostasis at 6 min was 0.95 (0.89 – 1.0) for TachoSil and 0.72 (0.60 – 0.83) for standard treatment; the difference was statistically significant ($p = 0.0006$). There was no evidence of heterogeneity in the odds ratios across centers.

Exploratory Efficacy Endpoints

The mean (median; range) duration of drainage, *i.e.* from the end of surgery to removal of drains, was 93 (46; 18 - 1,093) h in TachoSil and 67 (44; 15 - 687) h in standard treatment subjects.

The mean (median; range) volume of post-operative drainage was 1,005 (600; 75 - 5,240) ml in TachoSil and 932 (498; 100 - 9,100) ml in standard treatment subjects.

Twenty six (42%) TachoSil subjects had 51 post-operative transfusions; 22 (39%) standard subjects had 44 post-operative transfusions.

Re-operation was performed in three TachoSil subjects (5%) and eight standard treatment subjects (14%). The reasons for the three TachoSil subjects were iatrogenic puncture of the heart resulting in cardiac tamponade, revision of a subcutaneous haematoma and bleeding from the sternal marrow. For the eight standard treatment subjects that had a re-operation performed, the reasons were, as the TachoSil subjects, not related to the trial treatment and or target area.

In total, 27 (44%) Tachosil subjects and 31 (54%) standard treatment subjects had other post-operative complications.

Subgroup analysis

There were 10 TachoSil and 9 Standard subjects that had trial treatment before the protamine infusion. For these subjects, the treatment effect was not significant for both the primary (70% vs. 56%) and secondary (90% vs. 89%) efficacy endpoints. The treatment effect was significant in the rest subjects.

A greater proportion of patients in the TachoSil treatment group achieved hemostasis at 3 minutes than in the Standard group in both male and female patients. The results for female patients were less robust than those for the male patients.

Table 5. Hemostasis at 3/6 minutes by sex (TC-023-IM)

	Tachosil				Standard		
	N	3 min	6 min		N	3 min	6 min
Female	14	8 (57%)	14(100%)		17	7 (41%)	14(82%)
Male	45	36 (80%)	42 (93%)		43	13 (30%)	29(67%)
Age ≤65	24	16(67%)	21(88%)		21	6 (29%)	14(67%)
Age >65	35	28(80%)	35(100%)		39	14 (36%)	29(74%)

Reviewer's comment: The sex effect was consistent with the -(b)(4)- studies. However, the number of female subjects was too small in this study to make any confirmatory conclusion.

Sponsor's efficacy conclusion:

Based on the analysis of the primary efficacy endpoint; proportion of subjects with haemostasis at 3 minutes, TachoSil was superior to standard haemostatic treatment. The proportion (95% CI) of subjects achieving haemostasis at 3 minutes in the TachoSil group was 0.74 (0.64 – 0.86) versus 0.33 (0.21 – 0.45) in the standard group. This result

	TachoSil^a	CT^a	Total^a
	n (%)	n (%)	n (%)
Total number of patients screened			820
Total number of patients randomized	271	277	548
Patients randomized and received test treatment (ITT population)			
ITT population	270 (99.6)	274 (98.9)	544 (99.3)
Male : Female	174 (64.4) : 96 (35.6)	168 (61.3) : 106 (38.7)	342 (62.9) : 202 (37.1)
18–65 years : >65 years	158 (58.5) : 112 (41.5)	154 (56.2) : 120 (43.8)	312 (57.4) : 232 (42.6)
Patients completing visit of key stage of study			
Day of surgery			
ITT population	270 (99.6)	274 (98.9)	544 (99.3)
Male : Female	174 (64.4) : 96 (35.6)	168 (61.3) : 106 (38.7)	342 (62.9) : 202 (37.1)
18–65 years : >65 years	158 (58.5) : 112 (41.5)	154 (56.2) : 120 (43.8)	312 (57.4) : 232 (42.6)
Discharge from surgical ward			
ITT population	264 (97.4)	270 (97.5)	534 (97.4)
Male : Female	169 (64.0) : 95 (36.0)	165 (61.1) : 105 (38.9)	334 (62.5) : 200 (37.5)
18–65 years : >65 years	156 (59.1) : 108 (40.9)	152 (56.3) : 118 (43.7)	308 (57.7) : 226 (42.3)
Follow-up (1 month ± 10 days)			
ITT population	262 (96.7)	262 (94.6)	524 (95.6)
Male : Female	170 (64.9) : 92 (35.1)	161 (61.5) : 101 (38.5)	331 (63.2) : 193 (36.8)
18–65 years : >65 years	155 (59.2) : 107 (40.8)	147 (56.1) : 115 (43.9)	302 (57.6) : 222 (42.4)

The disposition and demographics of the overall population were consistent with that described for the individual studies, with a similar total number of patients in the TachoSil and Standard group.

3.2.2.3 Statistical Methodologies

All efficacy determinations in the individual studies and in the integrated analysis were performed on the ITT population. Analyses were not performed on the PP population for the integrated analyses.

Primary efficacy endpoint

- Time to hemostasis was defined as the recorded time from start of test treatment to hemostasis. Patients with a time to hemostasis longer than 10 minutes were censored at 10 minutes. Patients with missing time to hemostasis were imputed with a time censored at 10 minutes.

The null hypothesis of no difference in time to hemostasis between the 2 treatment groups was tested using a log-rank test, with treatment of ties based on a discrete hazards assumption, stratified by organ and/or region as appropriate. The median survival, with 95% CIs, based on Kaplan-Meier estimates, was calculated for each stratum for each treatment. The hazard ratio (based on a proportional hazards model) was also presented for each stratum for each treatment. In addition, the p-value from a log-rank test was displayed for each corresponding analysis. The Kaplan-Meier estimates were also displayed graphically, with each graph contrasting the treatment groups for each stratum.

- The proportion of patients achieving hemostasis at 3 minutes in the target area was analyzed using the CMH test controlling for organ. An additional overall analysis was performed controlling for region. Patients with missing time to hemostasis information were counted in the group of patients not having hemostasis by 3 minutes in agreement with the methods used in the individual study reports. An odds ratio estimate of the treatment difference from the CMH test, 95% CI for the estimate and the p-value from the CMH test statistic were displayed for each model. The Breslow-

Day test was used to test for homogeneity of odds ratios (i.e., treatment effect) across the controlling factor.

Secondary endpoint: The proportion of patients with hemostasis at 5 and 10 minutes was analyzed following the same method used for hemostasis at 3 minutes, i.e., using the CMH test stratified by organ.

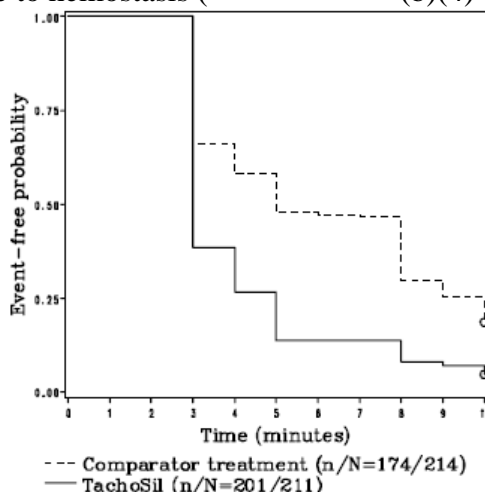
Subgroup analysis: performed by sex and age.

3.2.2.4 Results and Conclusions

Primary efficacy endpoint

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

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



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

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

Secondary endpoint

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

Subgroup analysis

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

Table 8. Hemostasis at 3 minutes (------(b)(4)-----, TC-023-IM)

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

Reviewer's comment: In study TC-023-IM, the treatment effect in females was not as big as in the males. Note that there were only 14 females in the TachoSil group in that study. The sex-related difference was not apparent in the integrated studies with large sample size. Therefore, sex may not be a concern in the hemostasis indication. However, it was observed that the older subjects had better hemostasis at 3 minutes than the younger subjects.

Sponsor's efficacy conclusion

The controlled study TC-023-IM provides support for the hemostasis indication in cardiovascular surgery. Of the 120 patients randomly assigned to treatment, 119 patients were analyzed for efficacy. Patients were Caucasian and were age 23 to 86 years. The results of this study showed that TachoSil was significantly better than comparator treatment for intraoperative hemostasis. A significantly greater proportion of patients in the TachoSil treatment group achieved hemostasis at 3 minutes and 6 minutes, the earliest intraoperative assessments of hemostasis, than in the comparator treatment group. In addition, the number of patients who needed reoperation was lower in the TachoSil group than in the comparator treatment group.

No differences in efficacy were observed for the subgroups based on sex and age in this study.

3.3 Evaluation of Safety

3.3.1 Exposure to drug

The clinical development of TachoSil has been accomplished over a period of 9 years starting in 2000. A total of 1038 patients were randomized in the 6 open-label, randomized, controlled clinical studies (------(b)(4)-----, and TC-023-IM) included in the integrated data set. Of these, 521 patients were treated with TachoSil. Pooled data from 6 studies were the primary population for safety analyses. A further 4063 patients, of whom 3839 received TachoSil, were treated in the 5 studies not included in the integrated data set.

Demographic data and baseline characteristics were comparable for the two groups.

Table 9. Demographic data and baseline characteristics by treatment (all studies pool)

	TachoSil N = 521	Comparator N = 511
Sex		
Male, n (%)	343 (65.8%)	324 (63.4%)
Female, n (%)	178 (34.2%)	187 (36.6%)
Age ^a		
Mean (SD), years	61.4 (11.70)	62.7 (10.76)
Range, years	19 - 85	18 - 88
18 – 65 years, n (%)	302 (58.0%)	282 (55.2%)
>65 years, n (%)	219 (42.0%)	229 (44.8%)
Caucasian, n (%)	521 (100%)	509 (99.6%)
Non-Caucasian, n (%)	0	2 (0.4%)
Mean (SD) height, cm	170.2 (8.96)	169.9 (8.57)
Mean (SD) weight, kg	76.7 (15.62)	76.1 (14.53)
Mean (SD) BMI ^b , kg/m ²	26.38 (4.633)	26.37 (4.551)
Smoking status: Smoker, n (%)	128 (24.6%)	124 (24.3%)
Nonsmoker, n (%)	331 (63.5%)	330 (64.6%)
Missing ^c , n (%)	62 (11.9%)	57 (11.2%)
Alcohol use: Yes, n (%)	134 (25.7%)	125 (24.5%)
No, n (%)	325 (62.4%)	329 (64.4%)
Missing ^c , n (%)	62 (11.9%)	57 (11.2%)

Overall, 41 patients (4.0%) were discontinued from study procedures. The reasons for discontinuation were summarized in Table 38.

Table 10. Patient discontinuation (all studies pool)

	TachoSil N = 521 n (%)	Comparator N = 511 n (%)	Total N = 1032 n (%)
Total number of patients discontinued	20 (3.8%)	21 (4.1%)	41 (4.0%)
Primary reason for discontinuation			
Adverse event	13 (2.5%)	7 (1.4%)	20 (1.9%)
Noncompliant with protocol	1 (0.2%)	3 (0.6%)	4 (0.4%)
Death ^a	1 (0.2%)	2 (0.4%)	3 (0.3%)
Other	5 (1.0%)	8 (1.6%)	13 (1.3%)
Missing	0	1 (0.2%)	1 (0.1%)

Excluding the condition under study, 475 patients (91.2%) in the TachoSil group and 469 patients (91.8%) in the comparator treatment group had a history of other medical conditions reported at baseline. There were some differences in the medical histories reported by patients in the -(b)(4)- studies and hemostasis studies.

Concomitant medication use was reported in 496 patients (95.2%) in the TachoSil group and 493 patients (96.5%) in the comparator group. The types of medications recorded were generally similar for the 2 treatment groups.

No formal hypotheses were written towards the integrated evaluation of safety. Safety variables recorded in the studies in the integrated analyses were: adverse events; clinical laboratory (hematology, coagulation factors, and liver function tests) evaluations; vital signs (blood pressure, heart rate, respiratory rate, and body temperature); and physical examinations.

3.3.2 Adverse Events

An AE was defined as any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and that did not necessarily have a causal relationship with this treatment.

Adverse events were reported in 247 patients (47.4%) in the TachoSil group and 238 patients (46.6%) of the comparator group in the All Studies pool.

Table 11. Summary of adverse events (all studies pool)

	TachoSil	Comparator
	N = 521	N = 511
	n (%)	n (%)
At least 1 AE	247 (47.4%)	238 (46.6%)
At least 1 treatment-related AE	36 (6.9%)	37 (7.2%)
At least 1 SAE	67 (12.9%)	61 (11.9%)
At least 1 SAE with a fatal outcome	13 (2.5%)	9 (1.8%)

In the TachoSil group, 70 of 546 AEs (12.8%) and in the comparator group 55 of 537 AEs (10.2%) were categorized by the Investigator as severe, and 45 patients (8.6%) in the TachoSil group and 33 patients (6.5%) in the comparator treatment group experienced at least 1 severe AE.

Table 12. Degree of AE by treatment (all studies pool)

	TachoSil	Comparator
	N = 521	N = 511
Total number of AEs	546	537
Mild	290	297
Moderate	186	185
Severe	70	55
Number (%) of patients with at least 1 AE	247 (47.4%)	238 (46.6%)
Mild	112 (21.5%)	124 (24.3%)
Moderate	90 (17.3%)	81 (15.9%)
Severe	45 (8.6%)	33 (6.5%)

There were 36 patients (6.9%) in the TachoSil group and 37 patients (7.2%) in the comparator treatment groups who experienced AEs that were considered by the investigator to be related to study treatment.

Table 13. Adverse events (by the investigator) related to study treatment (all studies pool)

Treatment-Related Adverse Event (Preferred Term)	TachoSil N = 521 n (%)	Comparator N = 511 n (%)
At least 1 treatment-related AE	36 (6.9%)	37 (7.2%)
Pyrexia	13 (2.5%)	10 (2.0%)
Procedural site reaction	4 (0.8%)	1 (0.2%)
Pneumothorax	3 (0.6%)	9 (1.8%)
Pleural effusion	3 (0.6%)	4 (0.8%)
Pain	2 (0.4%)	4 (0.8%)
Lung disorder	2 (0.4%)	1 (0.2%)
Hypertension	1 (0.2%)	2 (0.4%)
Anemia postoperative	1 (0.2%)	1 (0.2%)
Bronchopleural fistula	1 (0.2%)	1 (0.2%)
Cough	1 (0.2%)	1 (0.2%)
Abdominal pain	1 (0.2%)	0
C-reactive protein increased	1 (0.2%)	0
Drug ineffective	1 (0.2%)	0
Fatulence	1 (0.2%)	0
Insomnia	1 (0.2%)	0
Liver abscess	1 (0.2%)	0
Nervousness	1 (0.2%)	0
Postoperative abscess	1 (0.2%)	0
Postprocedural hemorrhage	1 (0.2%)	0
Pruritus	1 (0.2%)	0
Renal disorder	1 (0.2%)	0
Tachyarrhythmia	1 (0.2%)	0
Urinary retention	1 (0.2%)	0
Urticaria	1 (0.2%)	0
Wound abscess	1 (0.2%)	0
Abdominal abscess	0	1 (0.2%)
Aspiration bronchial	0	1 (0.2%)
Atrial fibrillation	0	1 (0.2%)
Body temperature increased	0	1 (0.2%)
Chills	0	1 (0.2%)
Fistula	0	1 (0.2%)
Fluid retention	0	1 (0.2%)
Headache	0	1 (0.2%)
Hematoma	0	1 (0.2%)
Hematuria	0	1 (0.2%)
Ileus	0	1 (0.2%)
Nausea	0	1 (0.2%)
Pneumonia	0	1 (0.2%)
Renal hematoma	0	1 (0.2%)
Subileus	0	1 (0.2%)
Syncope	0	1 (0.2%)
Vocal cord paralysis	0	1 (0.2%)

There were 22 deaths from all studies included in the integrated database, 13 deaths (2.5%) in the TachoSil group and 9 deaths (1.8%) in the comparator group. There were 4 deaths in the -(b)(4)- studies, 3 deaths (1.2%) in the TachoSil group and 1 death (0.4%) in the comparator treatment group. Eighteen of the 22 deaths in the integrated database occurred in the hemostasis studies (10 deaths [3.6%] in the TachoSil group and 8 deaths [3.0%] in the comparator group. Of these, 4 deaths, 2 in each treatment group occurred in study TC-023-IM. No AEs with a fatal outcome were considered by the investigator to be related to study treatment. All deaths were related to underlying illness or to complications of surgery.

Reviewer's comment: The mortality rate was not significantly different between TachoSil and the Standard groups statistically (2.5% vs. 1.8%) with a p-value of 0.52 by Fisher's Exact test. It is deferred to the clinical reviewer's judgment that whether the different number of deaths in the two groups is clinically meaningful.

Serious AEs were reported in 67 patients (12.9%) in the TachoSil group and 61 patients (11.9%) in the comparator group.

Table 14. Summary of SAE by system organ class (all studies pool)

System Organ Class	TachoSil N = 521 n (%)	Comparator N = 511 n (%)
At least 1 SAE	67 (12.9%)	61 (11.9%)
Respiratory, thoracic, and mediastinal disorders	20 (3.8%)	15 (2.9%)
Infections and infestations	16 (3.1%)	17 (3.3%)
Cardiac disorders	12 (2.3%)	12 (2.3%)
Injury, poisoning, and procedural complications	11 (2.1%)	7 (1.4%)
Gastrointestinal disorders	6 (1.2%)	7 (1.4%)
Renal and urinary disorders	6 (1.2%)	4 (0.8%)
Nervous system disorders	4 (0.8%)	6 (1.2%)
Hepatobiliary disorders	3 (0.6%)	4 (0.8%)
General disorders and administration site conditions	4 (0.8%)	2 (0.4%)
Vascular disorders	3 (0.6%)	6 (1.2%)
Neoplasms benign, malignant, and unspecified	2 (0.4%)	3 (0.6%)
Psychiatric disorders	0	2 (0.4%)
Blood and lymphatic system disorders	1 (0.2%)	0

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

Statistical issues of -----(b)(4)-----

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

Two (2) Pages Determined to be Non-Releasable: (b)(4)

Statistical issues of hemostasis

1. In Study TC-023-IM, there were some differences between the treatment groups regarding the surgical variables, such as the site of bleeding, type of bleeding, *etc.*

4.2 Conclusions and Recommendations

The results were in favor of TachoSil over the standard treatment with statistical significance regarding the efficacy -----(b)(4)----- and hemostasis in cardiovascular surgery (Study TC-023-IM). I have no objection to approving this product for the indication of haemostasis in cardiovascular surgery. Due to the sex effect, the center heterogeneity, and other considered factors, the statistical evidence was not very strong in -----(b)(4)-----, -----(b)(5)-----
-----.

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