



Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

Statistical Review and Evaluation – BLA (Final Memo)

BLA/Supplement Number: 125351/0

Product Name: Thrombin, Fibrinogen, patch

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

Applicant: Nycomed DANMARK APS/1825

Date(s): CBER Receipt Date: 05-Jun-2009

Review Priority: Standard

Statistical Branch: Therapeutics Evaluation Branch

Primary Statistical Reviewer: Chunrong Cheng, Ph.D./HFM-219

Concurring Reviewer: Jessica Kim, Ph.D., Team Leader
Therapeutic Evaluation Branch/HFM-219

Ghanshyam Gupta, Ph.D., Branch Chief
Therapeutic Evaluation Branch/HFM-219

Medical Office/Division: OBRR/DH/CRB

Clinical Reviewer(s): Kimberly Lindsey, MD./HFM-392

Project Manager: Jie He/HFM-380

Table of Contents

1. EXECUTIVE SUMMARY	4
2. INTRODUCTION	4
2.1 OVERVIEW	4
2.1.1 Product Information.....	4
2.1.2 Clinical Studies Reviewed	4
2.2 DATA SOURCE	5
3. STATISTICAL EVALUATION OF EFFICACY IN HEMOSTASIS	5
3.1 STUDY TC-023-IM	5
3.1.1 Study Design and Endpoints.....	5
3.1.2 Patient Disposition, Demographic and Baseline Characteristics	5
3.1.3 Statistical Methodologies.....	7
3.1.4 Results and Conclusions	8
3.2 INTEGRATED SUMMARY OF EFFICACY.....	9
3.2.1 Study Design and Endpoints.....	9
3.2.2 Patient Disposition, Demographic and Baseline Characteristics	10
3.2.3 Statistical Methodologies.....	10
3.2.4 Results and Conclusions	11
3.3 EVALUATION OF SAFETY	13
3.3.1 Exposure to drug.....	13
3.3.2 Adverse Events	15
4. SUMMARY AND CONCLUSIONS	17
4.1 MAJOR FINDINGS.....	17
4.2 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE	17
4.2 CONCLUSIONS AND RECOMMENDATIONS	18
DISTRIBUTION LIST.....	18

Table 1. Completed Clinical Studies on TachoSil	5
Table 2. Patient disposition (TC-023-IM)	6
Table 3. Demographic and baseline characteristics by treatment (TC-023-IM)	6
Table 4. Surgical variables by treatment (TC-023-IM)	7
Table 5. Other variables by treatment (TC-023-IM).....	7
Table 6. Hemostasis at 3/6 minutes by sex (TC-023-IM).....	9
Table 7. Primary and secondary efficacy endpoints (integrated hemostasis studies)	10
Table 8. Baseline features (------(b)(4)-----, TC-023-IM)	10
Table 9. Hemostasis at 3 minutes (------(b)(4)-----, TC-023-IM)	12
Table 10. Demographic data and baseline characteristics by treatment (all studies pool).....	13
Table 11. Patient discontinuation (all studies pool).....	14
Table 12. Summary of adverse events (all studies pool)	15
Table 13. Degree of AE by treatment (all studies pool)	15
Table 14. Adverse events (by the investigator) related to study treatment (all studies pool)	16
Table 15. Summary of SAE by system organ class (all studies pool)	16
Figure 1. Time to hemostasis (------(b)(4)-----).....	11

1. EXECUTIVE SUMMARY

The major statistical analyses were reproducible. The results were in favor of TachoSil over the standard treatment with statistical significance for the efficacy of hemostasis in cardiovascular surgery (Study TC-023-IM). -----(b)(4)-----

-----). This statistical review memo serves as the final review commitment for BLA 125351.

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 originally provided clinical data in support of the following intended indications:

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

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

2.1.2 Clinical Studies Reviewed

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)-----
-----) were used to provide further clinical evidence for TachoSil as an adjunct treatment of -----(b)(4)-----).

3064, and 6157) randomized to standard treatment received TachoSil instead and therefore both an ITT and an “as treated” (AT) analysis set existed.

Table 2. 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 3. Demographic and baseline characteristics by treatment (TC-023-IM)

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

However, there were some slight difference for the surgical variables between the TachoSil group and the Standard group listed in Tables 4 and 5.

Table 4. 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 5. 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 (provided in section 4.1 of this review) is needed to decide whether these differences in surgical variables were clinically meaningful.

3.1.3 Statistical Methodologies

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

Primary Efficacy Endpoint

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.

Secondary Efficacy Endpoint

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.

3.1.4 Results and Conclusions

Primary Efficacy Endpoint

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 Endpoint

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 of the 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.

Table 6. 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 treatment effect was larger in the male subjects than in the female subjects. 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 is supported by a significant difference with respect to the secondary efficacy endpoint; proportion of subjects with haemostasis at 6 minutes.

3.2 Integrated Summary of Efficacy

3.2.1 Study Design and Endpoints

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

The integrated analysis for all four hemostasis studies included a total of 270 patients who received TachoSil and 274 patients in Standard group.

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

Table 7. Primary and secondary efficacy endpoints (integrated hemostasis studies)

		---(b)(4)---	------(b)(4)----- -----, TC-023-IM
Primary	Time to hemostasis	Assessed	NA
	Patients with hemostasis at 3 min		Assessed
Secondary	Patients with hemostasis at 5 min	Assessed	NA
	Patients with hemostasis at 10 min	Assessed	NA

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Table 8 presents the patient disposition and demographic information pooled for the hemostasis studies (------(b)(4)-----, and TC-023-IM).

Table 8. Baseline features (------(b)(4)-----, TC-023-IM)

	TachoSil ^a n (%)	CT ^a n (%)	Total ^a 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.

3.2.3 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 endpoints

- 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 Cochran-Mantel-Haenszel (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 endpoints: 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.

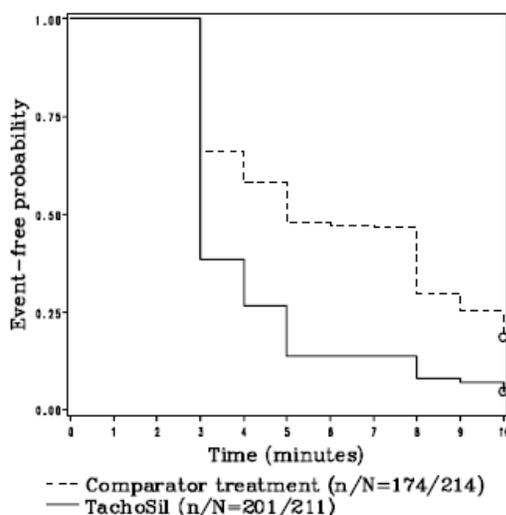
Subgroup analysis: performed by sex and age.

3.2.4 Results and Conclusions

Primary efficacy endpoints

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

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



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

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

Secondary endpoints

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

Subgroup analysis

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

Table 9. 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 large as that in the males. Note that there were only 14 females in the TachoSil group in that study. The sex-related difference was not apparent in the integrated studies with larger sample size. Therefore, sex may not be a concern in the hemostasis indication. However, it was observed that the older subjects had better hemostasis at 3 minutes than the younger subjects.

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 10. 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 (%)		
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 11. 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 medical 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 lung 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 12. Summary of adverse events (all studies pool)

	TachoSil N = 521 n (%)	Comparator N = 511 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 13. Degree of AE by treatment (all studies pool)

	TachoSil N = 521	Comparator 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 14. 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
Fiatulence	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.

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

Table 15. 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 Major 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)----- TC-023-IM), a greater percentage of patients (174 patients [64.4%]) in the TachoSil group achieved hemostasis at 3 min (another 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 .

4.2 Statistical Issues and Collective Evidence

1. In Study TC-023-IM, there were some slight differences between the treatment groups regarding the surgical variables, such as the site of bleeding, type of bleeding, *etc.* See page 8 of this review for details.

The FDA clinical reviewer provided the following input:

- Arterial bleeds are usually more of a hemostatic challenge. TachoSil had more arterial bleeds but the subjective "severity" of bleeding among the two groups

(TachoSil and Standard) was fairly comparable. As for target area, the aorta probably presents more "challenging" bleeding than the other sites.

- Blood transfusion triggers were not pre-specified and there were no algorithms for blood product transfusions; so it is unknown if there were differences in transfusion practices among surgeons and institutions that could have influenced the outcome. The same principle applies to the use of inhibitors of fibrinolysis.
2. In study TC-023-IM, the treatment effect in male subjects was larger than that in the female subjects. Note that there were only 14 females in the TachoSil group in that study. The sex-related difference was not apparent in the integrated studies with larger sample size. Therefore, sex may not be a concern in the hemostasis indication.
 3. In the sub-group analysis of the integrated studies, it was noticed that the older subjects (>65 years old) had better hemostasis at 3 minutes than the younger subjects (≤65 years old), though TachoSil outperformed the standard treatment in both subgroups. See page 13 for details. However, based on the available data, no conclusions about any relationship between gender and hemostatic treatment effect can be drawn.

4.2 Conclusions and Recommendations

The results were in favor of TachoSil over the standard treatment with statistical significance regarding the efficacy of hemostasis in cardiovascular surgery (Study TC-023-IM). I have no objection to approving this product for the indication of haemostasis in cardiovascular surgery.

1. 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.
2. There appeared no major statistical issue in the safety analyses.
3. I have no objection to approving this product for the indication of haemostasis in cardiovascular surgery.

DISTRIBUTION LIST

cc:

HFM-380/Jie He, RPM, OBRR/DBA/RPMB

DCC/HFM-99

HFM- 215/Chron

HFM- 392/Natalya Ananyeva, Ph.D., OBRR/DH/LH

HFM-392/Kimberly Lindsey, MD., OBRR/DH/CRB

HFM-392/Nisha Jain, MD., OBRR/DH/CRB, Branch Chief
HFM-215/Christopher Egelebo, RPM, OBE/DB
HFM-219/Jessica Kim, Ph.D., OBE/DB/TEB, Team Leader
HFM-219/Ghanshyam Gupta, Ph.D., OBE/DB/TEB, Branch Chief
HFM-215/Estelle Russek-Cohen, Ph.D., OBE/DB, Division Deputy Director
HFM-215/Henry Hsu, Ph.D., OBE/DB, Division Director