DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

FINAL STATISTICAL REVIEW AND EVALUATION

BLA SUPPLEMENT

BLA/Supplement Number:	103980.5601
Product Name:	Tisseel Fibrin Sealant (FS VH S/D 500 s-apr)
Indication(s):	Adjunct to Hemostasis
Applicant:	Baxter BioScience
Date(s):	Document Room Receive Date: 01-Apr-2011
Review Priority:	Standard
Statistical Branch:	CBER/OBE/DB/TEB (HFM-219)
Primary Statistical Reviewer:	Stan Lin, Ph.D.
Concurring Reviewer (1):	Jessica Kim, Ph.D., Team Leader, Therapeutics Evaluation Branch (HFM-219)
Concurring Reviewer (2):	Boguang Zhen, Ph.D., Acting Branch Chief Therapeutics Evaluation Branch (HFM-219)
Medical Office/Division:	Kimberly Lindsey, MD., CBER/OBRR/DBA
Project Manager:	Jie He, Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY

Overall results from the phase 2 (study 550602) and the phase 3 (study 550801) studies submitted in this application demonstrate the hemostasis efficacy in subjects undergoing vascular surgery (ePTFE graft placement including arterial bypasses and AV-shunts).

1.1 CONCLUSIONS AND RECOMMENDATIONS

Tisseel was licensed as an adjunct to hemostasis for cardiac and splenic surgery. Results of a phase 2 and a phase 3 vascular surgery studies are submitted to support an indication for general adjunct to hemostasis. Using a statistical significance level of 0.1 (10%), the phase 2 study was for proof-of-concept. It evaluated the efficacy and safety of TISSEEL (FS VH S/D 500 s-apr) for hemostasis in subjects undergoing vascular surgery (i.e., ePTFE graft placement including arterial bypasses and AV-shunts). The confirmatory Phase 3 study 550801 evaluated the vascular surgery indication and demonstrated the hemostasis efficacy in the same patient population.

The results from this phase 2 study (Protocol 550602) did not demonstrate statistically significant differences between FS-120 or FS-60 and manual compression (the control), at the pre-specified 10% significance level. However, the differences were deemed encouraging in proportion of hemostasis that a phase 3 study (Protocol 550801) was designed and conducted by the sponsor based on the success rates observed from the phase 2 study. This phase 3 study results demonstrated a significant difference between the treatment groups in the proportion of patients who achieved hemostasis 4 minutes post suture line closure after surgery. Taken together, these two studies appear to demonstrate efficacy of FS-120 in terms of the proportion of patients who achieved hemostasis 4 minutes post suture line closure after surgery.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

For the current supplement, the sponsor submits results from a phase 2 and a phase 3 vascular surgery studies. The phase 2 study was a proof-of-concept study. The phase 3 study was an efficacy-confirmatory study. The purpose of the phase 3 study (550801) was to compare safety and efficacy of FS VH S/D 500 s-apr (FS) versus manual compression in prosthetic ePTFE graft placement. The primary objective was to evaluate the efficacy of FS for hemostasis in subjects receiving peripheral vascular ePTFE conduits, as compared to a control arm treated with manual compression with surgical gauze pads. This study was a prospective, controlled, randomized, multicenter study involving a total of 140 evaluable subjects (70 subjects per treatment arm) undergoing ePTFE graft placement including arterio-arterial bypasses and AV shunts. The planned duration of subject participation was 30 days. The primary endpoint was the proportion of subjects who achieved hemostasis at 4 minutes. Hemostasis at the study suture line must have been maintained until closure of the surgical wound.

Subjects randomized to the FS VH S/D 500 s-apr group were treated once intraoperatively with FS VH S/D 500 s-apr at the study suture line and once intraoperatively with FS VH S/D 500 s-apr at the non-study suture line(s) (if there was bleeding that required treatment). If additional treatment was required to achieve hemostasis, the choice of the additional/alternative treatment was at the discretion of the investigator. Additional application of FS VH S/D 500 s-apr was allowed, however, no fibrin sealant other than FS VH S/D 500 s-apr was to be used. Subjects randomized to the control group were treated once intraoperatively with manual compression using surgical gauze pads at the study suture line and non-study suture line(s). If additional treatment was required to achieve hemostasis, the choice of the additional/alternative treatment was at the discretion of the investigator; however, neither FS VH S/D 500 s-apr nor any other fibrin sealant was to be used.

1.3 MAJOR STATISTICAL ISSUES AND FINDINGS

The studies together appear to show hemostasis efficacy in subjects undergoing vascular surgery. No major statistical issues were identified.

2. INTRODUCTION

Tisseel was first licensed as an adjunct to hemostasis for cardiac and splenic surgery in 1998. In the current submission, the sponsor presents data from a phase 2 and a phase 3 vascular surgery studies to support an indication extension for general adjunct to hemostasis. The phase 2 study 550602 is a proof-of-concept study conducted in the US. It evaluated the efficacy and safety of TISSEEL (FS VH S/D 500 s-apr) for hemostasis in subjects undergoing vascular surgery (ie, ePTFE [expanded polytetrafluoroethylene] graft placement including arterial bypasses and AV-shunts). The confirmatory Phase 3 study 550801 evaluated the vascular surgery indication in the same patient population.

2.1 DATA SOURCES

Data sources are included in the applicant electronic BLA submission. Select the link to view the submission roadmap: ----------(b)(4)----------

3. STATISTICAL EVALUATION

3.1 Protocol 550602 (Phase 2 study)

This study was a prospective, randomized, controlled, subject-blinded, multicenter study designed to evaluate the efficacy and safety of TISSEEL (FS VH S/D 500 s-apr) for hemostasis in subjects receiving peripheral vascular ePTFE conduits, as compared to a

control group treated by manual compression with surgical gauze pads. A maximum of 102 subjects receiving vascular ePTFE grafts were to be enrolled in the study, with approximately 75 fulfilling the entry criteria and be randomized and treated in 3 equal-sized groups. The sample size of 75 was based on the assumptions from the results of a previous pilot study. The proportion of subjects with hemostasis at 4 minutes for both FS VH S/D 500 s-apr groups (60 and 120 seconds polymerization time) was assumed to be 60%; and for manual compression, 25%.

Randomization was stratified by the severity of bleeding to keep the balance between the 3 treatment groups. The enrolled subjects who fulfilled the entry criteria were randomized and treated in 3 equal-sized groups. Two treatment groups (FS-60 and FS-120), which differed in polymerization/setting time (60 seconds versus 120 seconds) prior to opening the cross clamps, were treated with TISSEEL. In both TISSEEL groups, TISSEEL was applied onto the bleeding suture lines, while the treatment of the control group consisted of manual compression. Although the surgeon was free to decide the amount of TISSEEL needed, the cumulative dose was limited to 4-mL TISSEEL per treated suture line.

The primary efficacy endpoint is the proportion of subjects achieving hemostasis at the study suture line of the ePTFE graft at 4 minutes. Hemostasis must be maintained until closure of the surgical wound. Several secondary efficacy endpoints were included. The likelihood ratio chi-square test was carried out. If the overall test showed a statistically significant difference at a 10% two-sided level, then pair-wise comparisons between FS-60, FS-120 and manual compression were performed by the chi-square tests. The significance level was set to 10% two-sided for these pair-wise comparisons.

3.1.1 RESULTS

Data sets analyzed

The ITT population was all subjects who are randomized. Only subjects with major protocol violations (eg, violation of inclusion or exclusion criteria, randomization error) were to be excluded from the PP population. The ITT populations comprised all 73 randomized and treated subjects: 26 with FS-60, 24 with FS-120, and 23 with manual compression. The PP population consisted of the 65 subjects who met the criteria defined for the PP population in the study protocol.

Primary Efficacy Endpoint

Results for the intent-to-treat (ITT) population on the primary efficacy endpoint are summarized in Table 1 of the appendix. The highest proportion of subjects that achieved hemostasis at 4 minutes and maintained it until surgical closure was 62.5% (15/24) for FS-120 subjects, followed by 46.2% (12/26) for FS-60 subjects and 34.8% (8/23) for control subjects. However, these proportions are not significantly different. The overall two-sided p-value from the likelihood ratio chi-square test indicated that there was no

statistically significant difference at the 10% level in the comparison of hemostasis rates between the 3 treatment groups for the ITT population (P=0.1564) and the PP population (P=0.1944).

Reviewer's Comment: The results from this phase 2 study did not demonstrate statistically significant differences between FS-120 or FS-60 and manual compression (the control), at the 10% significance level. However, the differences were deemed encouraging enough in proportion of hemostasis that a phase 3 study was designed and conducted by the sponsor based on the success rates observed from the phase 2 study.

3.2 Protocol 550801 (Phase 3 study)

The purpose of the study was to compare the safety and efficacy of FS VH S/D 500 s-apr (with 120 seconds to allow polymerization, termed FS-120, or simply FS) versus manual compression in prosthetic ePTFE graft placement. This was a prospective, controlled, randomized, multicenter in a total of 140 evaluable subjects (70 subjects per treatment arm) undergoing ePTFE graft placement including arterio-arterial bypasses and AV shunts. The sample size derivation was based on results of the Phase 2 study (study 550602), 60% and 35% of hemostasis for FS VH S/D 500 s-apr and manual compression, respectively. Similar to the phase 2 study, the primary efficacy endpoint is the proportion of subjects achieving hemostasis at the study suture line of the ePTFE graft at 4 minutes. Hemostasis must be maintained until closure of the surgical wound. The statistical approach was also similar to the phase 2 study except a one-sided significance level of 0.025 was used

3.2.1 RESULTS

Analysis of Efficacy

Primary Efficacy Endpoint

A total of 176 subjects were enrolled (i.e., signed informed consent) at 24 study sites and screened for eligibility according to the inclusion/exclusion criteria described in the protocol. The number of subjects randomized and treated at each study site ranged from 0 to 13. Of the 176 subjects enrolled, 140 subjects were randomized and treated, and included in the ITT population; 132 subjects were included in the PP population. A total of 70 subjects were treated with FS, and 70 subjects were treated with manual compression (control). Baseline characteristics (age, weight, height, gender, race, and ethnicity) were examined and they were comparable across all treatment groups.

For the ITT population, results of hemostasis 4 minutes after treatment are summarized in Table 2 of the appendix (page 10 of this memo). The proportion of subjects that achieved hemostasis at the study suture line at 4 minutes and maintained it until surgical closure was 62.9% (44/70 subjects, 95% CI = 51.2% to 73.6%) in the FS-120 group and 31.4% (22/70 subjects; 95% CI = 21.4% to 42.8%) in the control group. The one-sided p-value from the likelihood ratio chi-square test indicated that there was a statistically significant difference at the one-sided 2.5% level in the comparison of hemostasis rates between the two treatment groups (P<0.0001). A sensitivity analysis (worst outcome analysis, i.e., all missing data were to be considered treatment failures) was performed on the ITT population as a secondary analysis to assess the influence of missing data on the primary results. Since there were no missing values for subjects who were included in the ITT population, the results of the sensitivity analysis were the same.

For the PP population, the proportion of subjects who achieved hemostasis at the study suture line at 4 minutes and maintained it until surgical closure was similar to that of the ITT population: 62.1% (41/66 subjects; 95% CI = 50.1% to 73.2%) in the FS group and 31.8% (21/66 subjects; 95% CI = 21.4% to 43.6%) in the control group. The one-sided p-value from the likelihood ratio chi-square test indicated that there was a statistically significant difference at the 2.5% one-sided level in the comparison of hemostasis rates between the two treatment groups (P=0.0002). These results are all supportive of the primary efficacy endpoint results.

> **Reviewer's Comment**: The study results demonstrated a significant difference between the treatment groups in the proportion of patients who achieved hemostasis 4 minutes post suture line closure after surgery.

3.3 Evaluation of Safety

There was no pre-specified statistical analyses plan for safety of this product. In studies 550602 and 550801 in subjects undergoing ePTFE graft placement, no notable difference was observed between the proportions of TISSEEL-treated subjects and control subjects who experienced AEs: 78/120 (65.0%) forTISSEEL subjects and 56/93 (60.2%) for control subjects.) The majority of AEs for both studies were said to be mild in severity and the proportion of mild, moderate, and severe AEs reported was similar between the 2 studies. In each study, 2 AEs were considered to be possibly related to TISSEEL. In study 550602, the only one related AE reported for TISSEEL was 1 non-serious incidence of incision site complication; the causal relationship to TISSEEL was determined to be unlikely but could not be completely ruled out by the investigator. In study 550801, the 1 related AE reported for TISSEEL was an incidence of operative haemorrhage that required additional sutures and reapplication of TISSEEL, as well as Gelfoam and thrombin, to achieve hemostasis. The event was said to be mild in severity and considered by the investigator to be possibly related to TISSEEL. The AEs most frequently reported in both treatment groups are expected in subjects undergoing vascular surgery without the use of fibrin sealant.

It appears, these data show that TISSEEL is safe and well-tolerated by subjects undergoing laparotomy to treat splenic injury, and peripheral vascular surgery; and no safety signals were detected during these clinical studies. Further analysis of safety is deferred to the clinical reviewer, Dr. Lindsey.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

The conduct of the study appears to have followed the protocol and the results from data collected and analyzed during this study appear to show that FS VH S/D 500 s-apr is superior to manual compression for hemostasis in subjects receiving peripheral vascular prosthetic ePTFE grafts, including arterio-arterial bypasses and AV shunting, at 4 minutes post suture line closure.

4.2 Conclusions and Recommendations

Results of a phase 2 and a phase 3 vascular surgery studies are submitted to support an indication for general adjunct to hemostasis. Using a statistical significance level of 0.1 (10%), the phase 2 study was for proof-of-concept. It evaluated the efficacy and safety of TISSEEL (FS VH S/D 500 s-apr) for hemostasis in subjects undergoing vascular surgery (ie, ePTFE graft placement including arterial bypasses and AV-shunts). The Phase 3 study evaluated the vascular surgery indication and demonstrated the hemostasis efficacy in the same patient population.

The results from this phase 2 study (Protocol 550602) did not demonstrate statistically significant differences between FS-120 or FS-60 and manual compression (the control), at the pre-specified 10% significance level. However, the differences were deemed encouraging in proportion of hemostasis that a phase 3 study (Protocol 550801) was designed and conducted by the sponsor based on the success rates observed from the phase 2 study. This phase 3 study results demonstrated a significant difference between the treatment groups in the proportion of patients who achieved hemostasis 4 minutes post suture line closure after surgery. Taken together, these two studies appear to demonstrate efficacy of FS-120 in terms of the proportion of patients who achieved hemostasis 4 minutes post suture line closure after surgery.

DISTRIBUTION LIST

cc:

Original/HFM-380/ Jie He
DCC/HFM-99
HFM- 215 /Chron
HFM-219/Jessica Kim, PhD
HFM-219/Bo Zhen, PhD
HFM-215/Estelle Russek Cohen, PhD

Appendix

Table 1.

Summary of Hemostasis at 4 Minutes After Treatment Application at the Study Suture Line
(Study 550602: Intent-to-Treat Analysis Set)

Treatment Group	Primary Hemostasis Achieved at 4 Minutes	Additional Treatment Required to Achieve Hemostasis	Intraoperative Rebleeding After Primary Hemostasis	Hemostasis at 4 Minutes
	n of N (%)	n of N (%)	n of N (%)	n of N (%)
FS 60	12 of 26 (46.2)	8 of 26 (30.8)	1 of 26 (3.8)	12 of 26 (46.2)
FS 120	15 of 24 (62.5)	6 of 24 (25.0)	0 of 24 (0.0)	15 of 24 (62.5)
Control	8 of 23 (34.8)	12 of 23 (52.2)	1 of 23 (4.3)	8 of 23 (34.8)

Table 2.

Summary of Hemostasis at 4 Minutes After Treatment Application at the Study Suture Line
(Study 550801: Intent-to-Treat Analysis Set)

Treatment Group	Primary Hemostasis Achieved at 4 Minutes	Additional Treatment Required to Achieve Hemostasis	Intraoperative Rebleeding After Primary Hemostasis	Hemostasis at 4 Minutesa
	n of N (%)	n of N (%)	n of N (%)	n of N (%)
FS-120	47 of 70 (67.1%)	13 of 70 (18.6%)	4 of 70 (5.7%)	44 of 70 (62.9%)
Control	22 of 70 (31.4%)	28 of 70 (40.0%)	1 of 70 (1.4%)	22 of 70 (31.4%)