



STATISTICAL REVIEW AND EVALUATION BLA

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Product Name: Evarrest (fibrin pad)

Indication(s): Adjunct to hemostasis for soft tissue bleeding

Applicant: Omrix Biopharmaceuticals

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1. EXECUTIVE SUMMARY

This is an original BLA for the sponsor's Fibrin Pad (FP) product. The FP is a sterile bio-absorbable combination product made from a flexible composite matrix coated with plasma-derived human fibrinogen and thrombin. The intended use of the FP is as an adjunct to hemostasis for soft tissue bleeding during retroperitoneal, intra-abdominal, pelvic, and (non-cardiac) thoracic surgery when control of bleeding by standard surgical methods of hemostasis is ineffective or impractical.

1.1 Conclusions and Recommendations

Although the Phase II study 400-07-002 met its primary efficacy objective, the information presented in this submission does not meet the standard of convincing evidence from at least two adequate and well-controlled trials described in FDA's *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. In favor of the FP, the treatment effect on rate of 4-minute hemostatic success relative to Surgicel in study 400-07-002 was quite large. However, there are serious and inevitable questions of generalizability and replicability raised by relying solely on evidence from a single small Phase II study to support product licensure. Furthermore, it is not clear that an adequate safety database has been established to date for FP in the indicated population, particularly given the concerns related to thrombotic events raised in study 400-07-002.

1.2 Brief Overview of Clinical Studies

The submission includes the results from one Phase II trial (study #400-07-002) to support the efficacy of the FP as an adjunct to hemostasis for soft tissue bleeding during retroperitoneal, intra-abdominal, pelvic, and (non-cardiac) thoracic surgery when control of bleeding by standard surgical methods of hemostasis is ineffective or impractical. In this study, 90 subjects with appropriate target bleeding sites (TBS) were randomized (2:1) to FP or Surgicel. Following the randomization period, an additional 51 subjects were enrolled in the FP arm in a non-randomized fashion. The primary endpoint was 4-minute hemostatic success (defined as achieving hemostasis within 4 minutes without a rebleed requiring treatment in the following 6 minutes). In the FP group, 59/60 subjects met the primary endpoints, while 16/30 control subjects met the primary endpoint. This was a statistically significant difference.

The sponsor also submitted supportive evidence for safety from two small Phase I trials (one of which was in a different indication from that pursued in this BLA) and from an ongoing Phase II trial.

1.3 Major Statistical Issues and Findings

The overall analytic plan was appropriate for the design of this Phase II trial. There are potential problems with the interpretation of p-values calculated by conventional methods for

secondary endpoints highly correlated with the primary endpoint in a triangular test-monitored trial. However, since the treatment effects on all hemostasis-related endpoints were large and the secondary endpoints are not being used to support labeling claims, this concern is not of practical importance.

The sponsor has included a claim in their draft label related to an increased treatment effect for FP in patients with moderate bleeding vs. patients with mild bleeding. This claim is not supported by an appropriate, pre-specified hypothesis test and should not be included in product labeling.

2. INTRODUCTION

2.1 Overview

This is an original BLA for the sponsor's Fibrin Pad (FP) product. The FP is a sterile bio-absorbable combination product made from a flexible composite matrix coated with plasma-derived human fibrinogen and thrombin. The FP is supplied in the form of a white to yellowish sterile implantable dry pad approximately 4 x 4 inches in size, which can be cut to size to accommodate a broad range of surgical procedures.

The intended use of the FP is as an adjunct to hemostasis for soft tissue bleeding during retroperitoneal, intra-abdominal, pelvic, and (non-cardiac) thoracic surgery when control of bleeding by standard surgical methods of hemostasis is ineffective or impractical. The intended route of application is direct application onto bleeding tissue during surgery.

The sponsor has performed four clinical studies of the FP (one of which is currently ongoing):

1. Study 400-07-002, "A Prospective Randomized Controlled Superiority Evaluation of Fibrin Patch (Fibrin Pad) as an Adjunct to Control Soft Tissue Bleeding during Abdominal, Retroperitoneal, Pelvic, and Thoracic Surgery."
2. Study 400-08-002, "A Prospective Randomized Controlled Superiority Evaluation of Fibrin Pad as an Adjunct to Control Severe Soft Tissue Bleeding during Abdominal, Retroperitoneal, Pelvic, and Thoracic Surgery."
3. Study FL-PN-001-IS, "A Prospective, Open-Label, Phase I Study Evaluating the Safety of Fibrin Fleece in Partial Nephrectomy."
4. -----
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2.2 Data Sources

The data sources reviewed include clinical study reports and protocols for the four studies listed above. The sponsor has also submitted electronic datasets in SAS TRANSPORT format for each trial listed above, except for Study 400-08-002, which is an ongoing trial. In response to an FDA information request dated January 31, 2011, the sponsor also submitted

SAS program files for each analysis reported for Study 400-07-002 (received as amendment 3 on 3/17/2011).

Any analyses performed within this review are based on the analysis-ready dataset provided by the sponsor (path: Crt/datasets/400-07-002/fda.xpt,) unless otherwise noted. The sponsor has also provided the SAS program file used to generate this analysis-ready dataset from the raw data files. I verified all efficacy results against the data provided by the sponsor using version 9.1 of SAS. I also performed spot checks of data and programs used to create demographic, baseline and safety tables. I verified the sponsor's triangular test design and monitoring results using version -----(b)(4)----- software package.

3. STATISTICAL EVALUATION

Of the four clinical trials included in the BLA, only one (400-07-002) is intended by the sponsor to support the efficacy of the FP. The other three trials have been included to provide supportive evidence of safety of the FP. (Study 400-08-002 was designed to assess efficacy as well as safety, but that trial is ongoing and efficacy results are not yet available.)

3.1 Evaluation of Efficacy

Study 400-07-002 was a Phase II trial entitled *A Prospective Randomized Controlled Superiority Evaluation of Fibrin Patch (Fibrin Pad) as an Adjunct to Control Soft Tissue Bleeding during Abdominal, Retroperitoneal, Pelvic, and Thoracic Surgery*. The trial began enrollment on March 26, 2008 and the final subject completed study procedures on April 24, 2009.

Study Design and Endpoints

Study 400-07-002 was a randomized controlled study intended to evaluate the superiority of FP to Surgicel when used as an adjunct to hemostasis when conventional methods of control were ineffective or impractical. Subjects ≥ 18 years of age requiring non-emergent, open, abdominal, retroperitoneal, pelvic or thoracic (non-cardiac) surgical procedures who provided written informed consent were evaluated intraoperatively by the surgeon for the presence of an appropriate soft tissue Target Bleeding Site (TBS). Subjects with an appropriate TBS were randomized 2:1 to FP or Surgicel, stratified by bleeding severity (mild vs. moderate bleeding).

The primary efficacy endpoint was the proportion of subjects achieving hemostatic success (i.e. no detectable bleeding) at the TBS at 4 minutes after randomization with no re-bleeding requiring treatment during a subsequent 6-minute observation period.

The secondary endpoints were:

- Proportion of subjects achieving hemostatic success at the TBS at 10 minutes following randomization (Success at 10 minutes was defined as the achievement of

- hemostasis within 10 minutes and no further bleeding requiring treatment during the final 6-minute observation period);
- Incidence of treatment failures (if hemostasis was not achieved within 4 minutes or if bleeding requiring additional intervention occurred during the 6 minute observation period);
 - Incidence of re-treatment at TBS;
 - Incidence of adverse events (AEs) that were potentially related to re-bleeding at the TBS;
 - Incidence of AEs that were potentially related to thrombotic events;
 - Incidence of AEs potentially related to transfusion exposure (Transfusion related lung injury, multiorgan system failure, transfusion reactions, infectious complications potentially related to transfusion).

The safety endpoints were:

- Adverse events
- Complete blood count
- Coagulation parameters

Patient Disposition, Demographic and Baseline Characteristics

A total of 141 subjects were enrolled in study 400-07-002. Ninety subjects were randomized (60 to FP and 30 to Surgicel), and the remaining 51 were treated with FP in the non-randomized portion of the study (see Statistical Methodologies, below). All 141 enrolled subjects received the allocated study treatment. Of the 141 subjects enrolled, 126 (89%) completed the study as planned. The disposition of the remaining 15 subjects was as follows: two subjects withdrew consent prior to study completion, four subjects were lost to follow-up post-operatively, seven subjects died prior to study completion, one subject was unwilling to travel to the center for follow-up and one subject was withdrawn because the clinic failed to notify the study site coordinator of visit rescheduling. Table 4 from the sponsor's clinical study report summarizes this information by treatment group.

Text Table 4 Reasons for Failure to Complete Study as Planned

	FP Randomized N=60	FP Non- Randomized N=51	SURGICEL N=30	Total N=141
Withdrew Consent	1 (1.7%)	1 (2.0%)	0 (0.0%)	2 (1.4%)
Lost to Follow-up	0 (0.0%)	2 (3.9%)	2 (6.7%)	4 (2.8%)
Death	2 (3.3%)	4 (7.8%)	1 (3.3%)	7 (5.0%)
Other	1 (1.7%)	0 (0.0%)	1 (3.3%)	2 (1.4%)

There were 180 documented protocol deviations, the most common of which were visit out of window and failure to perform specified laboratory tests. Four of the deviations were

classified by study personnel as ‘major’; these are summarized in Table 6 of the clinical study report.

Text Table 6 Major Protocol Deviations

Subject #	Treatment	Deviation Category	Details
21-103	FP Randomized	Randomization	Prior to the randomization procedure, envelope 21102 was misplaced, making 21103 the next sequential number to randomize for mild bleeding. The subject was treated as randomized.
22-114	FP Randomized	Study Procedure	PT, APTT and INR not performed prior to the procedure
12-201	FP Randomized	Inclusion/Exclusion Criteria	The TBS did not meet the criteria described in the protocol.*
14-108	FP non-randomized	Study Procedure	FP was not applied according to protocol (i.e. was applied upside-down)

There were three prospectively defined analysis sets: The intent-to-treat (ITT) set consisted of 90 randomized subjects, the per protocol (PP) set consisted of 87 ITT subjects without major protocol deviations, and the safety set consisted of all 141 subjects treated with study product. Tables 8 – 11 from the clinical study report summarize demographic and baseline characteristics for the safety set and ITT set.

Text Table 8 Subject Demography (Safety Set)

Category	Statistic	FP Randomized N = 60	SURGICEL (N = 30)	FP All (N = 111)	Total N = 141
Age (years)	Mean (SD)	59.9 (11.8)	58.5 (14.4)	61.5 (11.4)	60.9 (12.1)
Age (grouped)	18 - <50 years	11 (18.3%)	9 (30.0%)	16 (14.4%)	25 (17.7%)
	50 - <65 years	28 (46.7%)	12 (40.0%)	47 (42.3%)	59 (41.8%)
	65 - <75 years	12 (20.0%)	5 (16.7%)	32 (28.8%)	37 (26.2%)
	≥75 years	9 (15.0%)	4 (13.3%)	16 (14.4%)	20 (14.2%)
Gender	Male	39 (65.0%)	20 (66.7%)	69 (62.2%)	89 (63.1%)
	Female	21 (35.0%)	10 (33.3%)	42 (37.8%)	52 (36.9%)
Race	White	50 (83.3%)	23 (76.7%)	90 (81.1%)	113 (80.1%)
	Black/African American	10 (16.7%)	5 (16.7%)	21 (18.9%)	26 (18.4%)
	Asian	0 (0.0%)	1 (3.3%)	0 (0.0%)	1 (0.7%)
	Hispanic /Latino	0 (0.0%)	1 (3.3%)	0 (0.0%)	1 (0.7%)
BMI (kg/m²)	Mean (SD)	29.3 (6.7)	28.5 (6.5)	28.7 (6.9)	28.7 (6.8)
	Median	28.5	28.0	27.0	27.0
	(range)	18.0 – 50.0	(20.0 - 49.0)	17.0 – 53.0	17.0 – 53.0
	95% CI of mean	27.5; 31.0	26.1; 30.9	27.4; 30.0	27.5; 29.8
BMI (grouped)	Underweight	1 (1.7%)	0 (0.0%)	3 (2.7%)	3 (2.1%)
	Normal	13 (21.7%)	9 (30.0%)	24 (21.6%)	33 (23.4%)
	Overweight	22 (36.7%)	10 (33.3%)	44 (39.6%)	54 (38.3%)
	Obese	19 (31.7%)	10 (33.3%)	32 (28.8%)	42 (29.8%)
	Morbidly obese	5 (8.3%)	1 (3.3%)	8 (7.2%)	9 (6.4%)
History of smoking	Yes	40 (66.7%)	19 (63.3%)	74 (66.7%)	93 (66.0%)
	No	20 (33.3%)	11 (36.7%)	37 (33.3%)	48 (34.0%)

Text Table 9 Primary Operative Procedure (Safety Set)

Procedure	FP Randomized N = 60	SURGICEL (N = 30)	FP All (N = 111)	Total N = 141
Pulmonary Resection	15 (25.0%)	8 (26.7%)	29 (26.1%)	37 (26.2%)
Pancreatic duodenectomy, radical	8 (13.3%)	4 (13.3%)	14 (12.6%)	18 (12.8%)
Nephrectomy, radical	6 (10.0%)	0 (0.0%)	7 (6.3%)	7 (5.0%)
Prostatectomy, radical	2 (3.3%)	2 (6.7%)	5 (4.5%)	7 (5.0%)
Colectomy c/s anal anastomoses	2 (3.3%)	3 (10.0%)	3 (2.7%)	6 (4.3%)
Retroperitoneal tumor resection	2 (3.3%)	0 (0.0%)	5 (4.5%)	5 (3.5%)
Esophageal resection	3 (5.0%)	0 (0.0%)	4 (3.6%)	4 (2.8%)
Abdominoperineal resection	4 (6.7%)	0 (0.0%)	4 (3.6%)	4 (2.8%)
Cystectomy, radical	2 (3.3%)	0 (0.0%)	3 (2.7%)	3 (2.1%)
Gastrectomy	1 (1.7%)	1 (3.3%)	1 (0.9%)	2 (1.4%)
Low anterior resection	0 (0.0%)	1 (3.3%)	1 (0.9%)	2 (1.4%)
Pancreatectomy	1 (1.7%)	0 (0.0%)	2 (1.8%)	2 (1.4%)
Nephrectomy, partial	1 (1.7%)	0 (0.0%)	2 (1.8%)	2 (1.4%)
Nephrectomy, simple	0 (0.0%)	1 (3.3%)	0 (0.0%)	1 (0.7%)
Primary tumor reduction surgery	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.7%)
Prostatectomy, simple	0 (0.0%)	1 (3.3%)	0 (0.0%)	1 (0.7%)
Other*	13 (21.7%)	9 (30%)	30 (27.0%)	39 (27.7%)

Text Table 10 Anatomical Location of TBS (Safety Set)

Anatomical Location	FP Randomized N = 60	SURGICEL (N = 30)	FP All (N = 111)	Total N = 141
Retroperitoneal	22 (36.7%)	11 (36.7%)	49 (44.1%)	60 (42.6%)
Thoracic	22 (36.7%)	10 (33.3%)	40 (36.0%)	50 (35.5%)
Pelvic	12 (20.0%)	7 (23.3%)	16 (14.4%)	23 (16.3%)
Abdominal	4 (6.7%)	2 (6.7%)	6 (5.4%)	8 (5.7%)

Text Table 11 Tissue Type at TBS (Safety Set)

Tissue Type	FP Randomized N = 60	SURGICEL (N = 30)	FP All (N = 111)	Total N = 141
Lymph node bed	20 (33.3%)	8 (26.7%)	36 (32.4%)	44 (31.2%)
Fat	15 (25.0%)	5 (16.7%)	30 (27.0%)	35 (24.8%)
Loose areolar	10 (16.7%)	5 (16.7%)	17 (15.3%)	22 (15.6%)
Muscle	10 (16.7%)	3 (10.0%)	10 (9.0%)	13 (9.2%)
Lymphatic	1 (1.7%)	2 (6.7%)	2 (1.8%)	4 (2.8%)
Other	4 (6.7%)	7 (23.3%)	16 (14.4%)	23 (16.3%)

Reviewer Table 1, below, summarizes the type of procedures performed by treatment group. Of note, the number of procedures of each type are not well-balanced. In particular, there are relatively few retroperitoneal procedures.

Reviewer Table 1. Type of procedure, Safety analysis set

<i>Type of procedure</i>	<i>Surgicel (n=30)</i>	<i>FP Randomized (n=60)</i>	<i>FP Non- Randomized (n=51)</i>	<i>Total (n=141)</i>
Abdominal	13 (43.3%)	22 (36.7%)	22 (43.1%)	57 (40.4%)
Retroperitoneal	1 (3.3%)	10 (16.7%)	6 (11.8%)	17 (12.1%)
Pelvic	6 (20.0%)	7 (11.7%)	5 (9.8%)	18 (12.8%)
Thoracic	10 (33.3%)	21 (35.0%)	18 (35.3%)	49 (34.8%)

Statistical Methodologies

All efficacy analyses described in this section were prespecified in the study protocol. The protocol called for the primary endpoint of 4-minute hemostasis to be monitored for efficacy, inferiority or futility in a group sequential fashion using Whitehead's triangular test procedure for binary endpoints. The parameters of the triangular test boundary were vertical axis intercepts of $Z = \pm 4.49$, an upper boundary slope of 0.33 and a lower boundary slope of 1.00 (adjusted with the Christmas tree correction for discrete monitoring). These boundaries were chosen to give 90% power to detect a difference in 4-minute hemostatic success rate of 75% in the FP arm compared to 50% in the Surgicel arm ($\alpha = 0.05$, two-tailed). The first interim analysis was scheduled to occur after 90 randomized subjects, followed by additional interim analyses after each subsequent 30 randomized subjects. The maximum sample size for the trial was to be 210 subjects. In the event of early termination of the randomized portion of the trial for efficacy, additional subjects were to be enrolled into the FP arm of the study until approximately 100 subjects were treated with FP.

The primary null hypothesis tested was $H_0: P_C = P_F$ against $H_1: P_C \neq P_F$, where P_C is the proportion of subjects with 4-minute hemostatic success in the control group and P_F is the proportion of subjects with hemostatic success in the FP group. The p-value, confidence interval and estimated treatment difference for the primary analysis were calculated using the methods described by Whitehead, 1992 for triangular test-monitored trials. The secondary efficacy endpoints were analyzed using a logistic regression model with treatment and site/institution included in the model.

The primary analysis of all efficacy endpoints was performed using the ITT set, with a supportive analysis performed using the PP set. The sponsor outlined a sensitivity analysis approach to missing data on the primary endpoint in the study protocol. However, no data were missing on the primary endpoint and so these sensitivity analyses were not performed.

The sponsor also provided descriptive summaries of health economics endpoints, including length of stay, days in ICU and transfusion information.

Results and Conclusions

Primary endpoint

The first triangular test monitoring for the primary endpoint of 4-minute hemostasis occurred as planned after 90 subjects had been randomized (60 to FP, 30 to Surgicel). The efficacy boundary was crossed at this interim analysis and so no further subjects were randomized. An additional 51 subjects were subsequently enrolled into the FP arm on a non-randomized basis.

Tables 12 and 13 show the success rates on the primary endpoint for the ITT and PP sets, respectively. In addition to the primary analysis, the sponsor also performed separate analyses for the mild and moderate bleeding strata. Both pooled and within-strata tests were significant at the .05 level, with the FP showing greater hemostatic efficacy at 4 minutes than control, although it does not appear that an appropriate testing procedure was used for calculating stratum-specific p-values in triangular test-monitored trials (it is not clear if such a testing procedure exists). The sponsor has used Fisher's exact test for the within-strata comparisons.

Text Table 12 Primary Endpoint Results (ITT Set)

Bleeding Severity	FP Randomized	SURGICEL	p-value	Treatment Difference
All	59/60 (98.3%)	16/30 (53.3%)	<0.0001	45.0%
Mild	31/31 (100.0%)	12/15 (80.0%)	0.0300	20.0%
Moderate	28/29 (96.6%)	4/15 (26.7%)	<0.0001	69.9%

Text Table 13 Primary Endpoint Results (PP Set)

Bleeding Severity	FP Randomized	SURGICEL	p-value	Treatment Difference
All	57/57 (100.0%)	16/30 (53.3%)	<0.0001	46.7%
Mild	29/29 (100.0%)	12/15 (80.0%)	0.03	20.0%
Moderate	28/28 (100.0%)	4/15 (26.7%)	<0.0001	73.3%

Secondary endpoints

Results for the AE-related secondary efficacy endpoints are summarized below in Section 3.2. With respect to the hemostasis-related secondary endpoints, Table 14 shows the results for the secondary endpoint of 10-minute hemostasis, and Table 15 shows the results for the secondary endpoint of treatment failure. These endpoints are strongly correlated with the primary endpoint (strongly negatively correlated, in the case of treatment failure), and show similar patterns of results. The treatment effect for FP vs. Surgicel was attenuated for the 10-minute hemostasis endpoint relative to the effect for the 4-minute hemostasis endpoint.

Text Table 14 Hemostatic Success at 10 minutes (ITT Set)

Bleeding Severity	FP Randomized	SURGICEL	Treatment Difference
All	59/60 (98.3%)	22/30 (73.3%)	25.0%
Mild	31/31 (100%)	13/15 (86.7%)	13.3%
Moderate	28/29 (96.6%)	9/15 (60%)	36.6%

Text Table 15 Incidence of Treatment Failure (ITT Set)

Bleeding Severity	FP Randomized	SURGICEL	Treatment Difference
All	1/60 (1.7%)	14/30 (46.7%)	45.0%
Mild	0/31 (0.0%)	3/15 (20.0%)	20.0%
Moderate	1/29 (3.4%)	11/15 (73.3%)	69.9%

Twelve of the 30 control subject required re-treatment of the TBS after failing to achieve hemostasis at 4 minutes. In the FP randomized group, one subject required retreatment during the initial efficacy assessment. This subject was classified as having a major protocol deviation related to misidentification of an appropriate TBS, and was included as a treatment failure in the ITT set and excluded from the PP set.

The prespecified logistic regression analyses for the secondary endpoints were not provided in the clinical study report. Results from these analyses were requested by CBER in a Deficiencies letter dated January 31, 2011, and were provided by the sponsor in Amendment 3 to the BLA submission on March 17, 2011. These results are presented in the table labeled Stats Output 16.1.9.2.1. There were nominally statistically significant advantaged for FP

relative to Surgicel on the secondary endpoints of 10-minute hemostasis, treatment failure, TBS retreatment, bleeding-related AE incidence. There was no statistically significant difference in incidence of potential thrombotic-related AEs. The p-values from these analyses should be interpreted with caution, as the secondary endpoints are strongly correlated with the primary endpoint, and no adjustment has been made to the secondary endpoint analyses for the triangular test monitoring as described in Section 5.8 of Whitehead, 1992.

Stats Output 16.1.9.2.1
Secondary effectiveness - Model including treatment and center
ITT analysis set

		Treatment		Log-Odds-Ratio ^ (Fibrin Pad/Surgicel)		
Variable	Category	Fibrin Pad (N=60)	Surgicel (N=30)	Estimate	95% C.I. Limit	p-value
Success at 10 mins(secondary)&	Yes	59(98.3%)	22(73.3%)	2.446	(0.908, 3.983)	0.0003
	No	1(1.7%)	8(26.7%)			
Treatment failure +	Yes	1(1.7%)	14(46.7%)	-2.856	(-4.231, -1.481)	<.0001
	No	59(98.3%)	16(53.3%)			
Any TBS retreatment (incl SoC)	Yes	1(1.7%)	14(46.7%)	-2.856	(-4.231, -1.481)	<.0001
	No	59(98.3%)	16(53.3%)			
Potential bleeding related	Yes	0(0.0%)	3(10.0%)	-2.110	(-4.207, -0.014)	0.0305
	No	60(100.0%)	27(90.0%)			
Potential thrombotic related	Yes	1(1.7%)	2(6.7%)	-1.193	(-3.532, 1.145)	0.0826
	No	59(98.3%)	28(93.3%)			

In addition to the ITT and PP analyses, the sponsor provided a summary of hemostatic efficacy for the safety set, comprised of control subjects and both randomized and non-randomized FP subjects (Table 16). The non-randomized FP subjects showed similar hemostatic success to the randomized FP subjects.

Text Table 16 Summary of Hemostasis (Safety Set)

Parameter	FP All N=111	SURGICEL N=30	Treatment Difference
Hemostasis at 4 min; no rebleeding during 6 min observation period	109/111 (98.2%)	16/30 (53.3%)	44.9%
Hemostasis at 10 min; no rebleeding during final 6 min observation period	110/111 (99.1%)	22/30 (73.3%)	25.8%
No retreatment of the TBS required (including use of SoC)	109/111 (98.2%)	16/30 (53.3%)	44.9%
No re-bleeding at TBS between final observation and wound closure	111/111 (100%)	27/30 (90%)	10%

Health economics data

Tables 17 – 19 summarize the health economics data collected by the sponsor. Note that the p-values reported in Table 18 are based on an unspecified post-hoc analysis and consequently are not interpretable.

Text Table 17 Duration of Surgery and Hospital Stay (ITT and Safety Set)

Parameter	Statistic	FP Randomized N=60	SURGICEL N=30	FP All N=111
Duration of Surgery (min)	Mean \pm SD Range	247.8 \pm 140.4 48–670	253.4 \pm 141.8 51–523	230.9 \pm 131.7 38–670
Time in Operating Room (min)	Mean \pm SD Range	316.7 \pm 146.6 118 - 741	315.8 \pm 156.5 109 - 645	299.7 \pm 137.9 70 - 741
Total Stay in Hospital (nights)	Mean \pm SD Range	8.9 \pm 8.1 2 - 48	8.0 \pm 5.2 2 - 26	8.5 \pm 7.1 1 - 48
Post-Operative Stay in Hospital (nights)	Mean \pm SD Range	7.8 \pm 5.5 2 – 30	7.3 \pm 4.1 2 - 17	7.8 \pm 5.4 1 - 30

Text Table 18 Number of Subjects Transfused (ITT and Safety Set)

	FP Randomized	FP All	SURGICEL	SURGICEL vs. FP Randomized	SURGICEL vs. FP All
Transfusions until Discharge	22/60 36.7%	39/111 35.1%	14/30 46.7%	p=0.36	p=0.25
Transfusions Post Discharge to Day 30	0/59* 0.0%	5/103* 4.9%	4/27* 14.8%	p=0.009	p=0.07
Transfusion at any time during Study	22/60 36.7%	43/111 38.7%	16/30 53.3%	p=0.13	p=0.15

Text Table 19 Ventilator Usage and ICU Stay (ITT and Safety Set)

Parameter	Statistic	FP randomized N=60	FP All N=111	SURGICEL N=30
Subjects Requiring Ventilator	N* n (%)	60 59 (98.3)	111 107 (96.4)	30 29 (96.7)
Total ventilator usage duration (h)	N* Mean ± SD Range	57 12.0 ± 39.5 1.8-296.4	105 15.7 ± 44.5 1.0-296.4	29 32.4 ± 115.7 1.3-606.4
Subjects Requiring Ventilator post-operatively	N* n (%)	60 52 (86.7)	111 90 (81.1)	30 21 (70.0)
Total post-op ventilator usage duration (h)	N* Mean ± SD Range	52 3.7 ± 12.8 0.0-65.9	90 10.7 ± 38.0 0.0-238.4	21 38.1 ± 134.6 0.0-599.6
Subjects Spending Time in ICU	N* n (%)	60 26 (43.3)	111 46 (41.4)	30 16 (53.3)
Duration of ICU stay (days)	N* Mean ± SD Range	26 4.1 ± 5.4 1 - 27	46 4.4 ± 4.9 1 — 27	16 3.2 ± 3.8 0 - 14

3.2 Evaluation of Safety

The results for the secondary endpoints of incidence of AEs due to rebleeding, transfusion or thrombotic events are summarized in Table 26. Note that this summary includes the ITT set and does not include relevant AEs in the non-randomized FP group as prespecified in the protocol (see below for a summary of AEs in the safety set). As noted in Section 3.1, there was a significant advantage for the FP group in incidence of re-bleeding at the TBS, but no statistically significant difference in incidence of thrombotic events.

Text Table 26 AEs Potentially Related to Re-bleeding at TBS, Thrombotic Events or Transfusion Exposure (ITT Set)

No. of subjects experiencing AE Potentially related to:	FP Randomized N=60	SURGICEL (N = 30)
Re-bleeding at TBS	0 (0.0%)	3 (10.0%)
Transfusion*	0 (0.0%)	0 (0.0%)
Thrombotic Event	1 (1.7%)	2 (6.7%)

Table 22 shows the number of subjects with AEs in the safety set of study 400-07-002, and Table 23 shows the most common AEs by type.

Text Table 22 Number of Subjects Experiencing any AE, SAE, Severe Event, Event Requiring Treatment or Related Event (Safety Set)

	FP All (N = 111)	SURGICEL (N = 30)
Total number of AEs	796	250
<i>Number (%) of subjects with at least one in the following categories:</i>		
AE	105 (94.6%)	27 (90.0%)
SAE	40 (36.0%)	15 (50.0%)
Severe AE	27 (24.3%)	9 (30.0%)
AE requiring medical, surgical or other action	104 (93.7%)	25 (83.3%)
Related or possibly related AE	3 (2.7%)	2 (6.7%)

Text Table 23 AEs occurring in ≥ 20% of Subjects in any Treatment Group (Safety Set)

System Organ Class	Preferred Term	Number (%) of Subjects Experiencing Event	
		FP All N = 111	SURGICEL (N = 30)
Blood and Lymphatic System Disorders	Anemia	19 (17.1%)	7 (23.3%)
Gastrointestinal Disorders	Constipation	23 (20.7%)	4 (13.3%)
	Nausea	46 (41.4%)	14 (46.7%)
General Disorders and Administration Site Conditions	Pyrexia	22 (19.8%)	12 (40.0%)
Metabolism and Nutrition Disorders	Hyperglycemia	26 (23.4%)	6 (20.0%)
	Hypocalcemia	13 (11.7%)	8 (26.7%)
	Hypokalemia	29 (26.1%)	8 (26.7%)
	Hypomagnesemia	44 (39.6%)	15 (50%)
	Hypophosphatemia	24 (21.6%)	10 (33.3%)
Respiratory, Thoracic and Mediastinal Disorders	Atelectasis	20 (18.0%)	6 (20.0%)

Thrombotic events are of particular concern with this product due to the potentially thrombogenic mechanism of action. Although there was no significant difference in incidence of thrombotic events between the randomized FP and control groups (1/60 and 2/30 subjects with events, respectively), there were an additional 7 subjects with thrombotic events among the 51 non-randomized FP subjects. Thus, there were a total of 8 of 111 FP

subjects with thrombotic events (7.2%) vs. 2 of 30 control subjects (6.7%). Table 28 summarizes the thrombotic events observed in the study.

Text Table 28 AEs Potentially Related to Thrombotic Events (Safety Set)

Subject #	Treatment Group	Preferred Term	Post-Operative Day of Onset
22-106	SURGICEL	Pulmonary Embolism	Day 19
22-203	SURGICEL	Deep Vein Thrombosis	Day 4
11-101	FP Randomized	Embolism	Day 28
11-202	FP Non-Randomized	Pulmonary Embolism	Day 2
12-209	FP Non-Randomized	Pulmonary Embolism (Suspected)	Day 0*
		Deep Vein Thrombosis	Day 0*
14-109	FP Non-Randomized	Pulmonary Embolism	Day 20
		Deep Vein Thrombosis	Day 20
14-216	FP Non-Randomized	Pulmonary Embolism	Day 2
22-116	FP Non-Randomized	Stroke	Day 1
22-124	FP Non-Randomized	Pulmonary Embolism	Day 15
22-125	FP Non-Randomized	Intestinal Infarction	Day 13

There were seven deaths in the safety set during the study, 6 in the FP group (5.4%) and 1 in the control group (3.3%). Only one death was judged by the investigator to be possibly related to study therapy. These deaths are summarized in Table 30.

Text Table 30 Serious Adverse Events with Fatal Outcome (Safety Set)

Subject #	Treatment	SAE	Potential Causal Relationship to:	
			Study Treatment	Surgical Procedure
14-215	FP	Cardiopulmonary arrest	None	Possibly related
14-218	FP	Retroperitoneal bleed (not TBS)	None	Possibly related
15-203	FP	Sepsis related to perforated jejunum	None	None
21-109	FP	Cardiopulmonary arrest secondary to post-operative ileus	None	Related
21-207	FP	Massive GI bleed (not TBS)	Possibly related	Possibly related
22-116	FP	Stroke	None	Possibly related
		Respiratory failure	None	None
23-201	SURGICEL	Progression of cancer	None	Possibly related

3.3 Gender, Race, Age and Other Special/Subgroup Populations

There were no analyses by gender, race, age or other subgroup populations specified in the protocol, and the sponsor did not present the results of any such analyses. Reviewer Table 2 shows the number and percent of subjects achieving success on the primary endpoint by treatment assignment and by race, age or sex category.

Reviewer Table 2. Number (%) of Subjects Achieving 4-Minute Hemostasis by Treatment and Subgroup

<i>Subgroup</i>	<i>FP Randomized (n=60)</i>	<i>Surgicel (n=30)</i>	<i>FP Non- Randomized (n=51)</i>
Sex			
Female	20/21 (95%)	7/10 (70%)	21/21 (100%)
Male	39/39 (100%)	9/20 (45%)	29/30 (97%)
Age			
18-50 years	11/11 (100%)	6/9 (67%)	5/5 (100%)
51-65 years	26/27 (96%)	7/12 (58%)	19/19 (100%)
65-75 years	12/12 (100%)	2/5 (40%)	19/20 (95%)
≥75 years	9/9 (100%)	1/4 (25%)	7/7 (100%)
Race			
Asian	0/0	0/1 (0%)	0/0
Black or African American	10/10 (100%)	3/5 (60%)	11/11 (100%)
Hispanic or Latino	0/0	0/1 (0%)	0/0
White	49/50 (98%)	13/23 (81%)	39/40 (98%)

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

The sponsor has submitted the results of a single Phase II trial with 90 randomized subjects to support the efficacy of the FP. This study (400-07-002) met its primary efficacy goal of showing a statistically significant advantage for FP relative to Surgicel in rate of 4-minute hemostatic success in the indicated population of subjects with soft tissue bleeding during retroperitoneal, intra-abdominal, pelvic, and (non-cardiac) thoracic surgery when control of bleeding by standard surgical methods is ineffective or impractical. There were also statistically significant advantages for FP relative to Surgicel on the secondary hemostasis-related endpoints. This provides some supportive evidence of efficacy, but these endpoints are very strongly correlated with the primary endpoint and do not contribute substantial

independent information. There was also a significant advantage for FP relative to Surgical on the secondary endpoint of incidence of AEs related to re-bleeding, but not on the secondary endpoints of AEs related to transfusion or thrombotic events.

The overall analytic plan was appropriate for the design of this Phase II trial. There are potential problems with the interpretation of p-values calculated by conventional methods for secondary endpoints highly correlated with the primary endpoint in a triangular test-monitored trial. However, since the treatment effects on all hemostasis-related endpoints were large and the secondary endpoints are not being used to support labeling claims, this concern is not of practical importance.

The treatment effect for FP relative to control was smaller in the subgroup of subjects with mild bleeding (20 percentage points) than in the subgroup of subjects with moderate bleeding (70 percentage points). The sponsor has included the following statement and table in the draft labeling submitted with the BLA:

The treatment difference between Control and EVARREST was shown to be greater in subjects with moderate bleeding at the target bleeding site (TBS) than in subjects with mild bleeding (69.9% versus 20.0%, respectively) (see [Table 3](#)).

Table 3 Proportion (%) of subjects achieving hemostasis at 4 minutes

<u>Bleeding Severity</u>	<u>EVARREST</u>	<u>Control</u>	<u>p-Value</u>	<u>Treatment Difference</u>
All	59/60 (98.3%)	16/30 (53.3%)	< 0.0001	45.0%
Mild	31/31 (100.0%)	12/15 (80.0%)	0.0300	20.0%
Moderate	28/29 (96.6%)	4/15 (26.7%)	< 0.0001	69.9%

These claims are not supported by study 400-07-002: There was no formal significance test for an interaction between bleeding subgroup and treatment performed, and no such test was prespecified in the protocol. The stratum-specific hypothesis tests were also not prespecified in the protocol and were not performed by a procedure appropriate for triangular test-monitored trials.

In the aggregate, the adverse event profile was similar between the two study therapies. One potential point of concern for safety is the cluster of thrombotic events observed in the non-randomized FP group. Further analysis of safety data is deferred to the clinical review team.

4.2 Conclusions and Recommendations

Although the Phase II study 400-07-002 met its primary efficacy objective, the information presented in this submission does not meet the standard of convincing evidence from at least two adequate and well-controlled trials described in FDA's *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. In favor of the FP, the treatment effect on rate of 4-minute hemostatic success relative to Surgicel in study 400-07-002 was quite large, and hemostatic success appeared to be similar for the randomized and non-randomized FP subjects. However, there are serious and inevitable questions of generalizability and replicability raised by relying solely on evidence from a single small Phase II study to support product licensure. Furthermore, it is not clear that an adequate safety database has been established to date for FP in the indicated population, particularly given the concerns related to thrombotic events raised in study 400-07-002.

REFERENCES

Whitehead, J. *The Design and Analysis of Sequential Clinical Trials*, 2nd ed., Chichester: Ellis Horwood Limited, 1992.