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Applicant	ProFibrix BV
Established Name	Human Fibrinogen and Human Thrombin
(Proposed) Trade Name	Raplixa
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	Human plasma-derived thrombin
Indication(s) and Intended Population(s)	Raplixa is indicated as an aid to surgical hemostasis for mild to moderate bleeding from small vessels when control of bleeding by standard surgical techniques is ineffective or impractical. Raplixa may be used in conjunction with an absorbable gelatin.

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## GLOSSARY

AAA	aortic aneurysm
EMA	European Medicines Agency
GCP	Good clinical practice
CHMP	Committee for Medicinal Products for Human Use
FCGS	Fibrocaps plus gelatin sponge
GS	Gelatin sponge
ITT	Intent to Treat
SAE	Serious adverse event
Tstart	Time of Fibrocaps or gelatin sponge application
TBS	Target bleeding site
TEAE	Treatment-emergent adverse event
TTH	Time to hemostasis

### 1. Executive Summary

The applicant submitted a Biological License Application for Fibrocaps (proprietary name: Raplixa) for the indication of a general aid to surgical hemostasis for mild to moderate bleeding from small vessels when control of bleeding by standard surgical techniques is ineffective or impractical. The main difference of the product from other fibrin sealants is the mode of manufacturing (spray-drying). For the pivotal trial, the applicant demonstrated the superiority of Fibrocaps plus gelatin sponge (FCGS), as compared to gelatin sponge (GS) alone, for achieving hemostasis in subjects undergoing spine, liver, vascular or soft tissue surgery alone. Overall surgical site-related AEs occurred at similar rates in the FCGS and GS groups, 15% and 14%, respectively. Incision site pain occurred at the same rate, 13%, in both groups, and the remainder of events (postoperative wound infection, incision site erythema, incision site complication, incision site cellulitis, postoperative wound complication, and incision site infection and incision site pruritus) occurred in less than 1% of subjects in each group. The results from the application appear to support the use of Fibrocaps as a general aid to surgical hemostasis for the four types of surgeries.

### 2. Clinical and Regulatory Background

Fibrocaps is being developed under the general FDA and European Medicines Agency (EMA) guidelines that support marketing of fibrin sealant products manufactured for commercial use:

- CHMP Guideline on the Clinical Investigation of Plasma-derived Fibrin Sealant/Hemostatic Products
- FDA Guidance for Industry, “Efficacy Studies to Support Marketing of Fibrin Sealant Products Manufactured for Commercial Use”, Center for Biologics Evaluation and Research (CBER)
- Good Clinical Practice (GCP) regulations and International Conference on Harmonisation (ICH) guidelines
- ICH E6 (R1) Guideline for good clinical practice
- ICH E9 and E10 Guidelines on statistical methods and choice of control group

- ICH E3 for the content and structure of the clinical reports

In addition, specific input on Fibrocaps development was provided by both the FDA's CBER and the EMA's Committee for Medicinal Products for Human Use (CHMP) at a number of stages in the program (see Table 1 and Table 2).

Table 1: Key FDA Advice on Clinical Development of Fibrocaps

Stage	Regulatory Input <sup>1</sup>	Implementation
Pre-IND	Generate an adequate safety database including 80 to 100 subjects treated with Fibrocaps before proceeding to Phase 3	86 patients were enrolled and treated with Fibrocaps during the Phase 2 trials FC-002 US and FC-002 NL
	Evaluate efficacy and safety in at least three surgical indications for a general adjunct to hemostasis claim in surgery. If the surgical indications are combined into one pivotal trial, each surgical indication should be independently powered for efficacy	The Phase 2 and Phase 3 trials evaluated efficacy and safety in four different surgical indications. The four different indications in the Phase 3 trial (FC-004) were individually-powered for efficacy
EOP2	Evaluate immunogenicity at the beginning and end of the Phase 3 trial. Individuals who develop antibodies to thrombin or those who show clinical suspicion of antibodies to fibrinogen (i.e., excessive bleeding) should also be tested for antibodies to fibrinogen	Anti-thrombin antibody testing was performed for all patients at the beginning and end of the study. In addition, a screening algorithm was developed to identify patients for whom additional anti-fibrinogen antibody testing was to be performed.
	Perform an independent interim safety analysis, including an immunogenicity evaluation, as part of the Phase 3 trial after a minimum of 50 subjects have been exposed to the aseptically-manufactured version of Fibrocaps (CSL). In addition, safety should be reviewed by an independent data monitoring committee (IDMC) at pre-specified timepoints during the Phase 3 trial.	An independent interim safety analysis was performed after 100 subjects enrolled in the trial. In addition, the IDMC reviewed safety data (including immunogenicity) after approximately 50% of the total number of subjects were enrolled in the trial
	Change the primary efficacy endpoint for the Phase 3 trial from "difference in mean TTH over five minutes" to "incidence of hemostasis at five minutes" or a time to event analysis of TTH over the 5 minute assessment period.	Primary endpoint changed to TTH using a time to event analysis. The mean TTH and the incidence of hemostasis within three and five minutes were included as secondary efficacy endpoints

Source: Section 2.5 "Clinical Overview [Fibrocaps, Fibrin sealant]", page 7

Table 2: Key EMA Advice on Clinical Development of Fibrocaps

Stage	Regulatory Input	Implementation
Scientific Advice 2009	Ensure enrollment of a significant proportion of subjects undergoing vascular surgery and subgroup efficacy analyses planned specifically for these subjects	The Phase 3 trial consisted of four different individually-powered surgical indications, including subjects undergoing vascular surgery.
	Include patients who specifically require extraneously applied fibrin sealants due to anticoagulation therapy or underlying coagulopathies	All subjects undergoing vascular surgery in FC-004 were required to be heparinized according to the protocol. The majority of vascular surgery subjects were also on one or more anti-platelet agents. Subjects with prolonged prothrombin (PT) or partial thromboplastin (PTT) times due to drug treatment were eligible for enrollment in all surgical indications. As a matter of practice, many surgeons will not perform non-emergent surgery if patients have a significant underlying coagulopathy that could lead to intraoperative or postoperative bleeding complications.
Scientific Advice 2012	Conduct and analyze 4 individually powered parallel trials monitored by a single DMC	FC-004 included 4 individually powered, independently randomized, clinical settings which were monitored by a single DMC. Of note, this included a vascular setting to support the label claim of "suture support in vascular surgery". These studies were analyzed independently
	Randomization to occurred at time of TBS identification	Incorporated in protocol FC-004
	Missing data should be considered as described in EMA/CPMP/EWP/1776/99 Rev.1 Withdrawal of patients who don't receive treatment is not acceptable (include sensitivity analyses and maybe increase enrollment accordingly)	Advice incorporated
	Add an intent-to-treat (ITT) analysis set	An ITT analysis set was added.
	Explain use of 3 vials and endpoints TTH of 5 minutes instead of 10 minutes	Hemostasis at 10 min was not included in the clinical trial design. The last endpoint evaluated was 5 min. This is because most fibrin sealant products achieve hemostasis before 5 min; waiting for 10 min to evaluate hemostasis was not consistent with surgeons' current clinical practice. Further explanation on usage of the vials is provided in the Integrated Summary of Efficacy
	Add specific vascular surgery endpoints in which leakage due to intravascular blood pressure may cause major blood loss; add additional endpoint transfusion requirement, blood volume loss <sup>a</sup>	Transfusion requirements through Day 29
	Secondary efficacy endpoints should be: 1) TTH at 3 and 10 min, 2) Additional hemostatic measurement during 10 min observation, 3) Reoperation at the TBS at any time, 4) Transfusion requirements (RBC units through day 29), blood loss endpoint in some surgical indications <sup>a</sup>	The following secondary efficacy endpoints were included in the Phase 3 protocol: - Use of alternative hemostatic agents at TBS - Transfusion requirements through Day 29 - Need for re-operation at the TBS due to bleeding complications - Hemostasis at 3 min and 5 min (see discussion above)
	Evaluate health economics and outcomes research endpoints such as transfusion requirements and measurement of post-operative blood loss. These should be included as secondary efficacy endpoints requiring a more formal statistical analysis.	The following Health Economics Outcome Research (HEOR) endpoints were included in the protocol: - Duration of surgical procedure from incision to closure - Total hospital length of stay through Day 29 - Use of blood products (other than RBCs) - Need for re-operation at the TBS for complications other than bleeding

<sup>a</sup> It should be noted that blood loss was not able to be measured in these trials. The majority of bleeding has occurred prior to the identification of the target bleeding site (mild to moderate bleeding). For example, in hepatic resection the majority of bleeding occurs from transection of a major artery or vessel during the resection process. This bleeding is controlled with suture or ligature.

Source: Section 2.5 "Clinical Overview [Fibrocaps, Fibrin sealant]", page 8

## 2.1 Disease or Health-Related Condition(s) Studied

The target indication for Fibrocaps (human plasma-derived fibrinogen and thrombin) is an adjunct to haemostasis in patients undergoing surgical procedures. Fibrocaps is locally applied as a powder to surgical bleeding surfaces where it dissolves in blood or other aqueous fluids on contact, which allows thrombin to cleave fibrinogen into fibrin polymers that spontaneously crosslink to form a stable surface clot.

## 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Control of mild or moderate bleeding may be done by conventional surgical techniques including suture, ligature and cautery. The main difference of Fibrocaps from other fibrin sealants is the mode of manufacturing (spray-drying). ProFibrin uses (b) (4) supplied by (b) (4), both licensed (thrombin is licensed (b) (4) fibrinogen is licensed for (b) (4).

## 2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 3 presents the submission log to FDA relating to IND 14385.

Table 3: Historical View of ProFibrix Submissions to the FDA

Date	Information in the Submission/ Type of Submission	IND Serial #
14-sep-10	Clinical Hold Complete Response	14385_XXX
22-oct-10	Clinical Hold Complete Response II	14385_XXX
30-nov-10	Request for FDA comments on PreClinical Study	14385-001
3-dec-10	Informational IND Amendment (CMC/Non hold items)	14385-002
24-jan-11	1572s for (b) (6)	14385-003
28-feb-11	Type C Meeting Request - CMC	14385-006
14-mar-11	Type C meeting Briefing Package	14385-007
21-mar-11	Informational IND Amendment (CMC GMP2/Clinical FC-001 CSR) and 1572's	14385-008
5-may-11	Information amendment: FC-002 v3.1 and IB v3.1 to address requests in Summary of Internal meeting on April 15, 2011	14385-009
9-jun-11	Request for Type C meeting- CMC	14385-010
8-jul-11	Type C meeting Briefing Package	14385-011
31-aug-11	1572s sent to FDA	14385-012
12-oct-11	Conversion to electronic submissions	14385-012
2-nov-11	Updated 1572s	14385-013
28-nov-11	Type B EOP 2 Meeting Request	14385-014
22-dec-11	Type B Meeting Package	14385-015
23-jan-12	Annual report IND 14385	14385-016
16-mar-12	Information Amendment: Revised clinical protocol FC-004, DMC charter for FC-004	14385-017
1-may-12	Information in response to EOP2 questions	14385-018
11-may-12	Information requested by the FDA during the EOP2 meeting related to the Fibrospray Device, Updated information on specifications, 1572	14385-019
14-may-12	Request for Type C meeting - HF protocol	14385-020
15-jun-12	HF protocol Type C mtg package	14385-021
3-jul-12	Information amendment including QC assay validation, inter-laboratory transfer protocol, stability parameters, updated stability information for PPQ1	14385-022
24-jul-12	Response to request for information - User FMEA, Device Task Analysis	14385-023
2-aug-12	1572s	14385-024
16-aug-12	Revised HF protocol in response to FDA feedback	14385-025



Date	Information in the Submission/ Type of Submission	IND Serial #
29-aug-12	Redline version of revised HF protocol in response to FDA	14385-026
6-sep-12	Redline HF protocol after 2nd round FDA feedback	14385-027
10-oct-12	FC-004 protocol v.3, IB v.4, 1572s and CVs	14385-028
9-nov-12	FC-004 protocol v.4, 1572s and CVs, DMC letter	14385-029
17-dec-12	FC-004 protocol v.4.1, 1572s and CVs	14385-030
31-jan-13	Annual report IND 14385	14385-031
14-feb-13	Type C Mtg Request	14385-032
12-mar-13	FC-002 NL & US CSRs	14385-033
12-mar-13	Response to request for information - Clinical, updated protocol	14385-034
26-mar-13	Type C Mtg Package	14385-035
17-jul-13	Proprietary Name Review	14385-036
18-jul-13	1572 submission	14385-037
12-aug-13	Pre-BLA Type B Meeting Request	14385-038
10-sep-13	Pre-BLA Meeting Package	14385-039
9-dec-13	Pediatric Type C Meeting Request	14385-040
20-dec-13	Annual report IND 14385	14385-041
24-jan-14	Pediatric Type C Meeting Package	14385-042

Source: Section 1.2 “Reviewers Guide [Fibrocaps, Fibrin sealant]”, page 12

### **3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES**

#### **3.1 Submission Quality and Completeness**

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

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

#### **5.1 Review Strategy**

The applicant provided all SAS datasets composing their database for study FC-004. They provided multiple statistical macros that were used to statistically analyze data. My objective was to verify their results and evaluate the correctness of applied methods.



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

- 1.2 Reviewers Guide [Fibrocaps, Fibrin sealant]
- 2.5 Clinical Overview [Fibrocaps, Fibrin sealant]
- 2.7.3 Summary of Clinical Efficacy [Fibrocaps, Fibrin sealant]
- 2.7.4 Summary of Clinical Safety [Fibrocaps, Fibrin sealant]
- 2.7.6 Synopses of Individual Studies [Fibrocaps, Fibrin sealant]
- 5.3.5.1 FC-004-Clinical Study Report [Fibrocaps, Fibrin sealant]
- 5.3.5.1 FC-004-Statistical Analysis Plan

## 5.3 Table of Studies/Clinical Trials

The clinical development program for Raplixa is summarized in Table 4. All studies were randomized, single-blind, controlled, comparative efficacy and safety studies. The pivotal phase 3 study FC-004 is reviewed in this memo.

Table 4. Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3	FC-004	Module 5	Demonstrate superior efficacy profiles of Fibrocaps plus gelatin sponge versus gelatin sponge alone (Time to Hemostasis)	Randomized, single-blind, controlled trial Active (gelatin sponge)	Fibrocaps + (b) (4)  Initial dose of up to 1 vial (1 g) FC plus 1 sponge or 1 sponge alone, with repeat application allowed as needed; Topical	719	Spinal surgery, hepatic resection, vascular surgery and soft tissue dissection surgery.	≤ 5 mins	Complete CSR
Phase 2	FC-002 (US)	Module 5	Characterize the efficacy profiles of Fibrocaps plus gelatin sponge versus gelatin sponge alone (Time to Hemostasis)	Randomized, single-blind, controlled trial Active (gelatin sponge)	Fibrocaps (b) (4) (b) (4)  Initial dose of up to 1 vial (1.5 g) FC plus 1 sponge or 1 sponge alone, with repeat application allowed at 3 min; Topical	70	open surgical procedures: spinal surgery, vascular surgery (including peripheral artery bypass and arteriovenous graft formation for hemodialysis, including revisions), or general surgery (including hepatic resection and soft tissue dissection)	≤ 5 mins	Complete CSR
Phase 2	FC-002 (NL)	Module 5	Characterize the efficacy profiles of Fibrocaps plus gelatin sponge versus gelatin sponge alone (Time to Hemostasis)	Randomized, single-blind, controlled trial Active (gelatin sponge)	Fibrocaps (b) (4) (b) (4)  Initial dose of up to 1 vial (1.5 g) FC plus 1 sponge or 1 sponge alone, with repeat application allowed at 3 min; Topical	56	open hepatic resection	≤ 5 mins	Complete CSR

Source: Section 2.7.6 “Synopses of Individual Studies [Fibrocaps, Fibrin sealant]”, page 2

## **6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS**

### **6.1 Trial #1**

Study FC-004 is entitled “A Phase 3, Randomized, Single-Blind, Controlled Trial of Fibrocaps in Intraoperative Surgical Hemostasis (FINISH-3)”.

#### **6.1.1 Objectives (Primary, Secondary, etc)**

*Primary:*

The primary objective of the study is to demonstrate the superiority of FCGS, as compared to GS alone, for achieving hemostasis in subjects undergoing spine, liver, vascular or soft tissue surgery, when control of mild to moderate bleeding by standard surgical techniques is ineffective and/or impractical

*Secondary:*

Secondary study objectives are to further characterize the efficacy and safety profiles of FCGS, as compared to GS alone, in subjects undergoing spine, liver, vascular or soft tissue surgery, when control of mild to moderate bleeding by standard surgical techniques is ineffective and/or impractical.

#### **6.1.2 Design Overview**

FC-004 is a Phase 3, international, multi-center, randomized, single-blind, controlled trial in subjects undergoing spinal surgery, hepatic resection, vascular surgery and soft tissue dissection surgery. After establishing eligibility during screening and confirming continued eligibility on the day of surgery (Day 1), subjects were randomized in a single-blinded manner, in a 2:1 ratio to treatment with FCGS (active group) or GS alone (control group) when an appropriate target bleeding site (TBS) was identified. Randomization was stratified by four surgery types: spinal surgery, vascular surgery, hepatic resection, soft tissue dissection. Enrollment of 168 total subjects in each surgery type was anticipated. Subjects who were randomized but not treated with study drug were withdrawn from the study. Reasons for not receiving study drug include but are not limited to lack of an appropriate time to hemostasis (TTH) evaluation site, severe bleeding or a change in surgical procedure after the subject was randomized. Safety evaluations were conducted at screening, during and after surgery on Day 1, and on Days 2 and 29. The total duration on study was 29 days.

#### **6.1.3 Population**

The trial enrolled subjects undergoing one of the surgical procedures defined in Table 5 below and who had mild to moderate bleeding requiring the use of a topical hemostat.

Table 5. Surgical Indications and Procedures

Surgery Type	Phase 3 <sup>a</sup>
Spinal Surgery	Cervical, thoracic, or lumbar discectomy, corpectomy, laminectomy, lateral or interbody fusion.
Hepatic Resection	Hepatic wedge resection or anatomic resection of 1 to 5 contiguous hepatic segments, which may have been combined with surgical procedures involving the pancreas, gall bladder, bile duct or intestines. Subjects undergoing living-related liver donation were also eligible.
Vascular Surgery	Arterial bypass surgery: PTFE or Dacron including patching and revision procedures, and abdominal aorta aneurysm (AAA) <sup>c</sup> repair. Arteriovenous graft formation for hemodialysis access; Artificial graft (i.e., PTFE or Dacron) for hemodialysis access, including revision procedures <sup>b</sup> Carotid endarterectomy requiring a Dacron patch, where the suture line of the patch was used for TTH assessment.
Soft Tissue/General Surgery	Primary operative procedures included but were not limited to: abdominoplasty, lower anterior resections, abdominal perineal resections, distal pancreatectomy, esophagectomy, donor skin graft site in limited burn patients, and mastectomy <sup>d</sup>

<sup>a</sup> Based on eligibility criteria described in the protocol

<sup>b</sup> Anastomotic sites only at the arterial end of the graft were to be available for TTH measurement.

<sup>c</sup> Anastomotic sites at the proximal end of the graft, the distal end of the graft (AAA repair ONLY) or on the suture line of the patch were to be available for TTH

<sup>d</sup> TBS could not involve parenchymal, vascular (anastomotic or vascular repair sites), gastrointestinal, or genitourinary soft tissue

Source: Section 2.7.3 “Summary of Clinical Efficacy [Fibrocaps, Fibrin sealant]”, page 22

In addition, subjects had to meet the following inclusion criteria (pre-surgery):

1. Sign an institutional review board/independent ethics committee approved informed consent document
2.  $\geq 18$  years at time of consent

3. If female and of child-bearing potential, have negative pregnancy test during screening and is not breast-feeding.

#### **6.1.4 Study Treatments or Agents Mandated by the Protocol**

Fibrocaps is a ready-to-use fibrin sealant powder consisting of a blend of spray-dried human plasma-derived fibrinogen and human plasma-derived thrombin in a formulation containing trehalose and calcium chloride. One vial contains 1 gram of Fibrocaps that can cover a maximum surface area of approximately 100 cm<sup>2</sup> when applied with the Fibrospray device. This surface area should be adequate for the majority of surgical cases in this study. A single vial is allowed for the initial treatment of the TBS.

Gelatin sponge alone was chosen as an appropriate comparator for these trials in agreement with regulatory guidance obtained from both the FDA and the EMA. The gelatin sponges used were (b) (4) (absorbable gelatin sponge, (b) (4) (absorbable hemostatic gelatin sponge), which are commonly used hemostatic devices approved for use in the US (and the EU).

#### **6.1.6 Sites and Centers**

This trial was conducted at 28 sites in the United States and 29 sites in the European Union (EU) (United Kingdom, Belgium, and the Netherlands).

#### **6.1.8 Endpoints and Criteria for Study Success**

##### **Primary**

- Time to hemostasis within the 5-minute TTH assessment period. TTH assessments were made every 30 seconds until bleeding had stopped or the 5-minute time point had been reached.

##### **Secondary**

- Restricted mean TTH
- Proportion of subjects achieving hemostasis within 3 minutes
- Proportion of subjects achieving hemostasis within 5 minutes
- Use of alternative hemostatic agents at the TBS
- Transfusion requirements (red blood cell [RBC] usage through Day 29)
- Re-operation at the TBS for bleeding

##### **Safety**

- Incidence, severity, and relationship of treatment-emergent AEs
- Clinical laboratory abnormalities
- Proportion of subjects who developed anti-thrombin and (if appropriate, anti-fibrinogen antibodies)
- Incidence, nature, and severity of adverse events related to the Fibrospray delivery device

### 6.1.9 Statistical Considerations & Statistical Analysis Plan

SAS 9.1.3 was used for all analyses. The primary analysis compared TTH between treatment groups for each of the four surgery types. The difference in the TTH survival curves comparing FCGS to GS alone in each surgery type was tested using the log-rank statistic while ensuring an overall 2-sided significance level of 0.05 for each surgical setting. The Cox proportional hazards model was used to estimate the relative difference in the hazard for hemostasis comparing treatment arms. Estimates of the distribution of TTH were computed using the Kaplan-Meier method. Median TTH and the associated 2-sided 95% confidence interval were calculated using the Kaplan-Meier method.

Analyses of the secondary efficacy endpoints used a 2-sided significance level of 0.05. The difference in restricted mean TTH over 5 minutes was computed using Irwin's estimator (the difference in the area under the Kaplan-Meier estimator of TTH survival over 5 minutes [Irwin, J. O. (1949), "The Standard Error of an Estimate of Expectation of Life, with Special Reference to Expectation of Tumourless Life in Experiments with Mice," *The Journal of Hygiene*, 47 (2), 188]) and testing was based upon the normal approximation to the sampling distribution of Irwin's estimator. The difference in the probability of TTH over 3 and 5 minutes was tested using a 2-sample binomial test of proportions. The normal approximation was used along with a continuity correction for testing. Wald-based 95% confidence intervals for the difference in probability of TTH were computed using the normal approximation.

Secondary efficacy endpoints were ranked in order of analysis (restricted mean TTH, proportion achieving hemostasis within 3 minutes, proportion achieving hemostasis within 5 minutes) and were tested using a hierarchical, step-down procedure for pair-wise comparisons; i.e., testing began with the first secondary endpoint and proceeded in accordance with the order of analysis until the comparison between treatment groups for an endpoint was not statistically significant at the 2-sided, 0.05 level. At this point, no further comparisons were made.

Primary efficacy analyses were based on the efficacy population, defined as all subjects who were randomized, received study treatment, and had a TTH assessment recorded regardless of whether the measurement was censored; subjects were analyzed as randomized. The missing TTH values were not imputed; subjects with a missing TTH (i.e., no assessments of hemostasis at the Target Bleeding Site during the 5 minute assessment period) did not contribute to the primary analysis. All intermittently censored values were considered treatment failures for the purpose of the primary analysis. In the case of treatment failures, the maximum observable TTH of 5 minutes with censoring applied were imputed for TTH values censored within the 5 minute assessment period. An intermittently censored observation refers to an observation that is right censored between 0 and 5 minutes. More specifically, it refers to the case where some assessment between 0 and 5 minutes is missing and all subsequent measurements are missing as well.

The intent-to-treat (ITT) population was defined as all subjects randomized; they were analyzed as randomized regardless of treatment actually received. Sensitivity analyses

used the efficacy and ITT population. The safety population was defined as all subjects who were randomized and received study treatment; they were analyzed as treated.

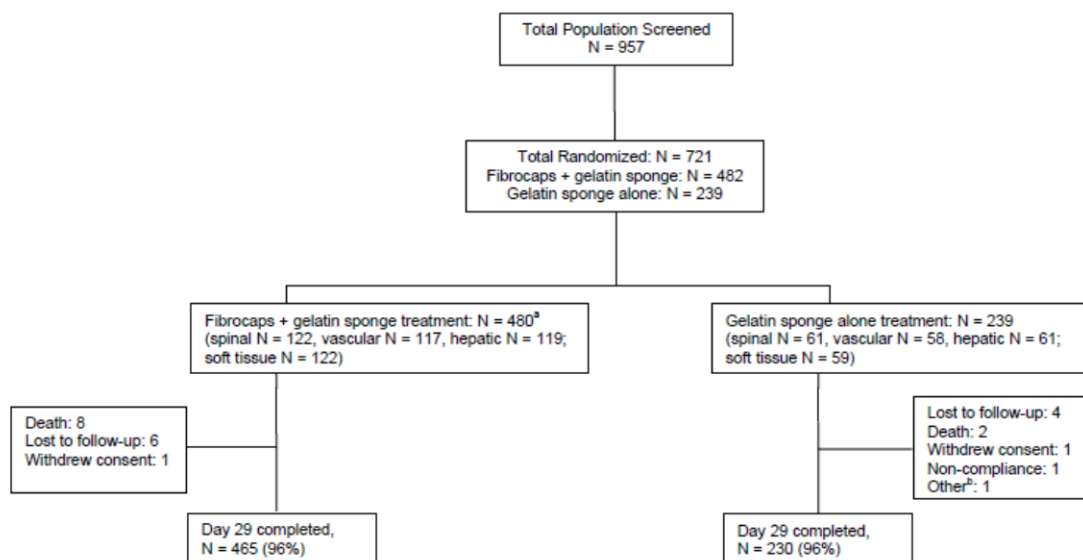
Three sensitivity analyses were conducted on the primary endpoint.

- Sensitivity Analysis 1: Missing TTH values prior to achieving hemostasis were considered treatment failures (i.e., failure at 5 minutes with censoring). The same Kaplan-Meier analyses performed for the primary endpoint was performed for the sensitivity analysis.
- Sensitivity Analysis 2: A “worst case” analysis of TTH was performed. Subjects with any missing hemostasis assessments in the FCGS group prior to achieving hemostasis were assigned to failure at 5 minutes with censoring. Subjects in the GS alone group had a TTH time imputed that is the first missing assessment time.
- Sensitivity Analysis 3: Subjects in the ITT population with no hemostasis assessment data at all were assigned to failure at 5 minutes with censoring.

#### 6.1.10 Study Population and Disposition

A total of 957 potential subjects were screened for this study; of these, 721 subjects (75%) were enrolled and randomized at 28 sites in the US and 29 sites in the EU (Figure 1). The majority of the 236 subjects who failed screening did so because they did not meet one of the eligibility criteria.

Figure 1: Disposition of Subjects



a Two subjects (one undergoing vascular surgery, one undergoing hepatic resection) were discontinued for “other” reasons prior to receiving study treatment.

b Subject did not return for final follow-up visit (Visit 4).

Source: Section 5.3.5.1 ”FC-004-Clinical Study Report [Fibrocaps, Fibrin sealant]”, page 39

### 6.1.10.1 Populations Enrolled/Analyzed

Of the 721 randomized subjects in the ITT population, 482 (67%) were randomized to the FCGS group and 239 (33%) were randomized to the GS only group. Two subjects randomized to the FCGS group were discontinued from the trial before receiving treatment (one because of lack of an appropriate TBS and the other for receiving blood product after randomization, which was a protocol violation). Therefore, the efficacy population had 719 subjects. The safety population was identical to the efficacy population and consisted of 719 subjects.

#### 6.1.10.1.1 Demographics

Demographics for all 721 subjects enrolled and randomized in this trial are summarized in Table 6. The overall study population was generally balanced with regard to sex (female = 46%) and the majority were white (88%). Median age at enrollment was 59.0 years (range, 19–91 years). The majority of subjects were < 65 years (461/721; 64%), 260/721 subjects (36%) were ≥ 65 years, and 79/721 (11%) were ≥ 75 years. The two treatment groups did not differ significantly in the distribution of age, sex or race.

Table 6: Demographics of Study Subjects

	Fibrocaps plus Gelatin Sponge (N=482)	Gelatin Sponge Alone (N=239)	All Patients (N=721)
Sex [n (%)]			
Male	268 ( 56)	124 ( 52)	392 ( 54)
Female	214 ( 44)	115 ( 48)	329 ( 46)
Childbearing Potential	63 ( 13)	34 ( 14)	97 ( 13)
Post-menopausal	85 ( 18)	49 ( 21)	134 ( 19)
Surgically Sterilized	66 ( 14)	32 ( 13)	98 ( 14)
Age at Consent (years) <sup>1</sup>			
n	482	239	721
Mean (SD)	57.4 (14.44)	58.1 (14.12)	57.6 (14.33)
Median	59.0	59.0	59.0
Q1, Q3	48.0, 68.0	49.0, 69.0	48.0, 69.0
Min, Max	19, 88	22, 91	19, 91
Age Category [n (%)]			
<65	311 ( 65)	150 ( 63)	461 ( 64)
≥65	171 ( 35)	89 ( 37)	260 ( 36)
Race [n (%)]			
White	422 ( 88)	210 ( 88)	632 ( 88)
Black or African American	42 ( 9)	20 ( 8)	62 ( 9)
Asian	8 ( 2)	3 ( 1)	11 ( 2)
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaskan Native	1 ( <1)	1 ( <1)	2 ( <1)
Other	7 ( 1)	4 ( 2)	11 ( 2)
Not Reported	2 ( <1)	1 ( <1)	3 ( <1)
Ethnic Origin [n (%)]			
Hispanic or Latino	40 ( 8)	18 ( 8)	58 ( 8)
Non-Hispanic or Latino	397 ( 82)	202 ( 85)	599 ( 83)
Not Reported	45 ( 9)	19 ( 8)	64 ( 9)
Surgery Type [n (%)]			
Spinal Surgery	122 ( 25)	61 ( 26)	183 ( 25)
Vascular Surgery	118 ( 24)	58 ( 24)	176 ( 24)
Arterial bypass surgery	92 ( 19)	51 ( 21)	143 ( 20)
Arteriovenous graft formation for hemodialysis access	13 ( 3)	3 ( 1)	16 ( 2)
Carotid endarterectomy	11 ( 2)	4 ( 2)	15 ( 2)
Hepatic Resection	120 ( 25)	61 ( 26)	181 ( 25)
Soft Tissue Dissection	122 ( 25)	59 ( 25)	181 ( 25)

<sup>1</sup> Age is calculated as the number of years between the date of birth and the date of informed consent, adjusted for whether the birthday has passed as of the date of informed consent.

Source: Section 5.3.5.1 “Study FC-004-Section 14 Tables”, page 16.

The demographics for each of the four surgery types are given in Tables 7-10. Younger subjects were in the FCGS group than in the GS alone group for vascular surgery (Table 8; 45% vs. 34%), and more men in the FCGS group had soft tissue dissection (Table 10;



33% vs. 24%). Otherwise, the two treatment groups were comparable in the distribution of age, sex and race for the four surgery types.

Table 7: Demographics (Randomized Population; Spinal Surgery)

	Fibrocaps plus Gelatin Sponge (N=122)	Gelatin Sponge Alone (N=61)	All Patients (N=183)
Sex [n (%)]			
Male	69 ( 57)	33 ( 54)	102 ( 56)
Female	53 ( 43)	28 ( 46)	81 ( 44)
Childbearing Potential	8 ( 7)	7 ( 11)	15 ( 8)
Post-menopausal	26 ( 21)	14 ( 23)	40 ( 22)
Surgically Sterilized	19 ( 16)	7 ( 11)	26 ( 14)
Age at Consent (years) <sup>1</sup>			
n	122	61	183
Mean (SD)	55.4 (13.75)	54.1 (13.79)	55.0 (13.74)
Median	57.0	55.0	56.0
Q1, Q3	45.0, 65.0	43.0, 63.0	44.0, 65.0
Min, Max	24, 86	23, 80	23, 86
Age Category [n (%)]			
<65	89 ( 73)	46 ( 75)	135 ( 74)
>=65	33 ( 27)	15 ( 25)	48 ( 26)
Race [n (%)]			
White	110 ( 90)	59 ( 97)	169 ( 92)
Black or African American	6 ( 5)	1 ( 2)	7 ( 4)
Asian	2 ( 2)	1 ( 2)	3 ( 2)
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaskan Native	1 ( <1)	0	1 ( <1)
Other	3 ( 2)	0	3 ( 2)
Not Reported	0	0	0
Ethnic Origin [n (%)]			
Hispanic or Latino	11 ( 9)	3 ( 5)	14 ( 8)
Non-Hispanic or Latino	109 ( 89)	58 ( 95)	167 ( 91)
Not Reported	2 ( 2)	0	2 ( 1)

Source: Section 5.3.5.1 "Study FC-004-Section 14 Tables]", page 18.

Table 8: Demographics (Randomized Population; Vascular Surgery)

	Fibrocaps plus Gelatin Sponge (N=118)	Gelatin Sponge Alone (N=58)	All Patients (N=176)
Sex [n (%)]			
Male	83 ( 70)	38 ( 66)	121 ( 69)
Female	35 ( 30)	20 ( 34)	55 ( 31)
Childbearing Potential	2 ( 2)	1 ( 2)	3 ( 2)
Post-menopausal	20 ( 17)	15 ( 26)	35 ( 20)
Surgically Sterilized	13 ( 11)	4 ( 7)	17 ( 10)
Age at Consent (years) <sup>1</sup>			
n	118	58	176
Mean (SD)	65.1 (10.50)	66.7 (9.88)	65.6 (10.30)
Median	65.0	68.0	66.0
Q1, Q3	58.0, 72.0	60.0, 73.0	59.0, 72.5
Min, Max	36, 88	39, 86	36, 88
Age Category [n (%)]			
<65	53 ( 45)	20 ( 34)	73 ( 41)
>=65	65 ( 55)	38 ( 66)	103 ( 59)
Race [n (%)]			
White	105 ( 89)	52 ( 90)	157 ( 89)
Black or African American	8 ( 7)	3 ( 5)	11 ( 6)
Asian	1 ( <1)	1 ( 2)	2 ( 1)
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaskan Native	0	0	0
Other	2 ( 2)	2 ( 3)	4 ( 2)
Not Reported	2 ( 2)	0	2 ( 1)
Ethnic Origin [n (%)]			
Hispanic or Latino	1 ( <1)	2 ( 3)	3 ( 2)
Non-Hispanic or Latino	89 ( 75)	48 ( 83)	137 ( 78)
Not Reported	28 ( 24)	8 ( 14)	36 ( 20)

Source: Section 5.3.5.1 "Study FC-004-Section 14 Tables]", page 20

Table 9: Demographics (Randomized Population; Hepatic Resection)

	Fibrocaps plus Gelatin Sponge (N=120)	Gelatin Sponge Alone (N=61)	All Patients (N=181)
Sex [n (%)]			
Male	76 ( 63)	39 ( 64)	115 ( 64)
Female	44 ( 37)	22 ( 36)	66 ( 36)
Childbearing Potential	11 ( 9)	6 ( 10)	17 ( 9)
Post-menopausal	25 ( 21)	12 ( 20)	37 ( 20)
Surgically Sterilized	8 ( 7)	4 ( 7)	12 ( 7)
Age at Consent (years) <sup>1</sup>			
n	120	61	181
Mean (SD)	60.5 (13.83)	61.5 (12.70)	60.9 (13.44)
Median	63.0	63.0	63.0
Q1, Q3	54.0, 70.5	54.0, 70.0	54.0, 70.0
Min, Max	21, 82	24, 91	21, 91
Age Category [n (%)]			
<65	65 ( 54)	33 ( 54)	98 ( 54)
>=65	55 ( 46)	28 ( 46)	83 ( 46)
Race [n (%)]			
White	117 ( 98)	55 ( 90)	172 ( 95)
Black or African American	1 ( <1)	3 ( 5)	4 ( 2)
Asian	1 ( <1)	1 ( 2)	2 ( 1)
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaskan Native	0	0	0
Other	1 ( <1)	1 ( 2)	2 ( 1)
Not Reported	0	1 ( 2)	1 ( <1)
Ethnic Origin [n (%)]			
Hispanic or Latino	4 ( 3)	4 ( 7)	8 ( 4)
Non-Hispanic or Latino	111 ( 93)	52 ( 85)	163 ( 90)
Not Reported	5 ( 4)	5 ( 8)	10 ( 6)

Source: Section 5.3.5.1 “Study FC-004-Section 14 Tables”, page 22.

Table 10: Demographics (Randomized Population; Soft Tissue Dissection)

	Fibrocaps plus Gelatin Sponge (N=122)	Gelatin Sponge Alone (N=59)	All Patients (N=181)
Sex [n (%)]			
Male	40 ( 33)	14 ( 24)	54 ( 30)
Female	82 ( 67)	45 ( 76)	127 ( 70)
Childbearing Potential	42 ( 34)	20 ( 34)	62 ( 34)
Post-menopausal	14 ( 11)	8 ( 14)	22 ( 12)
Surgically Sterilized	26 ( 21)	17 ( 29)	43 ( 24)
Age at Consent (years) <sup>1</sup>			
n	122	59	181
Mean (SD)	49.0 (14.21)	50.3 (13.88)	49.4 (14.08)
Median	48.5	49.0	49.0
Q1, Q3	38.0, 59.0	43.0, 59.0	39.0, 59.0
Min, Max	19, 79	22, 83	19, 83
Age Category [n (%)]			
<65	104 ( 85)	51 ( 86)	155 ( 86)
>=65	18 ( 15)	8 ( 14)	26 ( 14)
Race [n (%)]			
White	90 ( 74)	44 ( 75)	134 ( 74)
Black or African American	27 ( 22)	13 ( 22)	40 ( 22)
Asian	4 ( 3)	0	4 ( 2)
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaskan Native	0	1 ( 2)	1 ( <1)
Other	1 ( <1)	1 ( 2)	2 ( 1)
Not Reported	0	0	0
Ethnic Origin [n (%)]			
Hispanic or Latino	24 ( 20)	9 ( 15)	33 ( 18)
Non-Hispanic or Latino	88 ( 72)	44 ( 75)	132 ( 73)
Not Reported	10 ( 8)	6 ( 10)	16 ( 9)

Source: Section 5.3.5.1 “Study FC-004-Section 14 Tables”, page 24.

#### 6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

#### 6.1.10.1.3 Subject Disposition

The majority of subjects (695/719; 96%) completed the Day 29 safety assessments. Of the 24 subjects who prematurely discontinued from the trial after receiving treatment, 15

were in the FCGS group and nine were in the GS alone group. Reasons for premature discontinuation were death (10 subjects: eight FCGS, two GS alone), lost to follow-up (10 subjects: six FCGS, four GS alone), withdrawal of consent (two subjects: one FCGS, one GS alone), “other” (one subject: GS alone; subject did not return for their final follow-up visit), and non-compliance (one subject; GS alone).

Subject disposition by surgery type is given in Tables 11-14

Table 11: Subject Disposition (Spinal Surgery)

	Fibrocaps plus Gelatin Sponge	Gelatin Sponge Alone	All Patients
Surgery Type: Spinal Surgery			
Patients Signed ICF [n ]			206
Screen Failures [n ]			23
Patients Randomized [n (%)] <sup>1</sup>	122	61	183 ( 89)
Efficacy Population [n (%)] <sup>2</sup>	122 (100)	61 (100)	183 (100)
Safety Population [n (%)] <sup>3</sup>	122 (100)	61 (100)	183 (100)
Did Patient Complete Study? [n (%)]			
Yes	121 (>99)	60 ( 98)	181 ( 99)
No	1 ( <1)	1 ( 2)	2 ( 1)
Reason for Discontinuation [n (%)]			
Death	1 ( <1)	0	1 ( <1)
Lost to Follow-up	0	1 ( 2)	1 ( <1)
Adverse Event	0	0	0
Non-compliance	0	0	0
Other	0	0	0
Study Terminated by Sponsor	0	0	0
Withdrawal by Subject	0	0	0
Total Days on Randomized Study <sup>4</sup>			
n	122	61	183
Mean (SD)	35.0 (14.30)	30.9 (9.73)	33.6 (13.07)
Median	31.0	30.0	31.0
Q1, Q3	29.0, 33.0	28.0, 32.0	28.0, 33.0
Min, Max	6, 105	4, 96	4, 105

1 Percentages are based on the number of patients who signed the informed consent form (ICF). Number of patients randomized is the denominator for percentages for the rest of the table.

4 Total days on study are defined as the number of days from the date of randomization to the date of completion or discontinuation as provided on the study completion CRF page.

Source: Section 5.3.5.1 “Study FC-004-Section 14 Tables”, page 2.

Table 12: Subject Disposition (Vascular Surgery)

	Fibrocaps plus Gelatin Sponge	Gelatin Sponge Alone	All Patients
Surgery Type: Vascular Surgery			
Patients Signed ICF [n ]			230
Screen Failures [n ]			54
Patients Randomized [n (%)] <sup>1</sup>	118	58	176 ( 77)
Efficacy Population [n (%)] <sup>2</sup>	117 (>99)	58 (100)	175 (>99)
Safety Population [n (%)] <sup>3</sup>	117 (>99)	58 (100)	175 (>99)
Did Patient Complete Study? [n (%)]			
Yes	107 ( 91)	56 ( 97)	163 ( 93)
No	11 ( 9)	2 ( 3)	13 ( 7)
Reason for Discontinuation [n (%)]			
Death	5 ( 4)	1 ( 2)	6 ( 3)
Lost to Follow-up	4 ( 3)	0	4 ( 2)
Non-compliance	0	1 ( 2)	1 ( <1)
Other	1 ( <1)	0	1 ( <1)
Withdrawal by Subject	1 ( <1)	0	1 ( <1)
Adverse Event	0	0	0
Study Terminated by Sponsor	0	0	0
Total Days on Randomized Study <sup>4</sup>			
n	118	58	176
Mean (SD)	31.2 (15.27)	32.5 (10.75)	31.6 (13.93)
Median	29.0	30.0	29.0
Q1, Q3	27.0, 33.0	28.0, 35.0	27.0, 33.0
Min, Max	1, 112	14, 92	1, 112

1 Percentages are based on the number of patients who signed the informed consent form (ICF). Number of patients randomized is the denominator for percentages for the rest of the table.

4 Total days on study are defined as the number of days from the date of randomization to the date of completion or discontinuation as provided on the study completion CRF page.

Source: Section 5.3.5.1 “Study FC-004-Section 14 Tables”, page 3.

**Table 13: Subject Disposition (Hepatic Resection)**

	Fibrocaps plus Gelatin Sponge	Gelatin Sponge Alone	All Patients
Surgery Type: Hepatic Resection			
Patients Signed ICF [n ]			245
Screen Failures [n ]			64
Patients Randomized [n (%)] <sup>1</sup>	120	61	181 ( 74)
Efficacy Population [n (%)] <sup>2</sup>	119 (>99)	61 (100)	180 (>99)
Safety Population [n (%)] <sup>3</sup>	119 (>99)	61 (100)	180 (>99)
Did Patient Complete Study? [n (%)]			
Yes	116 ( 97)	59 ( 97)	175 ( 97)
No	4 ( 3)	2 ( 3)	6 ( 3)
Reason for Discontinuation [n (%)]			
Lost to Follow-up	2 ( 2)	2 ( 3)	4 ( 2)
Death	1 ( <1)	0	1 ( <1)
Other	1 ( <1)	0	1 ( <1)
Adverse Event	0	0	0
Non-compliance	0	0	0
Study Terminated by Sponsor	0	0	0
Withdrawal by Subject	0	0	0
Total Days on Randomized Study <sup>4</sup>			
n	120	61	181
Mean (SD)	31.0 (7.49)	29.4 (5.11)	30.5 (6.81)
Median	30.0	30.0	30.0
Q1, Q3	28.0, 33.0	27.0, 32.0	27.0, 33.0
Min, Max	1, 64	13, 46	1, 64

1 Percentages are based on the number of patients who signed the informed consent form (ICF). Number of patients randomized is the denominator for percentages for the rest of the table.

4 Total days on study are defined as the number of days from the date of randomization to the date of completion or discontinuation as provided on the study completion CRF page.

Source: Section 5.3.5.1 “Study FC-004-Section 14 Tables”, page 4.

**Table 14: Subject Disposition (Soft Tissue Dissection)**

	Fibrocaps plus Gelatin Sponge	Gelatin Sponge Alone	All Patients
Surgery Type: Soft Tissue Dissection			
Patients Signed ICF [n ]			276
Screen Failures [n ]			95
Patients Randomized [n (%)] <sup>1</sup>	122	59	181 ( 66)
Efficacy Population [n (%)] <sup>2</sup>	122 (100)	59 (100)	181 (100)
Safety Population [n (%)] <sup>3</sup>	122 (100)	59 (100)	181 (100)
Did Patient Complete Study? [n (%)]			
Yes	121 (>99)	55 ( 93)	176 ( 97)
No	1 ( <1)	4 ( 7)	5 ( 3)
Reason for Discontinuation [n (%)]			
Death	1 ( <1)	1 ( 2)	2 ( 1)
Lost to Follow-up	0	1 ( 2)	1 ( <1)
Other	0	1 ( 2)	1 ( <1)
Withdrawal by Subject	0	1 ( 2)	1 ( <1)
Adverse Event	0	0	0
Non-compliance	0	0	0
Study Terminated by Sponsor	0	0	0
Total Days on Randomized Study <sup>4</sup>			
n	122	59	181
Mean (SD)	30.2 (6.04)	30.3 (9.40)	30.2 (7.28)
Median	29.0	29.0	29.0
Q1, Q3	27.0, 32.0	27.0, 33.0	27.0, 32.0
Min, Max	19, 74	3, 66	3, 74

1 Percentages are based on the number of patients who signed the informed consent form (ICF). Number of patients randomized is the denominator for percentages for the rest of the table.

4 Total days on study are defined as the number of days from the date of randomization to the date of completion or discontinuation as provided on the study completion CRF page.

Source: Section 5.3.5.1 “Study FC-004-Section 14 Tables”, page 5.

### 6.1.11 Efficacy Analyses

#### 6.1.11.1 Analyses of Primary Endpoint(s)

The median TTH and hazard ratio are shown in Table 15 for each surgical setting. For each surgical indication, a statistically significant difference in the TTH distribution between FCGS to GS alone was obtained ( $p < 0.0001$  resulting from the Log Rank test). These results demonstrate that FCGS is superior to GS alone for achieving hemostasis.

Table 15: Time to Hemostasis by Surgery Type and Treatment

Surgery Type	Fibrocaps Plus Gelatin Sponge Median TTH, min. (95% CI)	Gelatin Sponge Alone Median TTH, min. (95% CI):	Cox Proportional Hazard Ratio	p-value <sup>a</sup>
Spinal (n=183)	1.0 (-, -)	2.5 (2.0, 3.0)	3.3	<0.0001
Vascular (n=175)	2.0 (1.5, 2.5)	4.0 (3, 5.0)	2.1	<0.0001
Hepatic Resection (n=180)	1.0 (1.0, 1.5)	2.0 (1.5, 2.5)	2.3	<0.0001
Soft Tissue Dissection (n=181)	1.5 (1.0, 1.5)	2.5 (2.0, 3.5)	3.4	<0.0001

<sup>a</sup> Log-rank test

Source: Section 2.7.3 “FC-004-Clinical Study Report [Fibrocaps, Fibrin sealant]”, page 11

#### 6.1.11.2 Analyses of Secondary Endpoints

The results in Table 16 present an analysis of the difference in the restricted mean TTH over 5 minutes using Irwin’s estimator (i.e., the difference in the area under the Kaplan-Meier estimator of TTH survival within 5 minutes) and the Tables 17-20 present the proportion of subjects achieving hemostasis at 3 and 5 minutes for each of the four surgery types.

Table 16: Restricted Mean TTH by Surgery Type and Treatment within 5 minutes at TBS.

	Fibrocaps Plus Gelatin Sponge Restricted Mean TTH, min. (SEM)	Gelatin Sponge Alone Restricted Mean TTH, min. (SEM)	Difference in Means	p-value <sup>a</sup>
Spinal (n=183)	1.2 (0.08)	2.7 (0.19)	-1.5	<0.0001
Vascular (n=175)	2.4 (0.14)	3.5 (0.2)	-1.1	<0.0001
Hepatic Resection (n=180)	1.5 (0.09)	2.5 (0.21)	-1.0	<0.0001
Soft Tissue Dissection (n=181)	1.5 (0.09)	3.1 (0.19)	-1.6	<0.0001

Source: Section 2.7.3 “FC-004-Clinical Study Report [Fibrocaps, Fibrin sealant]”, page 14

Table 17: Proportion of Subjects Achieving Hemostasis for Spinal Surgery

Parameter	Fibrocaps + Gelatin Sponge N=122	Gelatin Sponge Alone N=61
Patients achieving hemostasis within 3 minutes at TBS (% , 95% CI)	117 (96.0 % , 92%-99%)	40 (66.0% , 54% - 77%)
Difference in Probability (95% CI)	30% (18% - 43%)	
p-value	< 0.0001	
Patients achieving hemostasis within 5 minutes at TBS (% , 95% CI)	120 (98% , 96 - 100%)	50 (82% , 72 - 92%)
Difference in Probability (95% CI)	16% (6%- 26%)	
p-value	0.0012	

Source: Section 2.7.3 “Summary of Clinical Efficacy [Fibrocaps, Fibrin sealant]”, page 14

Table 18: Proportion of Subjects Achieving Hemostasis for Vascular Surgery

Parameter	Fibrocaps + Gelatin Sponge N=117	Gelatin Sponge Alone N=58
Patients achieving hemostasis within 3 minutes at TBS (% , 95% CI)	86 (73.5 % , 66%-82%)	23 (40.0% , 27% - 52%)
Difference in Probability (95% CI)	33.8% (19% - 49%)	
p-value	< 0.0001	
Patients achieving hemostasis within 5 minutes at TBS (% , 95% CI)	102 (87.1% , 81-93%)	38 (65.5. , 53-78%)
Difference in Probability (95% CI)	22% (0.08%- 35%)	
p-value	0.0019	

Source: Section 2.7.3 “Summary of Clinical Efficacy [Fibrocaps, Fibrin sealant]”, page 14

Table 19: Proportion of Subjects Achieving Hemostasis for Hepatic Resection

Parameter	Fibrocaps + Gelatin Sponge N=119	Gelatin Sponge Alone N=61
Patients achieving hemostasis within 3 minutes at TBS (% , 95% CI)	112 (94 % , 90%-98%)	43 (70.5% , 59% -82%)
Difference in Probability (95% CI)	23.6% (11% - 36%)	
p-value	0.0001	
Patients achieving hemostasis within 5 minutes at TBS (% , 95% CI)	117 (98% , 96-100%)	48 (78 , 68-89%)
Difference in Probability (95% CI)	19.6% (9%- 30%)	
p-value	0.0003	

Source: Section 2.7.3 “Summary of Clinical Efficacy [Fibrocaps, Fibrin sealant]”, page 15

Table 20: Proportions of Subjects Achieving Hemostasis for Soft Tissue Dissection

Parameter	Fibrocaps + Gelatin Sponge N=122	Gelatin Sponge Alone N=59
Patients achieving hemostasis within 3 minutes at TBS (% , 95% CI)	115 (94.3% , 90-98%)	33 (55.9% , 43 -69%)
Difference in Probability (95% CI)	38.3% (25% - 52%)	
p-value	P < 0.0001	
Patients achieving hemostasis within 5 minutes at TBS (% , 95% CI)	120 (98.4 , 96-100%)	44 (75.0 , 63-86%)
Difference in Probability (95% CI)	23.8% (12%- 35%)	
p-value	< 0.0001	

Source: Section 2.7.3 “Summary of Clinical Efficacy [Fibrocaps, Fibrin sealant]”, page 15

A statistically significant difference was observed between FCGS versus GS alone for the restricted mean TTH and in the percentage of subjects achieving hemostasis at both 3 and 5 minutes for all four surgery types. These data further demonstrate that FCGS is statistically superior to GS alone for achieving hemostasis.

**Reviewer Comment:** This reviewer verified the 95% CIs for hemostasis in Tables 17 - 20.

#### 6.1.11.3 Subpopulation Analyses

There was no difference in TTH measures (mean/median TTH, hazard ratio, restricted mean) when assessing various demographic subgroups (age, race, gender) across the surgical types.

An assessment of whether the application procedure impacted TTH measurements was performed for each surgery type. As shown in Table 21 there was no meaningful difference in median TTH whether Fibrocaps was applied using the Fibrospray Device or applied directly from the vial across all surgical indications.



Table 21: Median TTH by Application Procedure across Surgery Types

	Surgery Type			
	Spinal	Vascular	Hepatic Resection	Soft Tissue Dissection
Median TTH (min): Fibrocaps -Device applied <sup>a</sup> (n/N)	1.0 (28/122)	2.0 (1/117)	1.0 (114/119)	1.5 (115/122)
Median TTH (min): Fibrocaps -No Device <sup>a</sup> (n/N)	1.0 (94/122)	2.0 (116/117)	1.5 (5/119)	1.0 (7/122)

Source: Section 2.7.3 “Summary of Clinical Efficacy [Fibrocaps, Fibrin sealant]”, page 32

#### 6.1.11.4 Dropouts and/or Discontinuations

Few subjects were lost to follow up and deaths accounted for only 1% of discontinuation of the protocol (Table 22). No subjects discontinued treatment because of an AE. However, after the database was locked, it was noted that two subjects were erroneously captured as having discontinued treatment because of an AE (Subject 102-034 in the FCGS group for Grade 1 low hematocrit and Subject 300-012 in the GS alone group for Grade 2.) In both cases the events occurred after completion of study treatment and the surgical procedure. No TEAEs reported during the study were considered related to the Fibropray device.

Table 22: Dropouts and/or discontinuations and deaths (695 completed protocol of 721 randomized (96%))

Disposition	Phase 3 FC-004
Death	10
Lost to Follow-up	10
Withdrew Consent	2
Other	3
Non-compliance	1
Efficacy Evaluable	719 <sup>b</sup>

<sup>b</sup> Two subjects were randomized but not treated.

Source: Section 5.3.5.1 “Study FC-004-Section 14 Tables”, page 72

The three sensitivity analyses were conducted for each of the four surgery types. The results of these sensitivity analyses did not change the finding that FCGS was superior to GS alone at achieving hemostasis in all four surgical settings. The percent of patients without hemostasis within 5 minutes was low for the FCGS group. It was 2% in the spinal surgery population, 20% in the vascular surgery population, 4% in the hepatic resection population, and 3% in the tissue dissection population in comparison with 18% , 24% , 23%, and 25% correspondently in thr GS group.

## 6.1.12 Safety Analyses

### 6.1.12.1 Methods

Safety data were pooled across surgical indications.

Fibrocaps was applied using the spray device in 260/480 subjects (54%). Exposure by application method is presented in Table 23.

Table 23: Fibrocaps Exposure and Fibrospray Device Usage by Application Method (Safety Population; All Surgery Types)

All Surgery Types	Fibrospray Device [1] (N=260)	Directly from Vial/onto a Gelatin Sponge/Other Application method (N=220)
Fibrocaps Usage at Target Bleeding Site		
Vials Used		
0	0	0
1	242 ( 93)	206 ( 94)
2	17 ( 7)	12 ( 5)
3	1 (<1)	2 (<1)
Percentage Used per Vial		
Number of Vials	278	235
Mean (SD)	85.0 (22.59)	59.4 (35.59)
Median	100.0	60.0
Q1, Q3	80.0, 100.0	20.0, 100.0
Min, Max	10, 100	10, 100
Fibrocaps Usage at Non-Target Bleeding Site		
Vials Used		
0	0	0
1	37 ( 14)	59 ( 27)
2	15 ( 6)	7 ( 3)
3	1 (<1)	3 ( 1)
Percentage Used per Vial		
Number of Vials	70	82
Mean (SD)	55.0 (35.05)	54.5 (30.19)
Median	50.0	50.0
Q1, Q3	20.0, 100.0	30.0, 80.0
Min, Max	0, 100	10, 100
Fibrospray Device Usage [2]		
Number of Devices Used	262	
Nozzle Type		
Rigid Nozzle	185 ( 71)	
Flexible Nozzle	76 ( 29)	
Rigid and Flexible Nozzle	1 (<1)	

[1] Subject is counted in Fibrospray Device subgroup if either Fibrospray Device Used is indicated on Fibrocaps Accountability eCRF page or if use of Fibrospray Nozzle is indicated on Fibrospray Accountability eCRF page.

[2] Fibrospray device usage percentages are based on the number of devices used, not the number of patients.

Source: Section 5.3.5.1 "Study FC-004-Section 14 Tables", page 1267.

### 6.1.12.3 Deaths

A total of 10 subjects died during the trial: eight subjects treated with FCGS and two subjects treated with GS alone (Table 24). None of the deaths were considered by Investigators or the applicant to be related to study treatment.

Table 24: Listing of Deaths

Subject ID	Sex/Age (yrs)	Surgery Type	Treatment Group	System Organ Class/ Preferred Term/ Verbatim <sup>a</sup>	Study Day
104-033	Female/63	Hepatic	Fibrocaps + Sponge	Cardiac disorders/ Cardiac arrest/ Cardiac Arrest, Due To Preexisting Comorbidity	(b) (6)
402-002	Male/76	Soft tissue	Fibrocaps + Sponge	Neoplasms benign, malignant and unspecified (including cysts and polyps)/ Small intestine carcinoma/ Duodenal Adenocarcinoma	
101-009	Male/80	Spinal	Fibrocaps + Sponge	General disorders and administration site conditions/ Death/ Unknown Cause Of Death	
300-006	Female/77	Vascular	Fibrocaps + Sponge	Cardiac disorders/ Myocardial ischaemia/ Acute Myocardial Ischaemia	
300-019	Male/84	Vascular	Fibrocaps + Sponge	Cardiac disorders/ Myocardial infarction/ Myocardial Infarction	
303-004	Male/72	Vascular	Fibrocaps + Sponge	Infections and infestations/ Pneumonia/ Hospital Acquired Pneumonia	
307-003	Male/68	Vascular	Fibrocaps + Sponge	Vascular disorders/ Aortic aneurysm rupture/ Ruptured Thoracic Aortic Aneurysm	
308-001	Male/75	Vascular	Fibrocaps + Sponge	General disorders and administration site conditions/ Cardiac death / Fatal Cardiac Arrest	
102-038	Female/76	Soft tissue	Sponge alone	Infections and infestations/ Pneumonia/ Pneumonia	(b) (6)
204-007	Female/66	Vascular	Sponge alone	Gastrointestinal disorders/ Intestinal ischaemia/ Irreversible Bowel Ischaemia	

Source: Section 2.7.4 “Summary of Clinical Safety [Fibrocaps, Fibrin sealant]”, page 16

#### 6.1.12.4 Nonfatal Serious Adverse Events

At least one SAE occurred in 81 of 480 subjects (17%) in the FCGS group and in 29 of 239 subjects (12%) in the GS group. None of these events were considered to be related to the treatment.

#### 6.1.12.5 Adverse Events of Special Interest (AESI)

The categories of treatment-emergent adverse events (TEAEs) of interest were:

- *Surgical site-related events, which includes pain and infection suggestive of a higher complication rate*

Overall surgical site-related AEs occurred at similar rates in the FCGS and GS groups, 15% and 14%, respectively. Incision site pain occurred at the same rate, 13%, in both groups, and the remainder of events (postoperative wound infection, incision site erythema, incision site complication, incision site cellulitis, postoperative wound complication, and incision site infection and incision site pruritus) occurred in less than 1% of subjects in each group.

- *Thromboembolic events, which includes acute ischemic events like myocardial infarction, deep vein thrombosis and stroke*

Overall thromboembolic events occurred in 3% of both the FCGS and GS groups. Specific events, i.e., deep vein thrombosis, pulmonary embolism, vascular graft thrombosis, cardiac arrest, myocardial infarction, myocardial ischaemia, arterial thrombosis limb, arteriovenous fistula thrombosis, cerebral infarction, femoral artery occlusion, intestinal ischaemia, silent myocardial infarction, thrombosis and vena cava thrombosis, occurred in less than 1% of subjects in each treatment group.

- *Re-bleeding at the TBS, including post-procedural hemorrhage and hematomas*

Overall events related to re-bleeding from the surgical site occurred at similar rates in the FCGS and GS groups, 2% and 3%, respectively. Post-procedural hemorrhage occurred more frequently in the GS group (2%) as compared to the FCGS group (<1%) and the remainder of the events (haematoma, haemorrhage, post procedural haematoma, arterial haemorrhage, wound haematoma and wound haemorrhage) occurred in less than 1% of subjects in each treatment group.

- *Air emboli-associated events, which includes acute respiratory failure or cardiovascular collapse occurring intraoperatively following the use of the Fibrospray device*

Overall events suspected of being manifestations of air emboli occurred at the same rate, 3%, in both the FCGS and GS groups. Procedural hypotension occurred more frequently in the FCGS group (2%) as compared to the GS group (<1%), whereas respiratory failure occurred more frequently in the GS group (2%) as compared to the FCGS group (<1%). Respiratory distress occurred in less than 1% of subjects in each treatment group.

- *Hepatitis/HIV suggestive of viral transmission through Fibrocaps*

Since subjects were not routinely screened for hepatitis and HIV at study entry and the protocol did not provide for routine post-treatment testing, this aspect of the study is of

limited value. Spontaneous reports, even in the setting of a clinical trial, are inadequate to assess the risk.

Lower respiratory tract infection was the only AE with a statistically significant difference between the treatment groups, which occurred more frequently in the GS alone group (0 vs. 3%,  $p=0.001$ ).

## **10. CONCLUSIONS**

### **10.1 Statistical Issues and Collective Evidence**

Primary efficacy analyses for study FC-004 were based on the efficacy population ( $n=719$ ), which did not differ significantly from the ITT population ( $n=721$ ). It sought to test the difference in the TTH survival curves comparing FCGS to GS alone in each surgical type using the log rank statistic while ensuring an overall 2-sided significance level of 0.05 for each surgical type. For each surgical type, the median TTH was shorter with FCGS than with GS alone ( $p < 0.0001$  resulting from the log-rank test of the distributions). Three sensitivity analyses were conducted to assess the impact of missing data in the results comparing the efficacy population to the ITT population. The results of these sensitivity analyses did not change the finding that FCGS was superior to GS alone at achieving hemostasis in all four surgical settings. Among the secondary endpoints, a statistically significant difference was observed between FCGS versus GS alone for the percentage of subjects achieving hemostasis at both 3 and 5 minutes. These data further demonstrate that FCGS is statistically superior to GS alone for achieving hemostasis.

Post-procedural hemorrhage following use of FCGS occurred at a lower rate than with GS alone and does not appear to be a safety concern. No subjects discontinued treatment because of an AE. The 10 deaths (8 FCGS and 2 GS alone) were not related to study treatment.

### **10.2 Conclusions and Recommendations**

The results of study FC-004 demonstrated statistically significant superiority of FCGS over GS alone in all four surgery types.