

Application Type	Original Application
STN	125523/0
CBER Received Date	January 31, 2014
PDUFA Goal Date	January 31, 2015 extended to May 15, 2015
Division / Office	DH /OBRR
Priority Review	No
Reviewer Name(s)	Charles M. Maplethorpe M.D., Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	ProFibrix, BV.
Established Name	Fibrin Sealant, Human Fibrinogen Human Thrombin
(Proposed) Trade Name	Raplixa
Pharmacologic Class	Fibrin Sealant
Formulation(s), including Adjuvants, etc	<p>Raplixa is a dry powder composed of a mixture of human plasma-derived thrombin (b) (4) IU/gram) and human plasma-derived fibrinogen (79 milligrams/gram) as the active ingredients. Other ingredients include the following:</p> <ul style="list-style-type: none"> • calcium chloride (11 milligrams/gram), • trehalose (b) (4) milligrams/gram), • human plasma-derived albumin (component of the fibrinogen product; (b) (4)) • sodium citrate (b) (4)) • L-arginine hydrochloride (b) (4) milligrams/gram), and • sodium chloride (b) (4))
Dosage Form(s) and Route(s) of Administration	Topical application to bleeding site
Dosing Regimen	Apply to bleeding surface
Indication(s) and Intended Population(s)	Raplixa is indicated as an adjunct to surgical hemostasis in adults 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 sponge, (USP).
Orphan Designated (Yes/No)	No

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GLOSSARY

Insert text here

Abbreviation	Meaning
AAA	Abdominal aorta aneurysm
AE	Adverse event
Alb	Albumin
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Arteriovenous
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CHMP	Committee for Medicinal Products for Human Use
Cr	Creatinine
CRF	Case report form
CRO	Contract research organization
eCRF	Electronic case report form
ECG	Electrocardiogram
(b) (4)	(b) (4)
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good clinical practice
GMP	Good manufacturing practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International normalized ratio
IRB	Institutional review board
ITT	Intent to treat
IU	International units
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHRA	Medicines and Healthcare Regulatory Agency
mL	Milliliter
min	Minute
Na	Sodium
PE	Physical exam

Abbreviation	Meaning
PT	Prothrombin time
(b) (4)	(b) (4)
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SEM	Standard error of the mean
SWG	Scientific Working Group
TBili	Total bilirubin
TBS	Target bleeding site
Tstart	Start time of Raplixa application
TEAE	Treatment-emergent adverse events
TESAE	Treatment-emergent serious adverse events
TTH	Time to hemostasis
UK	United Kingdom
USA/US	United States of America
USP	United States Pharmacopeia
WBC	White blood cell
WHO-DRL	World Health Organization Drug Reference List

1. Executive Summary

Insert text here

Profibrix, Inc. has submitted STN125523 for a fibrin sealant product, Raplixa[®], for the following indication:

Raplixa is indicated as an ~~aid~~ adjunct to surgical hemostasis in adults 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 sponge, (USP).

Reviewer's comment: Fibrin sealants are an “adjunct” to hemostasis, not an “aid” to hemostasis. The indication has been corrected. Also, the “in adults” qualifier must be added because pediatric studies have been deferred.

Product.

Raplixa is a dry powder composed of a mixture of human plasma-derived thrombin (b) (4) and human plasma-derived fibrinogen (79 milligrams/gram) as the active ingredients. Other ingredients include the following:

- calcium chloride (11 milligrams/gram),
- trehalose (b) (4)

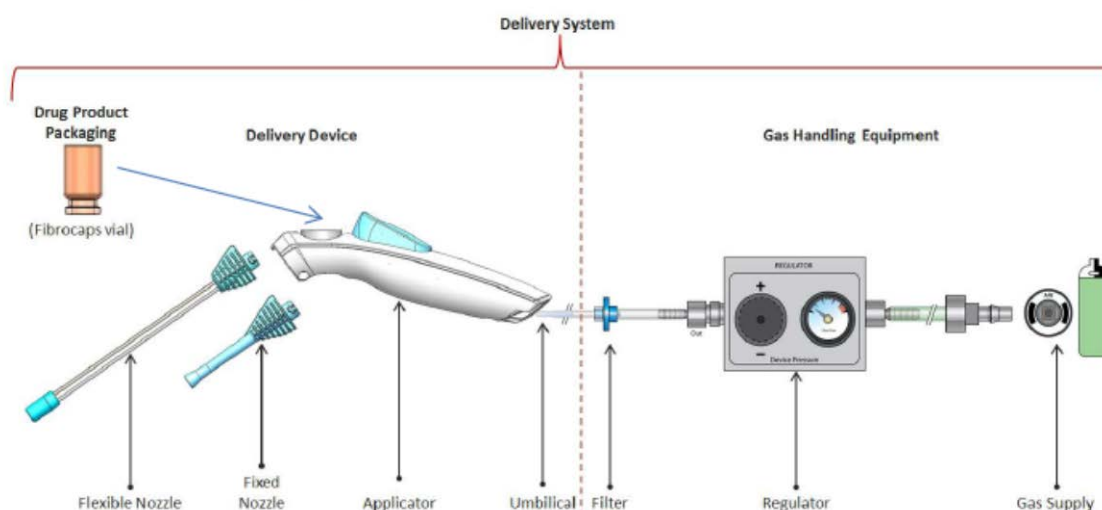
- human plasma-derived albumin (component of the fibrinogen product; (b) (4) ,
- sodium citrate (b) (4)
- L-arginine hydrochloride (b) (4) and
- sodium chloride (b) (4)

The thrombin (b) (4) and fibrinogen (b) (4) source materials are both licensed products of (b) (4) .

When applied to a bleeding surface, the moisture of the wound allows the thrombin to cleave the fibrinogen to form fibrin, thereby forming a fibrin clot.

The Raplixaspray delivery device is a Class II device that is being reviewed as a 510(k) application by CDRH. It is supplied separately from the Raplixa drug product. The device is intended to deliver Raplixa for topical application to bleeding areas that are difficult to access, or to large bleeding areas.

Figure 1: Fibrospray Device Set-up and System



Source: STN125523 module 3.2.R.1

Clinical Development – Pivotal Study FC-004.

The applicant chose to pursue a clinical development program to support an indication for use of Raplixa as an adjunct to hemostasis in general surgery. Therefore, the pivotal study FC-004 enrolled subjects undergoing one of four types of surgery: soft tissue dissection, hepatic, vascular, or spinal surgery. The following table further describes these four surgery types:

Spinal Surgery	Cervical, thoracic, or lumbar discectomy; corpectomy; laminectomy; lateral or interbody fusion; bleeding site not confined within a bony cavity
Vascular Surgery	Arterial bypass surgery; arteriovenous graft formation for hemodialysis access; carotid endarterectomy

Hepatic Resection	Hepatic wedge resection or anatomic resection of 1 to 5 contiguous hepatic segments, which may be combined with surgical procedures involving the pancreas, gall bladder, bile duct or intestines.
Soft Tissue Dissection	Primary procedure may include, but not limited to, abdominoplasty, lower anterior resections, abdominal perineal resections, distal pancreatectomy, esophagectomy, donor skin graft site in limited burn patients, and mastectomy

Adapted from STN125523 Protocol FC-004 v4.3 page 6

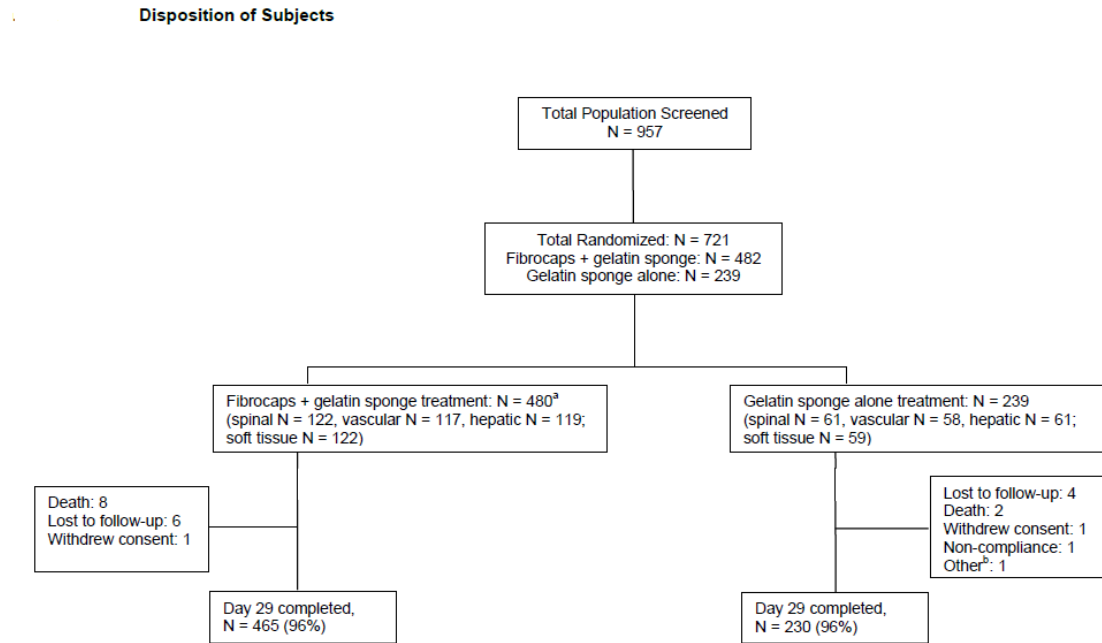
Subjects were adults without known allergies to study agent components (plasma-derived thrombin and fibrinogen, (b) (4) gelatin), and who had acceptable coagulation and liver function profiles (which could vary depending on the underlying medical condition).

The study design planned to enroll approximately 180 subjects into each surgery type using a 2:1 randomization to the test arm (Raplixa with gelatin sponge) or the control arm (gelatin sponge alone). A target bleeding site (TBS) with area less than 100 square centimeters was identified during surgery; the bleeding from the TBS had to be characterized as mild (oozing and/or capillary leakage) or moderate (gradual and steady flow) bleeding/oozing not controllable by conventional surgical techniques (suture, ligature, or cautery). Raplixa could be applied in one of three ways, depending on the nature of the TBS: 1) by sprinkling on the TBS followed by application of the gelatin sponge, 2) by sprinkling of Raplixa onto the gelatin sponge, and then application of this to the TBS, or 3) by using the Raplixaspray device.

The primary endpoint was time-to-hemostasis (TTH), censored at 5 minutes. Secondary endpoints included proportion of subjects achieving hemostasis at the TBS at 3 and 5 minutes, use of alternative hemostatic agents at the TBS, transfusion requirements through day 29, and re-operation of the TBS for bleeding.

Study FC-004 Results.

The following schema shows subject disposition for Study FC-004:



a Two subjects (1 undergoing vascular surgery, 1 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: STN125523 Study FC-004 Clinical Report page 39

The sex and race distribution of the enrolled subjects is shown in the following table:

	Raplixa + Gelatin Sponge										Gelatin Sponge Only									
	Female					Male					Female					Male				
Surgery Type	American Indian or Alaskan Native	Asian	Black or African American	Other	White	Asian	Black or African American	Not Reported	Other	White	American Indian or Alaskan Native	Asian	Black or African American	Not Reported	Other	White	Asian	Black or African American	Other	White
Hepatic Resection					44	1	1		1	72			2	1		19	1	1	1	35
Soft Tissue Dissection		3	24		55	1	3		1	35	1		12		1	31		1		13
Spinal Surgery	1	1	4	1	46	1	2		2	63		1	1			26				33
Vascular Surgery			6	1	26	1	2	2	1	74		1	1		1	16		2	1	34

Source: calculated from the demographics database for STN125523/0 Study FC-004

Reviewer's Comment: It can be seen that approximately 80 percent of subjects were caucasian; enrollment in other race groups was too small to permit valid conclusions within these groups. Enrollment by sex was reasonably balanced, permitting outcome comparisons by sex.

Study FC-004 Efficacy

The results for the primary endpoint, time-to-hemostasis within 5 minutes, are shown in the following table:

Time to Hemostasis by Surgery Type and Treatment

	Raplixa Plus Gelatin Sponge Median TTH, min. (95% CI)	Gelatin Sponge Alone Median TTH, min. (95% CI):	Cox Proportional Hazard Ratio	p-value^a
Spinal^b (n=183)	1.0 (-, -)	2.5 (2.0, 3.0)	3.3	<0.0001
Vascular^c (n=175)	2.0 (1.5, 2.5)	4.0 (3, 5.0)	2.1	<0.0001
Hepatic Resection^d	1.0 (1.0, 1.5)	2.0 (1.5, 2.5)	2.3	<0.0001
Soft Tissue Dissection^e (n=181)	1.5 (1.0, 1.5)	2.5 (2.0, 3.5)	3.4	<0.0001

^a Log-rank test

^b Raplixa + Gelatin Sponge n= 122; Gelatin Sponge Only n=61

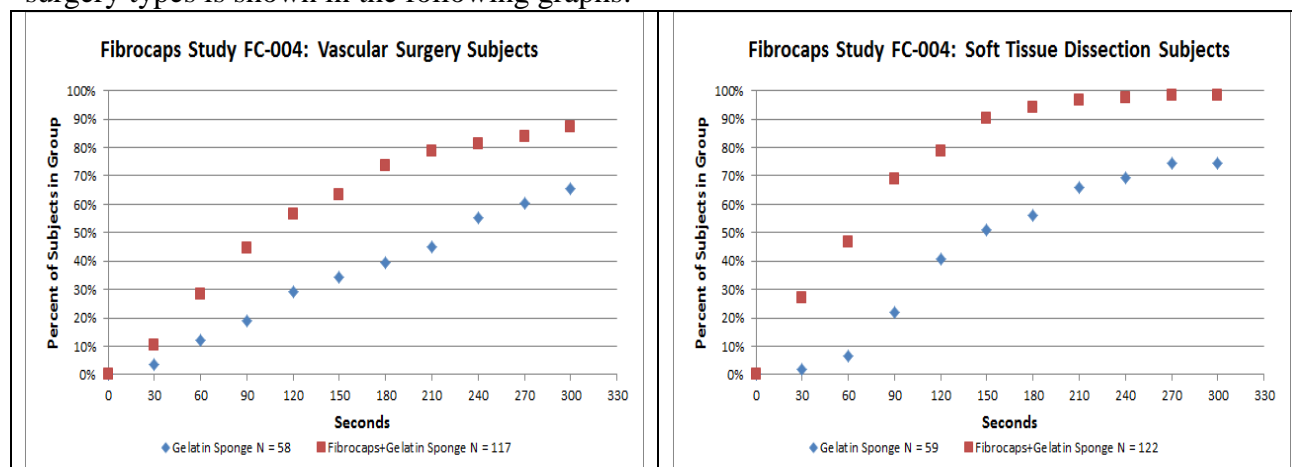
^c Raplixa + Gelatin Sponge n= 117; Gelatin Sponge Alone n=58

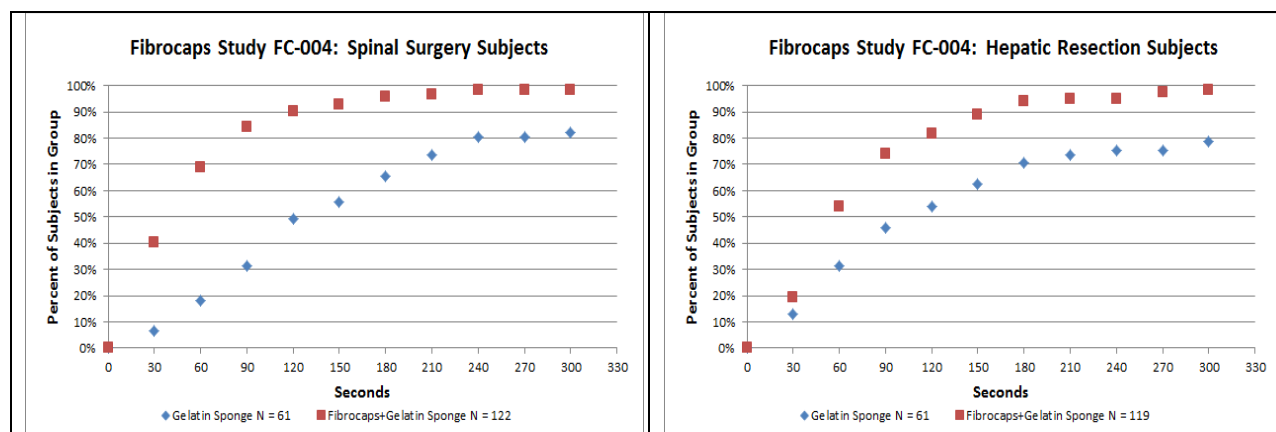
^d Raplixa + Gelatin Sponge n= 119; Gelatin Sponge alone n= 59

^e Raplixa + Gelatin Sponge n= 122; Gelatin Sponge alone n= 59

Source: STN125523 Study FC-004 Clinical Report page 44

A graphical representation of the primary endpoint results over the 5-minute interval for the four surgery types is shown in the following graphs:





Source: derived from analysis datasets submitted in STN125523

Reviewer's Comment: It can be seen that Raplixa hastens hemostasis by approximately one minute, depending on the surgery type, but that hemostasis is substantially achieved in both arms by the 5 minute time point.

Results for the secondary endpoints were either favorable for Raplixa, or not different from the control results. Raplixa had statistically significant better results for TTH at 3 and 5 minutes; had the same extent of use of alternative hemostatic agents at the TBS (1 percent vs. 3 percent for the control); had the same extent of RBC transfusion requirements through day 29 (8 percent vs. 9 percent for the control); and had no re-operations at the TBS for bleeding, whereas the control arm had one subject re-operated for bleeding at the TBS.

Study FC-004 Safety

The safety database is derived from the 480 subjects who were treated with at least one vial of Raplixa while undergoing spinal surgery, vascular surgery, hepatic resection, or soft tissue dissection. The method of exposure is summarized in the following table:

Study FC-004 for Target Bleeding Site: Number of Subjects in Administration Type by Surgery Type

	Sprinkled Directly from Vial	Raplixa Applied to Moist Gelatin sponge	Raplixa spray Device Used	Other¹
spinal surgery	8	83	28	4
vascular surgery	48	82	1	2
hepatic resection	8	1	124	0
soft tissue dissection	4	4	122	0
Total	68	170	275	6

¹In spinal surgery: in 1 subject Raplixa applied with dry gelatin sponge, in 1 subject Raplixa applied with (b) (4), in 2 subjects Raplixa was underdosed from protocol recommendation; in vascular surgery: in 1 subject Raplixa applied with dry gelatin sponge, in 1 subject Raplixa only 25 percent of dose applied

In the adult study FC-004 (randomized 2:1 Raplixa + gelatin sponge vs. gelatin sponge alone), treatment-emergent adverse events were experienced by 426 of 480 subjects in the Raplixa + gelatin sponge arm, and 214 of 239 subjects in the gelatin sponge alone arm.

Deaths. There were 10 deaths during the 30-day follow-up period (and 1 death in the post-study period). None of the deaths are attributable to the study agents, but appear to be caused by the underlying medical conditions.

Intensity of adverse events was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 or using the following scale for items not listed in the CTCAE v4.0:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)
- Life-threatening (subject is at risk of death due to AE)
- Death

Most adverse events were grade 1 or 2 severity; adverse events of \geq grade 3 were experienced by 105 of 480 subjects in the Raplixa + gelatin sponge arm, and 44 of 239 subjects in the gelatin sponge alone arm, but these were not considered to be adverse reactions to the treatment.

The most commonly reported adverse events (> 5 % subjects) were nausea, constipation, post-operative pain, pyrexia, and low blood pressure, with the majority considered mild in intensity. The following table shows the frequency of these adverse events in the four surgical categories by treatment:

Commonly reported AEs (> 5% subjects) in Raplixa Clinical Studies

	Phase 2 ^{a)}		Phase 3 ^{b)}		Total	
N (%) of Patients Preferred Term	FC+ G ^d (N=86)	G ^d (N=39)	FC+ G ^d (N=480)	G ^d (N=239)	FC+G ^d (N=566) ^{c)}	G ^d (N=278)
Patients With at Least One TEAE	79 (92)	32 (82)	426 (89)	214 (90)	505 (89)	246 (88)
Procedural pain	40 (47)	16 (41)	257 (54)	134 (56)	297 (52)	150 (54)
Nausea	26 (30)	13 (33)	120 (25)	48 (20)	146 (26)	61 (22)
Constipation	21 (24)	9 (23)	72 (15)	31 (13)	93 (16)	40 (14)
Incision site pain	5 (6)	3 (8)	63 (13)	32 (13)	68 (12)	35 (13)

	Phase 2 ^{a)}		Phase 3 ^{b)}		Total	
N (%) of Patients Preferred Term	FC+ G ^d (N=86)	G ^d (N=39)	FC+ G ^d (N=480)	G ^d (N=239)	FC+G ^d (N=566) ^{c)}	G ^d (N=278)
Pyrexia	7 (8)	5 (13)	37 (8)	11 (5)	44 (8)	16 (6)
Insomnia	5 (6)	2 (5)	41 (9)	10 (4)	46 (8)	12 (4)
Anaemia	4 (5)	2 (5)	33 (7)	17 (7)	37 (7)	19 (7)
Vomiting	11 (13)	2 (5)	26 (5)	12 (5)	37 (7)	14 (5)
Hypotension	2 (2)	2 (5)	38 (8)	16 (7)	40 (7)	18 (6)
Pruritus	3 (3)	1 (3)	33 (7)	8 (3)	36 (6)	9 (3)
Hypertension	1 (1)	0	25 (5)	10 (4)	26 (5)	10 (4)

Source: labeling submitted in the STN125523

a) FC-002 US and FC-002 NL clinical trials combined

b) FC-004 Pivotal Phase 3 clinical trial

c) Sorted on Total Raplixa + Gelatin subjects

d) FC+G = Raplixa plus Gelatin Sponge; G= Gelatin sponge alone

SAEs. Serious adverse events by surgery type, study arm, and body system are shown in the following table:

	Hepatic Resection				Soft Tissue Dissection				Spinal Surgery				Vascular Surgery			
	Sponge + F-caps		Sponge		Sponge + F-caps		Sponge		Sponge + F-caps		Sponge		Sponge + F-caps		Sponge	
	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects
ALL Serious AEs	26	20	12	8	43	24	13	7	17	12	2	2	33	25	18	12
Blood and lymphatic system disorders	1	1							2	2			2	2	1	1
Cardiac disorders	2	2	2	1	2	1							4	4		
Gastrointestinal disorders	2	2	3	3	8	6	1	1	1	1			3	3	3	3
General disorders and administration site conditions	1	1			1	1			2	2			1	1	2	2
Hepatobiliary disorders	1	1	1	1	1	1										
Infections and infestations	8	6	2	2	12	11	6	4	2	2			4	4	2	2
Injury, poisoning and procedural complications	7	7	3	2	7	5	1	1	4	4	1	1	8	7	2	2
Investigations					1	1	1	1								
Metabolism and nutrition disorders					3	3	1	1					3	2		
Musculoskeletal and connective tissue disorders									2	2	1	1				

	Hepatic Resection				Soft Tissue Dissection				Spinal Surgery				Vascular Surgery			
	F-caps + Sponge		Sponge		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge	
	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					1	1			1	1						
Nervous system disorders					1	1			1	1			1	1		
Psychiatric disorders									1	1					1	1
Renal and urinary disorders													1	1		
Respiratory, thoracic and mediastinal disorders	3	2	1	1	4	3	2	2	1	1					4	4
Vascular disorders	1	1			2	2	1	1					6	6	3	2

Reviewer's Comment: Although there is an apparent imbalance in total SAEs against Raplixa in the spinal surgery arm, a review of these adverse events does not allow a conclusion of causality.

Viral Safety. There were two subjects with treatment-emergent positive hepatitis C antibody test results. Subject 402-019, 55 y.o. African-American male, (Raplixa + sponge arm) had a positive result on November 9, 2012. Subject 402-003, 47 y.o. white male, (sponge alone arm) had a positive result on September 29, 2012. Both subjects were enrolled at Washington University, St. Louis MO. Both subjects were undergoing amputations (below-the-knee or partial foot) and were enrolled in the soft tissue dissection category of study FC-004.

Reviewer's comment: These two Hepatitis C seroconversions are most likely community-acquired, because the plasma-derived components are licensed products that have undergone viral safety validation procedures during manufacturing, and there are no additional cases that could implicate the this product, or the licensed products from which it is made.

RECOMMENDATION

Raplixa is safe and effective, and may be approved for the use as an adjunct to hemostasis in adults for mild to moderate bleeding from small vessels when control of bleeding by standard surgical techniques is ineffective or impractical.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Insert text here

Raplixia is a fibrin sealant intended to treat mild to moderate bleeding that arises in general surgery. FDA requires that fibrin sealants intended for a general surgery hemostasis indication be studied in several types of surgery that reflect the range of hemostatic difficulties encountered in surgery.

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

Insert text here

There are several licensed fibrin sealants and adjunct to surgical hemostasis products, including Tisseel, Evicel, EVARREST, Tachosil, CryoSeal, Recothrom and Evithrom.

2.3 Safety and Efficacy of Pharmacologically Related Products

Insert text here

The safety of fibrin sealant products is good, and not substantially different among products.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Insert text here

Adapted from STN125523 Study FC-004 Clinical Report, page 20:

Raplixia was studied in two Phase 2 studies (FC-002 US and FC-002 NL) in surgical indications where adjuncts to hemostasis are required to control bleeding: spinal surgery, major hepatic resection, and peripheral vascular surgery (i.e., peripheral arterial bypass surgery and arteriovenous graft formation for hemodialysis access).

In FC-002 NL, 56 subjects undergoing liver resection surgery were randomized 2:1 to receive Raplixia plus gelatin sponge (n=39) or gelatin sponge alone (n=17). In the Intent-to-Treat (ITT) analysis, a statistically significant reduction in the mean time to hemostasis (TTH) was observed with Raplixia, as compared to gelatin sponge alone (2.2 minutes vs. 4.4 minutes, $p=0.004$).

In FC-002 US, 70 subjects undergoing spinal, vascular, or general surgery were randomized 2:1 to Raplixia plus gelatin sponge (n=47) or gelatin sponge alone (n=23). A statistically significant reduction in the mean TTH was also observed with Raplixia in the ITT analysis, as compared to gelatin sponge alone (1.9 minutes vs. 4.8 minutes, $p<0.001$).

The safety profile of Raplixia plus gelatin sponge across both FC-002 studies (n=86) was considered acceptable with the most common (>10% of subjects) treatment-emergent adverse events (TEAEs) being post-operative pain, constipation, nausea, edema, vomiting and hypokalemia. The majority of TEAEs were classified as mild or moderate in

intensity. Thirtyfive treatment-emergent serious AEs (TESAEs) were reported, with 25 reported from subjects undergoing liver resection surgery and only one considered possibly related to Raplixa by the Investigator. There were no observed Raplixa-associated trends or safety signals related to changes in vital signs, physical examinations, coagulation laboratory parameters or anti-thrombin neutralizing antibodies.

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

Insert text here

- May 25, 2010, IND 14385 submitted for Fibrocap (Raplixa) fibrin sealant
- January 31, 2014, STN125523/0 submitted for Raplixa
- October 17, 2014, major amendment submitted to STN125523 for CMC issues, extending review period by 3 months
- March 5, 2015, the Pediatric Research Committee (PeRC) approved deferral of pediatric studies for ages 0 to 18 years
- May 2, 2015, first action due (approval) for STN125523/0

2.6 Other Relevant Background Information

Insert text here

Raplixa was called “Fibrocaps” and the Raplixa spray device was called “Fibrospray” during the clinical development phase.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

Insert text here

STN125523/0 is of high quality and complete in the clinical studies sections. The CMC sections have required multiple requests for information that have extended the review period.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Insert text here

Clinical studies in STN125523/0 conform to Good Clinical Practice and have integrity.

3.3 Financial Disclosures

Covered clinical study (name and/or number):		
Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>57</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>zero</u>		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3454): <u>zero</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p style="margin-left: 40px;">Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p style="margin-left: 40px;">Significant payments of other sorts: _____</p> <p style="margin-left: 40px;">Proprietary interest in the product tested held by investigator: _____</p> <p style="margin-left: 40px;">Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>57</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Insert text here

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Insert text here

Raplixa is a pre-mixed, ready to use blend of human plasma-derived thrombin and fibrinogen supplied as a ready to use dry-powder fibrin sealant in a glass 6 ml vial containing, as the standard configuration, 1.0 g of Raplixa.

Raplixa is supplied as a single strength 79 mg/g human fibrinogen and (b) (4) human thrombin per gram of powder. Raplixa is supplied in three different presentations 0.5 gram per vial, 1.0 gram per vial, and 2.0gram per vial.

Raplixa is used without reconstitution and can be applied directly onto the surgical bleeding site, where it dissolves readily on contact with aqueous fluids, such as blood, triggering an immediate conversion of the fibrinogen component into insoluble fibrin polymers by the active thrombin component.

Raplixa may be delivered to the surgical bleeding site directly from the vial, or by means of the Raplixaspray device, a sterile, single-use, dry powder spray device connected to an appropriate

air supply, or onto a moistened gelatin sponge that is then applied to the surgical bleeding site. Of note, Raplixa must be used in combination with a gelatin sponge.

4.2 Assay Validation

Insert text here

Not applicable.

4.3 Nonclinical Pharmacology/Toxicology

Insert text here

See Pharmacology/Toxicology review of La’Nissa Brown-Baker, Ph.D.

4.4 Clinical Pharmacology

Insert text here

4.4.1 Mechanism of Action

Insert text here

Raplixa provides the human coagulation proteins thrombin and fibrinogen in spray-dried form directly to the wound surface, where they become hydrated and form a clot.

4.4.2 Human Pharmacodynamics (PD)

Insert text here

Not applicable.

4.4.3 Human Pharmacokinetics (PK)

Insert text here

Not applicable.

4.5 Statistical

Insert text here

The statistical reviewer verified that the primary study endpoint analyses cited by the applicant were supported by the submitted data.”

4.6 Pharmacovigilance

Insert text here

Post-marketing surveillance will be by routine pharmacovigilance. Given the life-threatening nature of air or gas embolism, the sponsor will conduct targeted follow-up of events which may be indicative of air or gas embolism with a questionnaire. Additionally, the sponsor will attempt examination of the Fibrospray device used in such incidents for possible defects, as well as review of the AE and product complaints for Fibrospray devices with the same lot number.

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

5.1 Review Strategy

Insert text here

Protocol FC-004 enrolled adults undergoing soft tissue dissection surgery, vascular surgery, liver surgery, or spinal surgery. Therefore, the outcomes for these four surgery types are presented and analyzed as one clinical trial in this review.

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

Insert text here

The clinical studies were conducted under IND 13485. STN125523 contains all the information reviewed for this submission.

5.3 Table of Studies/Clinical Trials

Insert text here

Listing of Clinical Studies

Type of Study	Study Identifier	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	Demonstrate Superior efficacy profiles of Raplixa plus gelatin sponge versus gelatin sponge alone (Time to Hemostasis)	Randomized, single-blind, controlled trial Active (gelatin sponge)	Raplixa + (b) (4) vs. (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)	Characterize the efficacy profiles of Raplixa plus gelatin sponge versus gelatin sponge alone (Time to Hemostasis)	Randomized, single-blind, controlled trial Active (gelatin sponge)	Raplixa + (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	≤ 5 mins	Complete CSR

Type of Study	Study Identifier	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
						arteriovenous graft formation for hemodialysis, including revisions), or general surgery (including hepatic resection and soft tissue dissection)		
Phase 2	FC-002 (NL)	Characterize the efficacy profiles of Raplixa plus gelatin sponge versus gelatin sponge alone (Time to Hemostasis)	Randomized, single-blind, controlled trial Active (gelatin sponge)	Raplixa + (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: STN125523 module 5.2

5.4 Consultations

Insert text here

5.4.1 Advisory Committee Meeting (if applicable)

Insert text here

STN125523 was not presented to the Blood Products Advisory Committee because there were no questions that needed to be answered.

5.4.2 External Consults/Collaborations

Insert text here

There were no external consults.

5.5 Literature Reviewed (if applicable)

Insert text here

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 “A Phase 3, Randomized, Single-Blind, Controlled Trial of Topical Fibrocaps™ in Intraoperative Surgical Hemostasis”

Insert text here

6.1.1 Objectives (Primary, Secondary, etc)

Insert text here

Primary Objective:

- to demonstrate the superiority of Raplixa plus gelatin sponge, as compared to gelatin sponge 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 Objectives:

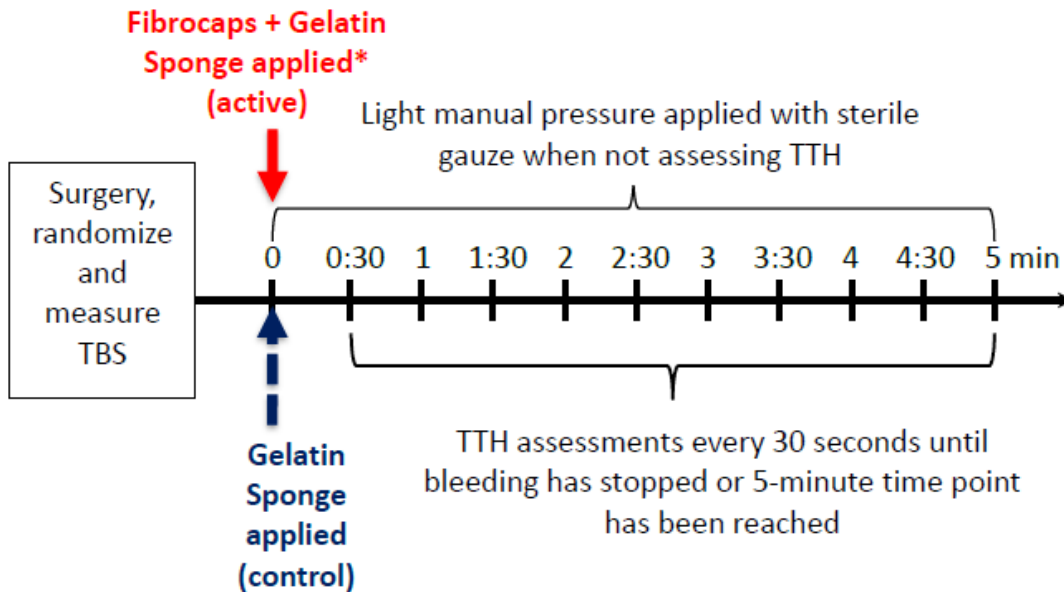
- to further characterize the efficacy and safety profiles of Raplixa plus gelatin sponge, as compared to gelatin sponge alone, in subjects undergoing spine, liver, vascular or soft tissue surgery, when control of mild to moderate bleeding by standard surgical techniques is ineffective and/or impractical
- to evaluate the health economics and outcomes data by analyzing the utilization of selected medical resources by treatment group

6.1.2 Design Overview

Insert text here

The following schema shows the trial design that was used for each of the four surgery categories:

Figure 1: TTH Assessment Schema



* TTH clock started as soon as the application of Fibrocaps or gelatin sponge to the TBS began.

Source: STN125523 Clinical Report page 24

6.1.3 Population

Insert text here

Subjects were undergoing one of four types of surgery: spinal, vascular, hepatic resection, or soft tissue dissection. The protocol further described these categories as follows:

Spinal Surgery	Cervical, thoracic, or lumbar discectomy; corpectomy; laminectomy; lateral or interbody fusion
Vascular Surgery	Arterial bypass surgery; arteriovenous graft formation for hemodialysis access; carotid endarterectomy
Hepatic Resection	Hepatic wedge resection or anatomic resection of 1 to 5 contiguous hepatic segments, which may be combined with surgical procedures involving the pancreas, gall bladder, bile duct or intestines.
Soft Tissue Dissection	Primary procedure may include, but not limited to, abdominoplasty, lower anterior resections, abdominal perineal resections, distal pancreatectomy, esophagectomy, donor skin graft site in limited burn patients, and mastectomy

Bleeding was required to be judged mild to moderate, and requiring the use of a topical hemostat.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Insert text here

Subjects were randomized to Raplixa (Raplixa) plus gelatin sponge, or to gelatin sponge alone.

6.1.5 Directions for Use

Insert text here

The Fibrocap powder could be sprinkled on the bleeding surface directly followed by application of the gelatin sponge, or first applied to the gelatin sponge before application to the bleeding surface, or applied by the spray device. The method depended on the nature of the bleeding site and investigator preference.

6.1.6 Sites and Centers

Insert text here

The following table shows the investigators and sites for study FC-004:

Site Number	Site Name	Principal Investigator
100	Hôpital Erasme, Bruxelles, BE	De Witte Olivier, Jean Marie, Pierre
101	Clinique du Park Léopold, CHIREC, Brussels, BE	Patrick Fransen M.D.
102	University Hospital Gen, BE	Prof. Dr. Piet Pattyn, MD, PhD
103	Militair Hospitaal Koningin Astrid, Brussel, BE	Dr. Thomas Rose, MD
104	UZ Gasthuisberg, Leuven, BE	Prof Baki Topal MD, PhD
105	UZ Gent, BE	Prof. Dr. Roberto Troisi, MD, PhD
200	St Radboud University Medical Centre Nijmegen, NL	Dr. Johannes Hendrik Willem de Wilt MD, PhD
201	Medisch Spectrum Twente, Enschede, NL	Dr. Robert Herman Geelkerken MD, PhD
202	Leiden University Medical Center, Leiden, NL	Prof. Jacob Frans Hamming, MD, PhD
203	Medisch Spectrum Twente, Enschede, NL	Dr. Joost M. Klaase, MD, PhD
204	Rijnstate Ziekenhuis – Locatie Arnhem, NL	Jan Willem Henricus Pieter Lardenoije, MD
205	University Medical Center Groningen, NL	Robert Jack Porte, MD, PhD
206	Amphia Hospital, Breda, NL	Arjen M. Rijken MD, PhD
207	Amphia Hospital, Breda, NL	Lijckle van der Laan, MD, PhD

Site Number	Site Name	Principal Investigator
208	Erasmus MC, Rotterdam NL	Cornelis Verhoef, MD, PhD
209	University Medical Center Groningen, NL	Clark J. Zeebregts MD, PhD
211	St Radboud University Medical Centre Nijmegen, NL	Jordanus Adan (Daan) van der Vliet MD, PhD
300	Hull Royal Infirmary, UK	Ian Chetter
301	Addenbrooke's Hospital, Cambridge, UK	Mr. Paul David Hayes BSc MV ChB MD FRC5
302	King's college Hospital, London UK	Prof Nigel David Heaton MB BS FRCS
303	Doncaster Royal Infirmary, Doncaster, UK	Mr. Woolagasen Ramalingham Pillay FCS(5A)MMedSc
304	Leeds General Infirmary, Leeds, UK	Mr. David Alexander Russell (MB, CHB, MD, FRCS (GenSurg)
305	Freeman Hospital, Newcastle upon Tyne, UK	Prof. Gerard Stansby (BA, MB, Chir.MA, FRCS, M.Chir)
306	Queen Elizabeth Hospital, Birmingham, UK	Mr Robert Peter Sutcliffe (MA MB BChir FRCS (Gen) MD)
307	University Hospital, Coventry, UK	Prof Christopher H E Imray (PhD FRCS, FRCP, FRGS, MB BS Dip Mnt Med, Dip Clin
308	St Georges University London, London, UK	Mr. ian Magnus Loftus BSc, MD, Ch8, MI
309	Arrowe Park Hospital, Wirral, UK	Mr. Stephen BlairFRCS Eng, FRCS Ed, MBBS, MS, LRCP
310	The York Hospital, York, UK	Mr Andrew Thompson BMedSci, FRCS(Gen), MD
311	University Hospital of South Manchester, Manchester, UK	Prof. Charles Nevin McCollum (MG, ChB, FRCS (London), FRCS (Edinburgh), MD)
400	Vascular Interventional Specialists of Orange County, Inc., Orange, CA, USA	Jeffrey Lawrence Ballard, MD, FACS

Site Number	Site Name	Principal Investigator
401	Virginia Mason Medical Center, Seattle, WA, USA	Thomas Biehl, MD
402	Washington University in St. Louis School of Medicine, St. Louis, MO, USA	Grant V. Bochicchio, MD
403	Washington University in St. Louis School of Medicine, St. Louis, MO, USA	William C. Chapman, MD
406	Lake Washington Vascular Surgeons, Bellevue, WA, USA Overlake Hospital Medical Center, Bellevue, WA, USA	Kathleen Gibson, MD Ashit C. Patel, MD
407	NorthShore University HealthSystem, IL, USA	NavYash Gupta, MD
408	Cardio-Thoracic Surgeons, Birmingham AL, USA	John Lytle Harlan, MD
409	Memorial Medical Center, Springfield, IL USA	Kim J. Hodgson, MD
410	University Hospital, Birmingham, AL, USA	William D. Jordan, Jr. MD
412	Lotus Clinical Research, LLC Pasadena, CA, USA	Shankar Lakshman, MD
413	Lotus Clinical Research, LLC, Pasadena, CA, USA	Max R. Lehfelddt, MD
414	Bluegrass Orthopaedics & Hand Care Research, Lexington, KY USA	Harry K. Lockstadt, MD
415	Oregon Health & Science University, Portland, OR, USA	Gregory L. Moneta, MD
416	MultiCare Health System Research Institute, Tacoma, WA,	William Morris, MD
417	Spine Surgery, Las Vegas, NV, USA	William S. Muir, MD
420	Northwestern University, Chicago, IL, USA	William Pearce, MD
423	Lotus Clinical Research, LLC Pasadena, CA, USA	Thomas S. Taylor, MD
424	Indiana Spine Group, Carmel, IN, USA	Kenneth Renkens, MD
426	Keck Medical Center of USC, Los Angeles, CA, USA	Linda, Sher, MD
427	Lotus Clinical Research, LLC Pasadena, CA, USA	Neil K Singla, MD

Site Number	Site Name	Principal Investigator
428	Lotus Clinical Research, LLC Pasadena, CA, USA	Sonia Singla, DO
429	University of North Texas Health Science Center at Fort Worth, Fort Worth, TX, USA	Albert H. O.-Yurvati, DO, FACOS, FICS, FAHA
430	Duke University Hospital, Durham, NC, USA	Jeffrey H. Lawson, MD, PhD
433	Boulder Neurosurgical Associates, Boulder, CO, USA	Alan Thomas Villavicencio, MD
434	Keck Medical Center of USC, Los Angeles, CA, USA	Karen Woo, MD
435	The Smart Clinic, Sandy, UT, USA	Stephen M. Hansen, MD
436	Washington University in St. Louis School of Medicine, St. Louis, MO, USA	Surendra Shenoy, MD
441	Northwest Orthopaedic Specialists, PS, Spokane, WA, USA	Antoine Tohmeh, MD

6.1.7 Surveillance/Monitoring

Insert text here

Study Visit Schedule

Visit 1 Days -30 to 1	Visit 2 Day 1	Visit 3 Day 2 (16-48 hrs Post-Treatment)	Visit 4 Day 29 ± 4 days
Screening/baseline	Surgery	Safety Follow-up	End of Study
ICF signing 2 Screening	Surgery TBS identification Randomization Treatment3 TTH assessment3 Safety evaluation Raplixaspray Device assessment	Safety evaluation	Safety evaluation

1. Screening may occur on Day 1 prior to surgery provided all screening evaluations have been completed and results are available for review prior to randomization
2. ICF signing must occur prior to all screening procedures and evaluations and may occur up to 30 days prior to surgery.
3. The start of Treatment is also the start of the 5-minute TTH assessment period and t=0 for TTH measurement.

Source: Protocol FC-004, v 4.3 page 20

Schedule of Assessments

Visit	1	2	3	4
Event	Screening/Baseline (Days -30 to 1)	Surgery (Day 1)	Follow-up^a (16-48 h post-surgery)	Follow-up (Days 25 to 33)
Informed Consent ^b	X			
Inclusion/ Exclusion Criteria	X	X ^c		
Medical History	X	X ^c		
Physical Examination, incl Weight, Height & Vital Signs ^d	X	X ^e	X	X

Visit	1	2	3	4
Event	Screening/Baseline (Days -30 to 1)	Surgery (Day 1)	Follow-up^a (16-48 h post-surgery)	Follow-up (Days 25 to 33)
CBC with differential ^f	X		X	X
Blood Chemistry Panel ^g	X		X	
Coagulation Panel ^h	X		X	X
Pregnancy Test ⁱ	X			
Immunogenicity Sample	X			X
Intra-operative Eligibility and Randomization		X		
Treatment and TTH Measurement		X		
Documentation of Surgical Procedure		X		
Raplixaspray Device Assessment ^j		X		
Adverse Events ^k		X	X	X
Concomitant Medications	X	X	X	X

a: For outpatient procedures, Visit 3 may be conducted over the phone with the PE conducted and labs collected prior to discharge on Day 1

b: Informed consent may be signed up to 30 days prior to surgery

c: Review and record any changes in medical conditions since screening visit

d: Weight and height are only collected at screening. Vital signs include resting BP, pulse and body temperature. PE performed at Screening and Visits 3 and 4

e: Only vital signs, collected pre-operatively

f: Includes hemoglobin, hematocrit, platelets and white blood cell count with differential

g: Na, K, BUN/Urea, Cr, Glu, Alb, AST, ALT, TBili

h: PT, aPTT, INR

i: For women of child-bearing potential only

j: For subjects treated using the Raplixaspray device to apply the Raplixa

k: k. Adverse events are collected from the time of randomization through Visit 4

Source: Protocol FC-004, v 4.3 page 22

6.1.8 Endpoints and Criteria for Study Success

Insert text here

A target bleeding site (TBS) with bleeding area less than 100 square centimeters was identified and the study agent was applied. Efficacy was scored if hemostasis occurred within 5 minutes. Use within the first 5 minutes of an alternative hemostatic agent, whether or not it contained thrombin, was considered a treatment failure.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Insert text here

Time to hemostasis (TTH) during 5 minutes was compared (log-rank statistic) within each indication (soft tissue dissection surgery, vascular surgery, liver surgery, or spinal surgery).

6.1.10 Study Population and Disposition

Insert text here

6.1.10.1 Populations Enrolled/Analyzed

Insert text here

Subjects were adults undergoing one of four types of surgery: vascular, liver, soft tissue dissection, or spinal surgery. Efficacy was analyzed on all subjects randomized within a surgery category and who had a time-to-hemostasis assessment, i.e. an Intent-to-Treat (ITT) Population consisting of all subjects randomized was used in sensitivity analyses of efficacy.

6.1.10.1.1 Demographics

Insert text here

The sex and race distribution of the enrolled subjects is shown in the following table:

	Raplixa + Gelatin Sponge										Gelatin Sponge Only									
	Female					Male					Female					Male				
Surgery Type	American Indian or Alaskan Native	Asian	Black or African American	Other	White	Asian	Black or African American	Not Reported	Other	White	American Indian or Alaskan Native	Asian	Black or African American	Not Reported	Other	White	Asian	Black or African American	Other	White
Hepatic Resection					44	1	1		1	72			2	1		19	1	1	1	35
Soft Tissue Dissection		3	24		55	1	3		1	35	1		12		1	31		1		13
Spinal Surgery	1	1	4	1	46	1	2		2	63		1	1			26				33
Vascular Surgery			6	1	26	1	2	2	1	74		1	1		1	16		2	1	34

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Insert text here

Use of (b) (4) are a potential confounder for hemostatic agents. The following table shows the use of concomitant medications in the (b) (4) group:

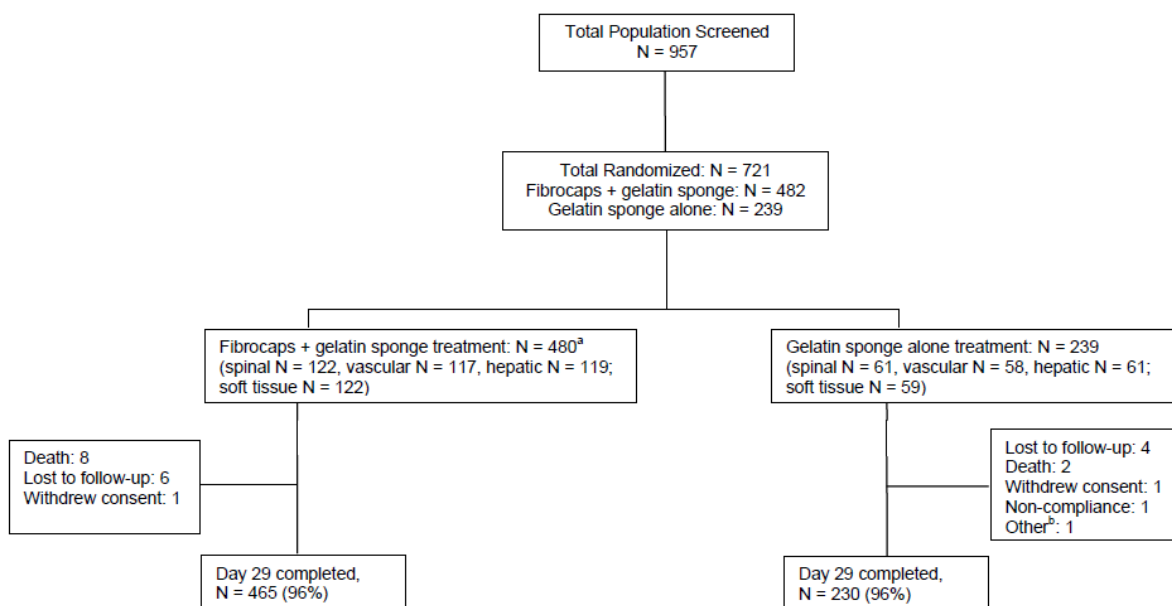
Subject	Treatment Arm	Surgery Type
403-001	Raplixia + Gelatin Sponge	Hepatic Resection
403-001	Raplixia + Gelatin Sponge	Hepatic Resection
105-036	Raplixia + Gelatin Sponge	Hepatic Resection
413-013	Raplixia + Gelatin Sponge	Soft Tissue Dissection
417-003	Raplixia + Gelatin Sponge	Spinal Surgery
435-010	Raplixia + Gelatin Sponge	Spinal Surgery
427-010	Gelatin Sponge Only	Spinal Surgery

Reviewer's comment: Use of (b) (4) was 9 to 1 in the test arm versus the control arm. Therefore, this potential confounding affect, if present, would be against the test agent.

6.1.10.1.3 Subject Disposition

Insert text here

Figure 2: Disposition of Subjects



- ^a Two subjects (1 undergoing vascular surgery, 1 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: STN125523 Study FC-004 Clinical Report page 39

6.1.11 Efficacy Analyses

Insert text here

6.1.11.1 Analyses of Primary Endpoint(s)

Insert text here

The results for the primary endpoint, time-to-hemostasis within 5 minutes, is shown in the following table:

Time to Hemostasis by Surgery Type and Treatment

	Raplixa Plus Gelatin Sponge Median TTH, min. (95% CI)	Gelatin Sponge Alone Median TTH, min. (95% CI):	Cox Proportional Hazard Ratio	p-value^a

	Raplixa Plus Gelatin Sponge Median TTH, min. (95% CI)	Gelatin Sponge Alone Median TTH, min. (95% CI):	Cox Proportional Hazard Ratio	p-value^a
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

^a Log-rank test

Source: STN125523 Sudy FC-004 Clinical Report page 44

6.1.11.2 Analyses of Secondary Endpoints

Insert text here

Restricted Mean TTH by Surgery Type and Treatment

	Raplixa Plus Gelatin Sponge Restricted Mean TTH, min. (SEM)	Gelatin Sponge Alone Restricted Mean TTH, min. (SEM)	Difference in Means	p-value^a
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

^a Restricted mean based on Irwin estimator and tested using normal approximation

SEM: standard error of the mean

Source: STN125523 Sudy FC-004 Clinical Report page 49

Proportion of Subjects Achieving Hemostasis at 3 and 5 Minutes

	Spinal (n=183)	Vascular (n=175)	Hepatic Resection (n=180)	Soft Tissue Dissection (n=181)
Probability of hemostasis at 3 minutes				
Raplixa plus gelatin sponge	0.96	0.74	0.94	0.94
Gelatin sponge alone	0.66	0.40	0.70	0.56
Difference in probability (95% CI)	0.30 (0.18 , 0.43)	0.34 (0.19 , 0.49)	0.24 (0.11 , 0.36)	0.38 (0.25 , 0.52)
p-value ^a	<0.0001	<0.0001	<0.0001	<0.0001
Probability of hemostasis at 5 minutes				
Raplixa plus gelatin sponge	0.98	0.87	0.98	0.98
Gelatin sponge alone	0.82	0.66	0.79	0.75
Difference in probability (95% CI)	0.16 (0.06 , 0.26)	0.22 (0.08 , 0.35)	0.20 (0.09 , 0.30)	0.23 (0.12 , 0.35)
p-value ^a	0.0012	0.0019	0.0003	<0.0001

^a Wald-based normal approximation of binomial with continuity correction

Source: STN125523 Study FC-004 Clinical Report page 50

Use of Alternative Hemostatic Agents at the TBS. Six of 480 subjects (1 percent) in the Raplixa arm and 7 of 239 subjects (3 percent) in the control gelatin sponge arm were treated with alternative hemostatic agents (thrombin, epinephrine, oxidized cellulose, Tisseel).

Transfusion Requirements through Day 29. Thirty-eight of 480 subjects (8 percent) in the Raplixa arm and 7 of 239 subjects (9 percent) in the control gelatin sponge arm were administered red blood cells (RBCs). Transfusion was similar between treatment arms for all surgeries except hepatic surgery, in which RBCs were administered to 15 percent of the subjects in the Raplixa arm and to 23 percent of subjects in the control gelatin sponge arm.

Reoperation at the TBS for Bleeding. One subject in the control gelatin sponge arm in vascular surgery was re-operated at the TBS for bleeding.

6.1.11.3 Subpopulation Analyses

Insert text here

Eighty-eight percent of subjects were caucasian, rendering analysis by race not meaningful.

6.1.11.4 Dropouts and/or Discontinuations

Insert text here

6.1.11.5 Exploratory and Post Hoc Analyses

Insert text here

Raplixaspray Device Usage and Performance. The Raplixaspray device was used in 260 of the 480 subjects in the Raplixa arm (54 percent of subjects). It was used for almost all subjects in hepatic surgery and soft tissue dissection surgery (97 percent and 94 percent of subjects, respectively). It was used in only 24 percent of subjects in spinal surgery, and 1 percent of subjects in vascular surgery. A questionnaire gave results that showed the Raplixaspray device to be easy to assemble and prepare for use, and showed it to accurately deliver Raplixa to the TBS.

6.1.12 Safety Analyses

6.1.12.1 Methods

Insert text here

The safety database is derived from the 480 subjects who were treated with at least one vial of Raplixa while undergoing spinal surgery, vascular surgery, hepatic resection, or soft tissue dissection.

The method of exposure is summarized in the following table:

**Study FC-004 for Target Bleeding Site:
Number of Subjects in Administration Type by Surgery Type**

	Sprinkled Directly from Vial	Raplixa Applied to Moist Gelatin sponge	Raplixaspray Device Used	Other
spinal surgery	8	83	28	4
vascular surgery	48	82	1	2
hepatic resection	8	1	124	0
soft tissue dissection	4	4	122	0
Total	68	170	275	6

6.1.12.2 Overview of Adverse Events

Insert text here

6.1.12.3 Deaths

Insert text here

There were 10 deaths during the 30-day follow-up period (and 1 death in the post-study period). None of the deaths are attributed to the study agents.

From STN125523/0 Study FC-004 Clinical Report Appendix Section 16.2.7:

FC-004: SAE Case Narratives for Deaths

1. **PRO-0601-00071 – USA -- ADENOCARCINOMA -- GELATIN SPONGE ALONE**

Subject 402-002 is a 76-year-old Caucasian male who underwent soft tissue dissection while enrolled in ProFibrix Study FC-004 and experienced an **SAE of adenocarcinoma**. During the duodenal resection on 29-AUG-2012, the subject was treated with 1 vial of Raplixa, Raplixaspray device with flexible nozzle, and 1 (b) (4) sponge at the omental area.

On (b) (6) days post treatment, the subject was receiving hospice care for an inoperable duodenal adenocarcinoma at an extended care facility and died due to the adenocarcinoma.

The subject's relevant medical and surgical history includes adenocarcinoma and COPD. Relevant concomitant medication taken at the onset of the SAE included cefepime and vancomycin. Previously reported SAEs for this subject include pneumonia on 03-SEP-2012 (reference case PRO-0601-00058) and accidental removal of J-tube on 12-SEP-2012 (reference case PRO-0601-00062).

No action was taken with Raplixa, Raplixaspray device or (b) (4) due to the event. The Investigator assessed the adenocarcinoma as CTCAE grade 5/Death and not related to Raplixa, Raplixaspray device, or (b) (4). A possible alternate cause of the event was the subject's medical history of chronic obstructive pulmonary disease (COPD). The Sponsor agrees with the Investigator's assessment.

Reviewer's comment: This death in the gelatin sponge control arm does not appear to be related to the study agent.

2. **PRO-0601-00095 – UK – ACUTE MYOCARDIAL ISCHAEMIA
FIBROCAPS/GELATIN**

Subject 300-006 is a 77-year-old Caucasian female who underwent vascular surgery while enrolled in ProFibrix Study FC-004 and experienced an **SAE of acute myocardial ischaemia**. During the bilateral common femoral endarterectomy and femoro-femoral cross-over grafting on 14-NOV-2012, the subject was treated with Raplixa 1 vial and 1 (b) (4) gelatin sponge.

On (b) (6) day post treatment, the subject suffered cardiopulmonary arrest and died. On 1 (b) (6) a chest X-ray revealed the subject's central venous pressure (CVP) line was in good position. Arterial blood gas results included pH 6.93, partial pressure of carbon dioxide (pCO₂) 6.7 kPa, partial pressure of oxygen (pO₂) 51.5 kPa, base excess (BE) -20.8 mmol/L, oxygen saturation (sO₂) 99.9%, and bicarbonate (HCO₃) 8.8 mmol/L. Blood electrolytes included sodium (Na) 128 mmol/L, potassium (K) 8.6 mmol/L, and calcium (Ca) 0.88 mmol/L. The subject was treated with hetastarch (Volulyte), noradrenaline, and 2 units of packed red blood cells for hypotension. She also received amiodarone for atrial fibrillation (AF) and 50% dextrose with 15 mL of insulin. She had a myocardial infarction and immediately prior to going into cardiac arrest, her

blood pressure (BP) was 72/30 mmHg. The subject's relevant medical and surgical history includes anemia, asthma, hypertension, hypercholesterolemia, hypothyroidism, and angina pectoris. No concomitant medications were reported. The death certificate stated the cause of death as myocardial ischemia

No action was taken with Raplixa or (b) (4). The investigator assessed the death as CTCAE grade 5/death and not related to Raplixa, Raplixaspray or (b) (4). A possible alternate cause of the event was the surgical procedure and the underlying cardiovascular disease. The Sponsor agrees with the Investigator's assessment.

Reviewer's comment: This death in the Raplixa + gelatin sponge test arm does not appear to be related to the study agent.

3. **PRO-0601-00127 – BELGIUM -- CARDIAC ARREST -- FIBROCAPS/GELATIN**

Subject 104-033 is a 63-year-old Caucasian female who underwent hepatic resection while enrolled in ProFibrix Study FC-004 and experienced an **SAE of cardiac arrest**. During the left hepatectomy on 14-DEC-2012 the subject was treated with Raplixa 1 vial, Raplixaspray device with flexible nozzle, and 2 (b) (4) gelatin sponges.

On (b) (6) days post treatment, the subject had low pressure that was unable to be measured, and she reported feeling unwell for the past 24 hours. Her vital signs included blood pressure (BP) 65/45 mmHg, pulse 89, and oxygen saturation (O2 sat) 99% on 2L of oxygen (O2). Laboratory results included sodium 136.7 mmol/L (reference range 135.0-145.0), potassium 5.03 mmol/L (reference range 3.50-5.10), chloride 90.8 mmol/L (reference range 98.0-107.0), bicarbonate 22.2 mmol/L (reference range 22.0-29.0), creatine kinase muscle brain (CK-MB) 10.4 ug/L (reference range <=4.9), and troponin total (T) 1.340 ug/L (reference range <=0.013). The subject suddenly felt very nauseated, lost consciousness, and was gasping for breath. Her pulse could no longer be felt and she was given adrenaline and chest compressions were initiated. She regained consciousness; however, after a few minutes, she again became nauseated, had pulseless electrical activity (PEA), and lost consciousness. Due to her pre-existing pulmonary hypertension and cardiac co-morbidity, she developed sudden cardiac arrest. She was resuscitated with adrenaline and recovered spontaneous circulation (ROSC). During transport to the cardiac care unit (CCU), the subject suffered PEA another two times. Advanced life support (ALS) was restarted and adrenaline was administered. The subject had ROSC again. Upon arrival to the CCU, the subject once again had PEA and resuscitation was resumed. The subject had broad complexes on scope, did not recover output, and had no shockable rhythm. Despite further resuscitation, the subject developed asystole. Adrenaline was administered and ALS was provided for 10 minutes, prior to the decision to stop resuscitation. On (b) (6), the subject died and the event had a fatal outcome. The cause of death was reportedly cardiac arrest.

The subject's relevant medical and surgical history included pulmonary hypertension, obesity, hyperlipidemia, mild obstructive pulmonary disease, critical aortic stenosis, cardiac decompensation, and cholangiocarcinoma. No concomitant medications were reported. There were no previously reported SAEs for this subject.

No action was taken with Raplixa or (b) (4). The Investigator assessed the cardiac arrest as CTCAE grade 5/Death and not related to Raplixa, Raplixa spray device, and (b) (4). A possible alternate cause of the event was the subject's medical history of pulmonary hypertension and cardiac decompensation. The Sponsor agrees with the Investigator's assessment.

Reviewer's comment: This death in the Raplixa + gelatin sponge test arm does not appear to be related to the study agent.

4. **PRO-0601-00141 – BELGIUM – DEATH -- FIBROCAPS/GELATIN**

Subject 101-009 is an 80-year-old Caucasian male who underwent spinal surgery while enrolled in ProFibrix Study FC-004 and experienced an **SAE of death**. During the surgery on 09-JAN-2013, the subject was treated with Raplixa 1 vial, Raplixa spray device with fixed/rigid nozzle, and 1 (b) (4) gelatin sponge.

On (b) (6) days post treatment, the subject died suddenly at home due to unknown causes. The subject had no signs or symptoms prior to his death. There were no relevant laboratory or diagnostic test results for the event. On 22-JAN-2013, the subject's wife called the site to report his death. An autopsy was not performed and the death certificate was not available. A possible alternate cause of the event was the subject's age. The event did not involve the site of treatment with the study product.

The subject had no relevant medical and surgical history. There were no relevant concomitant medications taken at the onset of the SAE. There were no previously reported SAEs for this subject.

No action was taken with Raplixa or (b) (4). The investigator assessed the event of death as unlikely related to Raplixa, (b) (4) device, and (b) (4). The Sponsor agrees with the Investigator's assessment.

Reviewer's comment: This death in the Raplixa + gelatin sponge test arm does not appear to be related to the study agent.

5. **PRO-0601-00158 -- UNITED KINGDOM -- CARDIAC ARREST -- FIBROCAPS/GELATIN**

Subject 308-001 is a 75-year-old Caucasian male who underwent vascular surgery while enrolled in ProFibrix Study FC-004 experienced an **SAE of fatal cardiac arrest**. During the hybrid thoracoabdominal aneurysm repair on 31-JAN-2013, the subject was treated with Raplixa 1 vial and 1 (b) (4) gelatin sponge.

The subject was recovering as expected from the major surgical procedure on 31-JAN-2013. On an unknown date the subject experienced confusion, increasing drowsiness, hearing voices and agitation. He was observed to be leaning to the left but with good power bilaterally in arms and legs with some intention tremor. On 06-FEB-2013,

computed tomography (CT) of the head showed no acute hemorrhage; low attenuation in the left subinsular white matter that does not extend to the cortex with no associated edema but suspicious for a sub-acute left middle cerebral artery territory infarct. On 06-FEB-2013, abnormal laboratory results included urea 9.5 mmol/L (reference range 2.5-7.8), creatinine 129 umol/L (reference range 60-110), albumin 14 g/L (reference range 35-50), C-reactive protein 98.2 mg/L (reference range 0.0-10.0), troponin I 124 ng/L (reference range 0-50), hemoglobin (Hb) 92.0 g/L (reference range 130-180), hematocrit (Hct) 0.28 (reference range 0.41-0.52), International Normalized Ratio (INR) of 1.4 (reference range 0.8-1.1), activated partial thromboplastin time (APTT) of 1.49 (reference range 0.85-1.15) and thrombin time of 23 (reference range 11-16). On the morning of (b) (6), the subject felt acutely unwell. While awaiting investigation, he had sudden cardiac arrest and died. During resuscitation, the subject was treated with fentanyl, suxamethonium, metaraminol and adrenaline. The death certificate was not available.

The subject's relevant medical and surgical history included a recent stroke. No concomitant medications were reported. There were no previously reported SAEs for this subject.

No action was taken with Raplixa or (b) (4). The Investigator assessed the fatal cardiac arrest as CTCAE grade 5/death and not related to Raplixa and (b) (4). The event did not involve the site of treatment with the investigational product. A possible alternate cause of the event was the surgical procedure and the subject's medical history of thoracoabdominal aortic aneurysm and recent stroke. The Sponsor agrees with the Investigator's assessment.

Reviewer's comment: This death in the Raplixa + gelatin sponge test arm does not appear to be related to the study agent. The prolonged coagulation times at the time of the stroke are concerning for possible late antibody (thrombin, fibrinogen) effects. There are no baseline antibody results reported for this subject, although baseline aPTT and PT were normal, with INR elevated. On day 2, aPTT was still normal, but PT and INR were elevated. The subject died on day (b) (6) which is at the beginning of the period for the appearance of an antibody response; anti-thrombin antibody responses were infrequent in this study, and could have been false positives. The abnormal coagulation studies on day (b) (6) are more likely to reflect inadequate coagulation factor production by the liver.

6. PRO-0601-00169 – BELGIUM – PNEUMONIA -- GELATIN SPONGE ALONE

Subject 102-038 is a 76-year-old Caucasian female who underwent soft tissue dissection while enrolled in ProFibrix Study FC-004 and experienced an **SAE of pneumonia**. During the gastroenterostomy on 07-FEB-2013, the subject was treated with 1 (b) (4) gelatin sponge at the target bleeding site of fat.

On 09-FEB-2013, 2 days post treatment, the subject experienced an SAE of peritonitis (reference case PRO-0601-00162), which resulted in prolonged hospitalization. The subject had intestinal/gallbladder fluid leakage into her abdominal drain and the subject was returned to the operating room for re-exploration without a clear site of perforation identified. On 13-FEB-2013, the subject experienced an event of respiratory insufficiency

(PRO-0601-00164), which was considered life-threatening. A thoracic x-ray revealed pleural fluid. The subject was transferred to the intensive care unit and she was given a rebreathing mask, intensive respiratory kinesitherapy, and her pleural fluid was drained. On 14-FEB-2013, the subject was transferred back to the ward and the event was considered resolved.

On 16-FEB-2013, a thoracic X-ray revealed bilateral pneumonia. The subject continued on fluconazole (Diflucan) and piperacillin/tazobactam (Tazocin). On (b) (6), the subject's experienced labored breathing and agitation. Her family agreed to provide only comfort therapy for the subject. She was started on morphine and the palliative support team was called for her care. At (b) (6), the subject died due to pneumonia, while she was surrounded by her family. The Investigator clarified that the event of peritonitis was ongoing at the time of death.

No action was taken with (b) (4). The investigator assessed the pneumonia as CTCAE grade 5/death and not related to (b) (4). A possible alternate cause of the event was the surgical procedure. The Sponsor agrees with the Investigator's assessment.

Reviewer's comment: This death in the gelatin sponge control arm does not appear to be related to the study agent.

7. **PRO-0601-00174 – UK -- MYOCARDIAL INFARCTION --
FIBROCAPS/GELATIN**

Subject 300-019 is an 84-year-old Caucasian male who underwent vascular surgery while enrolled in ProFibrix Study FC-004 and experienced an **SAE of myocardial infarction**. During the abdominal aortic aneurysm (AAA) repair on 01-MAR-2013, the subject was treated with Raplixa 2 vials and 2 (b) (4) gelatin sponges.

(b) (6) post-operatively, the subject suffered a myocardial infarction while in the ICU and subsequently developed multi-organ failure. Prior to the subject's death on (b) (6), his vital signs included blood pressure (BP) 45/32 mmHg and pulse 86 times/min. Clinically significant laboratory results included urea 17.8 mmol/L (reference range 2.1-7.6), creatinine 499 umol/L (reference range 56-127), white blood cell count $19.6 \times 10^9/L$ (reference range 4.0-11.0), platelet count $118 \times 10^9/L$ (reference range 150-400), neutrophils $16.45 \times 10^9/L$ (reference range 2.0-7.7), creatine kinase 567 u/L (reference range 24-195), troponin T 54 ng/L, C-reactive protein 290.0 mg/L (reference range 0-8), glucose 10.5 mmol/L (reference range 3.6-6.0), prothrombin time 14.9 sec (reference range 10.0-13.5), and activated partial thromboplastin time (aPTT) 113.8 sec (reference range 26.0-37.0).

The subject's relevant medical and surgical history included hypertension, hypercholesterolemia, prostate cancer, and left nephrectomy. Relevant concomitant medications included simvastatin, amlodipine, finasteride, losartan, dalteparin, heparin, and paracetamol.

The subject's death certificate listed the primary causes of death as myocardial infarction and ischaemic heart disease.

No action was taken with Raplixa or (b) (4). The investigator assessed the cardiac event as CTCAE grade 5/death and not related to Raplixa and (b) (4). A possible alternate cause of the event was the surgical procedure and the underlying cardiac disease. The Sponsor agrees with the Investigator's assessment.

Reviewer's comment: This death in the Raplixa + gelatin sponge test arm does not appear to be related to the study agent.

8. **PRO-0601-00180 – NETHERLANDS -- BOWEL ISCHEMIA -- GELATIN SPONGE ALONE**

Subject 204-007 is a 66-year-old Caucasian female who underwent vascular surgery while enrolled in ProFibrix Study FC-004 and experienced an **SAE of bowel ischaemia**. During the surgery on 21-FEB-2013, the subject was treated with 1 (b) (4) gelatin sponge.

On 12-MAR-2013, 19 days post treatment, the subject had diarrhea with blood. The subject's C-reactive protein (CRP) was 238 mg/L (N: 0-9). A sigmoidoscopy confirmed bowel ischaemia and stenting of the arteria mesenterica superior was not possible. On 13-MAR-2013, a laparoscopy revealed ischaemia of the total intestinal tract. Sepsis occurred due to the bowel ischaemia. The event had a fatal outcome as there were no therapeutic options available. The subject was given palliative therapy with morphine and haloperidol; all other medications were stopped and the subject's tube was removed. On (b) (6), the subject died due to the event of bowel ischaemia, followed by sepsis. A death certificate was not available and an autopsy was not performed.

The subject's relevant medical and surgical history includes chronic obstructive pulmonary disease (COPD). Relevant concomitant medications taken at the onset of the SAE included morphine, prednisolone, and haloperidol. Previously reported SAEs for this subject include pulmonary insufficiency on 02-MAR-2013 (reference case PRO-0601-00175).

No action was taken with (b) (4). The Investigator assessed the bowel ischaemia followed by sepsis as CTCAE grade 5/death and not related to (b) (4). The event did not involve the site of treatment with the investigational product. A possible alternate cause of the event was the surgical procedure. The Sponsor agrees with the Investigator's assessment.

Reviewer's comment: This death in the gelatin sponge control arm does not appear to be related to the study agent.

9. **PRO-0601-00184 – UK -- RUPTURE THORACIC AORTIC ANEURYSM -- FIBROCAPS/GELATIN**

Subject 307-003 is a 68-year-old Caucasian male who underwent vascular surgery while enrolled in ProFibrix Study FC-004 and experienced an **SAE of rupture thoracic aortic aneurysm**. During the carotid subclavian bypass on 06-MAR-2013, the subject was treated with Raplixa 1 vial and 1 (b) (4) gelatin sponge.

On 11-MAR-2013, the subject was discharged from the hospital. He was fit and well upon discharge, and had no wound or bleeding issues during his hospitalization. On (b) (6) days after treatment, the subject was found dead at home having suffered the event of ruptured thoracic aortic aneurysm.

The subject's relevant medical and surgical history includes thoracoabdominal aneurysm. Relevant concomitant medications taken at onset of the SAE included perindopril, bendroflumethiazide, doxazosin, amlodipine, labetalol, paracetamol, and aspirin. There were no previously reported SAEs for this subject.

No action was taken with Raplixa or (b) (4). The Investigator assessed the rupture thoracic aortic aneurysm as CTCAE grade 5/death and not related to Raplixa and (b) (4) since the rupture occurred at a site distant from the treated site. A possible alternate cause of the event was the subject's medical history. The Sponsor agrees with the Investigator's assessment.

Reviewer's comment: This death in the Raplixa + gelatin sponge test arm does not appear to be related to the study agent.

10. **PRO-0601-00185 – UK -- HOSPITAL ACQUIRED PNEUMONIA -- FIBROCAPS/GELATIN**

Subject 303-004 is a 72-year-old Caucasian male who underwent vascular surgery while enrolled in ProFibrix Study FC-004 and experienced an **SAE of hospital acquired pneumonia**. During the surgery on 05-FEB-2013, the subject was treated with Raplixa 1 vial and 2 (b) (4) gelatin sponges.

On 19-FEB-2013, 14 days post-treatment, the subject presented with a two day history of shortness of breath and increased confusion. A chest infection and exacerbation of chronic obstructive pulmonary disease (COPD) was suspected, so the subject was started on intravenous antibiotics and steroids. The subject was also noted to have dysphagia and aspiration was suspected. A peripherally inserted central catheter (PICC) line was placed and total parental nutrition (TPN) was started on 01-MAR-2013. The subject continued to generally deteriorate; he was unable to clear secretions and was fatigued. End of life care was commenced and the subject died on (b) (6). An autopsy was performed; however, results were not reported.

The subject's relevant medical and surgical history includes chronic obstructive airways disease (COAD) and ischemic heart disease (IHD). No concomitant medications were reported. There were no previously reported SAEs for this subject.

No action was taken with Raplixa or (b) (4). The Investigator assessed the hospital acquired pneumonia as CTCAE grade 5/death and not related to Raplixa and (b) (4). The event did not involve the site of treatment with the investigational product. A possible alternate cause of the event was the subject's medical history of COAD and IHD. The Sponsor agrees with the Investigator's assessment.

Reviewer's comment: This death in the Raplixa + gelatin sponge test arm does not appear to be related to the study agent.

11. PRO-0601-00207* -- BELGIUM -- LIVER FAILURE/Euthanasia -- GELATIN SPONGE ALONE

Subject 105-017 is a 72-year-old Caucasian male who underwent hepatic resection while enrolled in ProFibrix Study FC-004 and experienced an SAE of euthanasia following prolonged hospitalization following cardiac and liver failure. During the surgery on 30-NOV-2012, the subject was treated with 1 (b) (4) gelatin sponge.

On 02-JAN-2013, 33 days post-treatment, the subject developed liver failure and was admitted to an outside hospital. It was noted that the liver failure was due to partial portal vein thrombosis and cardiac failure. On (b) (6) days post treatment and after the subject was off study, the subject died due to euthanasia and the event had a fatal outcome. A death certificate was not available and an autopsy was not performed.

Since the subject was admitted to an outside hospital, there were no signs or symptoms of the event available and no laboratory or diagnostic tests results available. The subject remained hospitalized until his death.

The subject's relevant medical history included chronic liver disease and ischemic heart disease (See Cases PRO-0601-00207, PRO-0601-00106 and PRO-0601-00168).

No action was taken with (b) (4). The investigator assessed the liver failure as CTCAE grade 5/death and not related to (b) (4). The Sponsor agrees with the Investigator's assessment.

**Euthanasia occurred after the study follow-up period, so is not an on-study death*

Reviewer's comment: This death in the gelatin sponge control arm does not appear to be related to the study agent.

6.1.12.4 Nonfatal Serious Adverse Events

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Study FC-004: Serious Adverse Events by Treatment and Surgery Type

		Hepatic Resection				Soft Tissue Dissection				Spinal Surgery				Vascular Surgery			
		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge	
		AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects
ALL Serious AEs		26	20	12	8	43	24	13	7	17	12	2	2	33	25	18	12
Blood and lymphatic system disorders		1	1							2	2			2	2	1	1
Blood and lymphatic system disorders	Anaemia	1	1							2	2			1	1		
Blood and lymphatic system disorders	Leukocytosis													1	1		
Blood and lymphatic system disorders	Thrombocytopenia															1	1
Cardiac disorders		2	2	2	1	2	1							4	4		
Cardiac disorders	Atrial fibrillation	1	1			1	1										
Cardiac disorders	Cardiac arrest	1	1											1	1		
Cardiac disorders	Cardiac failure			1	1												
Cardiac disorders	Myocardial infarction			1	1									1	1		
Cardiac disorders	Myocardial ischaemia					1	1							1	1		
Cardiac disorders	Silent myocardial infarction													1	1		
Gastrointestinal disorders		2	2	3	3	8	6	1	1	1	1			3	3	3	3
Gastrointestinal disorders	Abdominal pain lower	1	1														
Gastrointestinal disorders	Anal haemorrhage					2	1										
Gastrointestinal disorders	Gastric perforation					1	1										

		Hepatic Resection		Soft Tissue Dissection		Spinal Surgery		Vascular Surgery	
		F-caps + Sponge		F-caps + Sponge		F-caps + Sponge		F-caps + Sponge	
		AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects
Gastrointestinal disorders	Gastroduodenal haemorrhage				1		1		
Gastrointestinal disorders	Gastrointestinal haemorrhage				1	1	1		
Gastrointestinal disorders	Ileus			1	1			2	2
Gastrointestinal disorders	Ileus paralytic				1		1		
Gastrointestinal disorders	Impaired gastric emptying			1	1		1		
Gastrointestinal disorders	Intestinal ischaemia								1
Gastrointestinal disorders	Localised intraabdominal fluid collection			1	1				
Gastrointestinal disorders	Pancreatitis acute							1	1
Gastrointestinal disorders	Small intestinal obstruction							1	1
Gastrointestinal disorders	Small intestinal ulcer haemorrhage	1	1						
General disorders and administration site conditions		1	1					2	2
General disorders and administration site conditions	Cardiac death							1	1
General disorders and administration site conditions	Chest pain								1

		Hepatic Resection				Soft Tissue Dissection				Spinal Surgery				Vascular Surgery			
		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge	
		AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects
General disorders and administration site conditions	Death									1	1						
General disorders and administration site conditions	Hernia obstructive															1	1
General disorders and administration site conditions	Malaise	1	1														
General disorders and administration site conditions	Pyrexia									1	1						
General disorders and administration site conditions	Unintentional medical device removal by patient					1	1										
Hepatobiliary disorders		1	1	1	1	1	1										
Hepatobiliary disorders	Gallbladder perforation					1	1										
Hepatobiliary disorders	Hepatic failure			1	1												
Hepatobiliary disorders	Hepatic function abnormal	1	1														
Infections and infestations		8	6	2	2	12	11	6	4	2	2			4	4	2	2
Infections and infestations	Abdominal abscess	2	2	1	1	2	2										
Infections and infestations	Abdominal sepsis					1	1										
Infections and infestations	Cellulitis													1	1		
Infections and infestations	Infectious peritonitis	1	1														
Infections and infestations	Liver abscess	1	1														

		Hepatic Resection				Soft Tissue Dissection				Spinal Surgery				Vascular Surgery			
		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge	
		AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects
Infections and infestations	Lower respiratory tract infection															1	1
Infections and infestations	Lung infection	1	1														
Infections and infestations	Osteomyelitis							1	1								
Infections and infestations	Peritonitis							1	1								
Infections and infestations	Pneumonia					2	2	1	1					2	2	1	1
Infections and infestations	Postoperative wound infection					3	3			1	1						
Infections and infestations	Psoas abscess							1	1								
Infections and infestations	Rectal abscess			1	1												
Infections and infestations	Sepsis	2	2			1	1										
Infections and infestations	Septic shock					1	1										
Infections and infestations	Subcutaneous abscess					1	1										
Infections and infestations	Subdiaphragmatic abscess	1	1														
Infections and infestations	Urinary tract infection							1	1								
Infections and infestations	Urosepsis									1	1						
Infections and infestations	Wound infection					1	1	1	1					1	1		
Injury, poisoning and procedural complications		7	7	3	2	7	5	1	1	4	4	1	1	8	7	2	2
Injury, poisoning and procedural complications	Anaesthetic complication									1	1						
Injury, poisoning and procedural	Anastomotic													1	1		

		Hepatic Resection				Soft Tissue Dissection				Spinal Surgery				Vascular Surgery			
		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge	
		AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects
complications	haemorrhage																
Injury, poisoning and procedural complications	Anastomotic leak					1	1							1	1		
Injury, poisoning and procedural complications	Arteriovenous fistula thrombosis													1	1		
Injury, poisoning and procedural complications	Fall									1	1						
Injury, poisoning and procedural complications	Gastrointestinal anastomotic leak			1	1	3	3										
Injury, poisoning and procedural complications	Gastrointestinal disorder postoperative					1	1										
Injury, poisoning and procedural complications	Pancreatic leak					1	1										
Injury, poisoning and procedural complications	Post procedural bile leak	2	2	2	2												
Injury, poisoning and procedural complications	Post procedural haematoma	1	1			1	1										
Injury, poisoning and procedural complications	Post procedural haemorrhage	1	1											1	1		
Injury, poisoning and procedural complications	Postoperative fever	1	1														
Injury, poisoning and procedural complications	Procedural pain							1	1								
Injury, poisoning and procedural	Pseudomeningocele									1	1						

		Hepatic Resection				Soft Tissue Dissection				Spinal Surgery				Vascular Surgery			
		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge	
		AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects
complications																	
Injury, poisoning and procedural complications	Seroma									1	1	1	1	1	1	1	1
Injury, poisoning and procedural complications	Small-for-size liver syndrome	2	2														
Injury, poisoning and procedural complications	Vascular graft thrombosis													2	1	1	1
Injury, poisoning and procedural complications	Vascular pseudoaneurysm													1	1		
Investigations						1	1	1	1								
Investigations	Hepatitis C antibody positive					1	1	1	1								
Metabolism and nutrition disorders						3	3	1	1					3	2		
Metabolism and nutrition disorders	Dehydration					2	2										
Metabolism and nutrition disorders	Electrolyte imbalance													1	1		
Metabolism and nutrition disorders	Hyperglycaemia					1	1										
Metabolism and nutrition disorders	Hypovolaemia							1	1					2	2		
Musculoskeletal and connective tissue disorders										2	2	1	1				
Musculoskeletal and connective tissue disorders	Back pain									1	1	1	1				
Musculoskeletal and connective tissue disorders	Intervertebral disc protrusion									1	1						

		Hepatic Resection				Soft Tissue Dissection				Spinal Surgery				Vascular Surgery			
		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge	
		AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						1	1			1	1						
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Meningioma									1	1						
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Small intestine carcinoma					1	1										
Nervous system disorders						1	1			1	1			1	1		
Nervous system disorders	Cerebral infarction					1	1										
Nervous system disorders	Paraplegia									1	1						
Nervous system disorders	Transient ischaemic attack													1	1		
Psychiatric disorders										1	1					1	1
Psychiatric disorders	Delirium															1	1
Psychiatric disorders	Mental status changes									1	1						
Renal and urinary disorders														1	1		
Renal and urinary disorders	Renal failure acute													1	1		
Respiratory, thoracic and mediastinal disorders		3	2	1	1	4	3	2	2	1	1					4	4
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome					2	2										
Respiratory, thoracic and mediastinal disorders	Chylothorax					1	1										
Respiratory, thoracic and mediastinal	Dyspnoea															1	1

		Hepatic Resection				Soft Tissue Dissection				Spinal Surgery				Vascular Surgery			
		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge		F-caps + Sponge		Sponge	
		AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects	AEs	Subjects
disorders																	
Respiratory, thoracic and mediastinal disorders	Hypercapnia	1	1														
Respiratory, thoracic and mediastinal disorders	Pleural effusion	1	1														
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	1	1							1	1					1	1
Respiratory, thoracic and mediastinal disorders	Pulmonary oedema			1	1												
Respiratory, thoracic and mediastinal disorders	Respiratory depression					1	1	1	1								
Respiratory, thoracic and mediastinal disorders	Respiratory failure							1	1							2	2
Vascular disorders		1	1			2	2	1	1					6	6	3	2
Vascular disorders	Aortic aneurysm rupture													1	1		
Vascular disorders	Arterial haemorrhage							1	1								
Vascular disorders	Deep vein thrombosis					1	1									1	1
Vascular disorders	Hypotension					1	1										
Vascular disorders	Lymphorrhoea													3	3		
Vascular disorders	Peripheral ischaemia													2	2	2	1
Vascular disorders	Vena cava thrombosis	1	1														

6.1.12.5 Adverse Events of Special Interest (AESI)

Insert text here

There were two subjects with treatment-emergent positive hepatitis C antibody test results. Subject 402-019, 55 y.o. African-American male, (Raplixia + sponge arm) had a positive result on November 9, 2012. Subject 402-003, 47 y.o. white male, (sponge alone arm) had a positive result on September 29, 2012. Both subjects were enrolled at Washington University, St. Louis MO. Both subjects were undergoing amputations (below-the-knee or partial foot) and were enrolled in the soft tissue dissection category of study FC-004.

Reviewer's comment: These two Hepatitis C seroconversions are most likely community-acquired, because the plasma-derived components are licensed products that have undergone viral safety validation procedures during manufacturing, and there are no additional cases that could implicate the this product, or the licensed products from which it is made.

6.1.12.6 Clinical Test Results

Insert text here

Number of Subjects with Abnormally High or Low Lab Values after Treatment (Day 2 or Day 29) by Surgery Type

Lab Test	Hepatic Resection				Soft Tissue Dissection				Spinal Surgery				Vascular Surgery			
	HIGH		LOW		HIGH		LOW		HIGH		LOW		HIGH		LOW	
	F + G N=1 20	G N=6 1	F + G N=1 20	G N=6 1	F + G N=1 22	G N=59	F + G N=1 22	G N=59	F + G N=1 22	G N=61	F + G N=1 22	G N=61	F + G N=1 18	G N=58	F + G N=1 18	G N=58
Activated Partial Thromboplastin Time	34 (28%)	18 (30%)	21 (18%)	8 (13%)	36 (30%)	11 (19%)	20 (16%)	6 (10%)	3 (2%)	2 (3%)	20 (16%)	7 (11%)	24 (20%)	18 (31%)	11 (9%)	4 (7%)
Alanine Amino-transferase	106 (88%)	54 (89%)	0 (0%)	0 (0%)	16 (13%)	2 (3%)	1 (1%)	0 (0%)	13 (11%)	8 (13%)	4 (3%)	1 (2%)	6 (5%)	3 (5%)	1 (1%)	2 (3%)
Albumin	0 (0%)	0 (0%)	78 (65%)	39 (64%)	0 (0%)	0 (0%)	49 (40%)	22 (37%)	0 (0%)	0 (0%)	19 (16%)	7 (11%)	0 (0%)	0 (0%)	63 (53%)	36 (62%)
Aspartate Aminotransferase	114 (95%)	57 (93%)	0 (0%)	0 (0%)	24 (20%)	8 (14%)	1 (1%)	1 (2%)	22 (18%)	14 (23%)	1 (1%)	0 (0%)	23 (19%)	14 (24%)	1 (1%)	0 (0%)
Basophils	2	1 (2%)	10	4 (7%)	5	1 (2%)	11	7 (12)	9	6 (10)	8	3 (5%)	3	1 (2%)	3	1 (2%)

Lab Test	Hepatic Resection				Soft Tissue Dissection				Spinal Surgery				Vascular Surgery			
	HIGH		LOW		HIGH		LOW		HIGH		LOW		HIGH		LOW	
	F + G N=1 20	G N=6 1	F + G N=1 20	G N=6 1	F + G N=1 22	G N=59	F + G N=1 22	G N=59	F + G N=1 22	G N=61	F + G N=1 22	G N=61	F + G N=1 18	G N=58	F + G N=1 18	G N=58
	(2%))	(8%))	(4%))	(9%))	(7%))	(7%))	(3%))	(3%))
Basophils/ Leukocytes	7 (6%)	3 (5%))	0 (0%)	0 (0%))	1 (1%)	1 (2%))	0 (0%)	0 (0%))	7 (6%)	4 (7%))	6 (5%)	3 (5%))	12 (10%)	2 (3%))	0 (0%)	0 (0%))
Bilirubin	73 (61%)	26 (43%)	0 (0%)	0 (0%))	7 (6%)	3 (5%))	7 (6%)	3 (5%))	7 (6%)	1 (2%))	2 (2%)	1 (2%))	13 (11%)	1 (2%))	6 (5%)	1 (2%))
Blood Urea Nitrogen	19 (16%)	5 (8%))	11 (9%)	5 (8%))	4 (3%)	4 (7%))	16 (13%)	8 (14%)	8 (7%)	5 (8%))	11 (9%)	6 (10%)	32 (27%)	14 (24%)	8 (7%)	4 (7%))
Creatinine	23 (19%)	3 (5%))	25 (21%)	14 (23%)	5 (4%)	3 (5%))	32 (26%)	13 (22%)	6 (5%)	3 (5%))	4 (3%)	3 (5%))	40 (34%)	21 (36%)	12 (10%)	11 (19%)
Eosinophils	27 (23%)	16 (26%)	22 (18%)	11 (18%)	17 (14%)	4 (7%))	9 (7%)	4 (7%))	9 (7%)	3 (5%))	30 (25%)	14 (23%)	9 (8%)	6 (10%)	24 (20%)	13 (22%)
Eosinophils/	19	10	30	13	7	3	3	0	9	5	25	8	19	10	59	34

Lab Test	Hepatic Resection				Soft Tissue Dissection				Spinal Surgery				Vascular Surgery			
	HIGH		LOW		HIGH		LOW		HIGH		LOW		HIGH		LOW	
	F + G N=1 20	G N=6 1	F + G N=1 20	G N=6 1	F + G N=1 22	G N=59	F + G N=1 22	G N=59	F + G N=1 22	G N=61	F + G N=1 22	G N=61	F + G N=1 18	G N=58	F + G N=1 18	G N=58
Leukocytes	(16 %)	(16 %)	(25 %)	(21 %)	(6%)	(5%)	(2%)	(0%)	(7%)	(8%)	(20 %)	(13 %)	(16 %)	(17 %)	(50 %)	(59 %)
Erythrocytes	0 (0%)	1 (2%)	101 (84 %)	52 (85 %)	0 (0%)	0 (0%)	101 (83 %)	52 (88 %)	2 (2%)	2 (3%)	60 (49 %)	28 (46 %)	1 (1%)	1 (2%)	102 (86 %)	44 (76 %)
Glucose	65 (54 %)	38 (62 %)	0 (0%)	0 (0%)	42 (34 %)	16 (27 %)	1 (1%)	1 (2%)	77 (63 %)	37 (61 %)	1 (1%)	0 (0%)	69 (58 %)	34 (59 %)	2 (2%)	0 (0%)
Hematocrit	0 (0%)	1 (2%)	104 (87 %)	55 (90 %)	1 (1%)	1 (2%)	109 (89 %)	54 (92 %)	3 (2%)	0 (0%)	55 (45 %)	22 (36 %)	1 (1%)	1 (2%)	100 (85 %)	45 (78 %)
Hemoglobin	0 (0%)	0 (0%)	111 (93 %)	56 (92 %)	0 (0%)	0 (0%)	110 (90 %)	54 (92 %)	1 (1%)	1 (2%)	59 (48 %)	22 (36 %)	0 (0%)	0 (0%)	96 (81 %)	48 (83 %)
Leukocytes	86 (72 %)	39 (64 %)	7 (6%)	1 (2%)	43 (35 %)	14 (24 %)	9 (7%)	6 (10 %)	52 (43 %)	28 (46 %)	1 (1%)	1 (2%)	55 (47 %)	30 (52 %)	1 (1%)	0 (0%)

Lab Test	Hepatic Resection				Soft Tissue Dissection				Spinal Surgery				Vascular Surgery			
	HIGH		LOW		HIGH		LOW		HIGH		LOW		HIGH		LOW	
	F + G N=1 20	G N=6 1	F + G N=1 20	G N=6 1	F + G N=1 22	G N=59	F + G N=1 22	G N=59	F + G N=1 22	G N=61	F + G N=1 22	G N=61	F + G N=1 18	G N=58	F + G N=1 18	G N=58
Lymphocytes	2 (2%)	0 (0%)	70 (58%)	30 (49%)	4 (3%)	0 (0%)	49 (40%)	27 (46%)	5 (4%)	0 (0%)	30 (25%)	19 (31%)	0 (0%)	2 (3%)	33 (28%)	21 (36%)
Lymphocytes/ Leukocytes	3 (3%)	1 (2%)	103 (86%)	52 (85%)	14 (11%)	7 (12%)	54 (44%)	32 (54%)	5 (4%)	0 (0%)	78 (64%)	39 (64%)	0 (0%)	2 (3%)	89 (75%)	48 (83%)
Monocytes	54 (45%)	30 (49%)	4 (3%)	2 (3%)	29 (24%)	5 (8%)	0 (0%)	0 (0%)	36 (30%)	17 (28%)	9 (7%)	6 (10%)	50 (42%)	26 (45%)	2 (2%)	2 (3%)
Monocytes/ Leukocytes	46 (38%)	24 (39%)	6 (5%)	1 (2%)	19 (16%)	5 (8%)	5 (4%)	0 (0%)	17 (14%)	7 (11%)	15 (12%)	12 (20%)	89 (75%)	42 (72%)	1 (1%)	0 (0%)
Neutrophils	75 (63%)	41 (67%)	6 (5%)	1 (2%)	49 (40%)	19 (32%)	5 (4%)	7 (12%)	68 (56%)	33 (54%)	2 (2%)	0 (0%)	54 (46%)	34 (59%)	1 (1%)	0 (0%)
Neutrophils/ Leukocytes	92 (77)	42 (69)	6 (5%)	2 (3%)	57 (47)	32 (54)	16 (13)	8 (14)	75 (61)	36 (59)	6 (5%)	1 (2%)	81 (69)	47 (81)	2 (2%)	3 (5%)

Lab Test	Hepatic Resection				Soft Tissue Dissection				Spinal Surgery				Vascular Surgery			
	HIGH		LOW		HIGH		LOW		HIGH		LOW		HIGH		LOW	
	F + G N=1 20	G N=6 1	F + G N=1 20	G N=6 1	F + G N=1 22	G N=59	F + G N=1 22	G N=59	F + G N=1 22	G N=61	F + G N=1 22	G N=61	F + G N=1 18	G N=58	F + G N=1 18	G N=58
	%)	%))	%)	%)	%)	%)	%)	%))	%)	%))
Platelet	16 (13 %)	11 (18 %)	40 (33 %)	25 (41 %)	17 (14 %)	3 (5%)	12 (10 %)	4 (7%)	5 (4%)	4 (7%)	17 (14 %)	11 (18 %)	16 (14 %)	8 (14 %)	33 (28 %)	13 (22 %)
Potassium	6 (5%)	3 (5%)	4 (3%)	2 (3%)	5 (4%)	3 (5%)	3 (2%)	5 (8%)	1 (1%)	2 (3%)	4 (3%)	1 (2%)	6 (5%)	6 (10 %)	3 (3%)	3 (5%)
Prothrombin Intl. Normalized Ratio	63 (53 %)	28 (46 %)	39 (33 %)	21 (34 %)	30 (25 %)	9 (15 %)	7 (6%)	2 (3%)	8 (7%)	1 (2%)	23 (19 %)	11 (18 %)	21 (18 %)	12 (21 %)	36 (31 %)	19 (33 %)
Prothrombin Time	63 (53 %)	29 (48 %)	19 (16 %)	10 (16 %)	29 (24 %)	9 (15 %)	28 (23 %)	16 (27 %)	30 (25 %)	12 (20 %)	3 (2%)	1 (2%)	53 (45 %)	25 (43 %)	5 (4%)	3 (5%)
Sodium	3 (3%)	1 (2%)	20 (17 %)	6 (10 %)	4 (3%)	3 (5%)	7 (6%)	4 (7%)	0 (0%)	2 (3%)	6 (5%)	5 (8%)	3 (3%)	1 (2%)	21 (18 %)	8 (14 %)

Reviewer's Comment: Notable differences between the test arm and control arm are highlighted in yellow. The three largest differences are discussed as follows:

1. Creatinine (day 2) in hepatic resection surgery was higher in the test group (23 subjects) than in the control day-2 group (3 subjects). Eleven of the 23 subjects in the test group also had high creatinine levels at baseline, whereas all three subjects in the control group had high creatinine levels at baseline. Therefore, the change from baseline to day 2 for abnormal elevation of the creatinine was 12 subjects in the test group, and zero subjects in the control group. The creatinine elevations are borderline, and this effect is not seen across all surgery categories. This may be a statistical fluke.
2. Alanine Aminotransferase (day 2) in soft tissue dissection surgery was higher in the test group (16 subjects) than in the control day-2 group (2 subjects). Two of the 16 subjects in the test group also had high Alanine Aminotransferase levels at baseline, one subject in the control group had high Alanine Aminotransferase levels at baseline. Therefore, the change from baseline to day 2 for abnormal elevation of the Alanine Aminotransferase was 14 subjects in the test group, and one subject in the control group. Only 4 of the 14 subjects have AAT elevations 3-fold higher than the ULN. The AAT elevations are not seen across all surgery categories. The reason for the imbalance in AAT elevations between test and control groups in the soft tissue dissection surgery subgroup is not clear, but probably is not from the test agent.
3. Bilirubin (day 2) in vascular surgery was higher in the test group (13 subjects) than in the control group (1 subjects). Two of the 13 subjects in the test group also had high bilirubin levels at baseline, whereas no subject in the control day-2 group had high bilirubin levels at baseline. Therefore, the change from baseline to day 2 for abnormal elevation of the bilirubin was 11 subjects in the test group, and one subject in the control group. The reason for the imbalance in AAT elevations between test and control groups in the vascular surgery subgroup is not clear, but probably is not from the test agent.

6.1.12.7 Dropouts and/or Discontinuations

Insert text here

See [6.1.10.1.3](#) “Subject Disposition”. Nine-six percent (96%) of subjects completed the day 29 safety assessments. Fifteen (15) of the 24 subjects who failed to complete the day 29 safety assessments were in the Raplixa arms. Reasons for completion for these 15 Raplixa subjects were death (8 subjects), lost to follow-up (6 subjects), and withdrawal of consent (1 subject). Reasons for completion for the 9 control gelatin sponge subjects were death (1 subject), lost to follow-up (4 subjects), withdrawal of consent (1 subject), failed to return for final visit (1 subject), and non-compliance (1 subject). One subject in the control gelatin sponge group died after the day 29 safety assessment (died day 61), but is included in the dropout/discontinuation number by the applicant.

6.1.13 Study Summary and Conclusions

Insert text here

Study FC-004 enrolled approximately 120 subjects into the Raplixa + gelatin sponge test arms in 4 surgery types: soft tissue dissection surgery, hepatic surgery, vascular surgery, and spinal surgery. The primary endpoint was the proportion of subjects achieving hemostasis within 5 minutes after the study agent was applied to a target bleeding site. Study FC-004 met its primary endpoint for all four surgery types, with an acceptable safety profile.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

Insert text here

9.1.1 Human Reproduction and Pregnancy Data

Insert text here

There were no reproduction or pregnancy studies.

9.1.2 Use During Lactation

Insert text here

There were no studies on the effects on lactation.

9.1.3 Pediatric Use and PREA Considerations

Insert text here

Study FC-004 only enrolled adults. Pediatric studies are deferred, as approved at the March 5, 2015, meeting of the Pediatric Research Committee (PeRC).

9.1.4 Immunocompromised Patients

Insert text here

There were no studies in immunocompromised patients.

9.1.5 Geriatric Use

Insert text here

Results were similar in the geriatric and non-geriatric groups, as shown in the following table)

Study FC-004: Time-to-Hemostasis (TTH) by Age Group

Age Group		Raplixa + gelatin sponge	gelatin sponge
		N = 89	N = 46
< 65 years	Median TTH	1.0	2.5
	Mean TTH	1.2	2.8
		N = 33	N = 15
≥ 65 years	Median TTH	1.0	2.0
	Mean TTH	1.2	2.4

Source: STN125523/0 Study FC-004 Clinical Report Table 21.2 page 161

10. CONCLUSIONS

Insert text here

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Insert text here

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Surgery creates large areas of bleeding that must be addressed before surgical closure. 	<ul style="list-style-type: none"> Raplixa has demonstrated safety and efficacy for use as an adjunct to hemostasis in four types or surgery: soft tissue dissection, vascular, hepatic, and spinal surgery.
Current Treatment Options	<ul style="list-style-type: none"> There are several fibrin sealant products available for use as an adjunct to hemostasis in various surgical settings. 	<ul style="list-style-type: none"> There is no unmet medical need because the clinical studies have not demonstrated a more significant clinical benefit from the use of Raplixa compared to that of other adjunct to hemostasis products.
Clinical Benefit	<ul style="list-style-type: none"> The indication for use as an adjunct to hemostasis in adult surgery is supported by the results of the IND study FC-004 	<ul style="list-style-type: none"> Raplixa has demonstrated clinical benefit for use as an adjunct to hemostasis in adult surgery, according to the surrogate endpoint

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	<p>(845 subjects, 566 randomized to Raplixa).</p> <ul style="list-style-type: none"> Fibrin sealant products, when used as adjuncts to hemostasis, have not been able to demonstrate a traditional clinical benefit based on mortality or morbidity endpoints. For this reason, CBER decided to accept the surrogate endpoints of time-to-hemostasis or percent of subjects achieving hemostasis at a defined time point as acceptable primary endpoints for licensure. Perhaps the major benefit from the licensure of these products has been the decreased use of the surgical practice of “home brew” fibrin sealants made from fresh frozen plasma and licensed thrombin. These “home brew” products are thought to have a greater risk compared licensed fibrin sealant products that are validated to be virally safe. 	<p>time-to-hemostasis, censored at 5 minutes.</p>
Risk	<ul style="list-style-type: none"> Raplixa contains human thrombin and human fibrinogen, and therefore, there is a theoretical risk for perturbation of the coagulation system. Administration by the Raplixaspray device carries a potential risk of air embolism if used 	<ul style="list-style-type: none"> All the evidence indicates that the risk associated with the use of Raplixa as an adjunct to hemostasis is minor. There is no evidence of an increased risk for thrombogenicity or increased immunogenicity, however, continued surveillance for

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	inappropriately	these events is advisable.
Risk Management	<ul style="list-style-type: none">• Potential for perturbation of the coagulation system (e.g. thrombogenicity)• Potential for air embolism	<ul style="list-style-type: none">• Routine monitoring could detect a coagulopathy problem, if such exists.• Labeling and routine monitoring could prevent or detect the potential air embolism problem. Given the life-threatening nature of air or gas embolism, the sponsor will conduct targeted follow-up of events which may be indicative of air or gas embolism with a questionnaire. Additionally, the sponsor will attempt examination of the Fibrospray device used in such incidents for possible defects, as well as review of the AE and product complaints for Fibrospray devices with the same lot number.

11.2 Risk-Benefit Summary and Assessment

Insert text here

The benefit-risk assessment is favorable.

11.3 Discussion of Regulatory Options

Insert text here

There are no clinical post-marketing requirements or requirements other than the requirement for conducting deferred pediatric studies.

11.4 Recommendations on Regulatory Actions

Insert text here

I recommend that STN125523/0 be approved.

11.5 Labeling Review and Recommendations

Insert text here

The approved package insert is attached.

11.6 Recommendations on Postmarketing Actions

Insert text here

A deferred pediatric study is planned. No other post-marketing commitments or requirements are recommended.

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