22 January 2015
EMA/CHMP/747327/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Raplixa

International non-proprietary name: human fibrinogen / human thrombin

Procedure No. EMEA/H/C/002807/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Raplixa
Applicant:	ProFibrix BV Darwinweg 24 2333 CR Leiden NETHERLANDS
Active substance:	human fibrinogen / human thrombin
International Non-proprietary Name:	human fibrinogen / human thrombin
Pharmaco-therapeutic group (ATC Code):	local haemostatics, other haemostatics (B02BC30)
Therapeutic indication:	Supportive treatment where standard surgical techniques are insufficient for improvement of haemostasis. Raplixa must be used in combination with an approved gelatin sponge. Raplixa is indicated in adults over 18 years of age.
Pharmaceutical form:	Sealant powder
Strength:	79 mg/g / 726 IU/g
Route of administration:	Epilesional use
Packaging:	vial (glass)
Package size:	1 vial

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List of abbreviations

aPTT	Activated partial thromboplastin time
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BAC2	Biological Active Component
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPK	Creatine kinase
CT	Computed tomography
DVT	Deep venous thrombosis
ECG	Electrocardiogram
EF	Ejection fraction
FC	Fibrocaps (Raplixa)
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal disease
ICH	International Conference on Harmonization
ICU	Intensive care unit
ITT	Intent to treat
LLL	Left lower lobe
m	Million
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRSA	Methicillin-resistant *Staphylococcus aureus*
NG	Nasogastric
PCA	Patient controlled anesthesia
PICC	Peripherally inserted central venous catheter
PP	Per protocol
PREA	Pediatric Research Equity Act
PT	Prothrombin time
PTFE	Polytetrafluoroethylene
PTT	Partial thromboplastin time
RBC	Red blood cell
SAE	Serious adverse event
SICU	Surgical intensive care unit
SUSAR	Suspected unexpected serious adverse reaction
TBS	Target bleeding site
TnBP	tri-n-butyl phosphate
TPN	Total parenteral nutrition
TTH	Time to hemostasis
Triton X-100	octyl phenyl-polyethylene glycol ether
VAC	Vacuum assisted closure
VQ	Ventilation-perfusion
WBC	White blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant ProFibrix BV submitted on 28 October 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Raplixa, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 December 2012. The eligibility to the centralised procedure under Article 3(2) (b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The applicant applied for the following indication:

"Supportive treatment where standard surgical techniques are insufficient:

Fibrocaps (human plasma-derived fibrinogen and thrombin) is used as an adjunct to haemostasis in patients undergoing surgical procedures when control of mild or moderate bleeding by conventional surgical techniques including suture, ligature and cautery is ineffective or impractical and as suture support for haemostasis in vascular surgery".

The indication granted by the CHMP is:

"Supportive treatment where standard surgical techniques are insufficient for improvement of haemostasis. Raplixa must be used in combination with an approved gelatin sponge".

Raplixa is indicated in adults over 18 years of age.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that human fibrinogen / human thrombin was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0157/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0157/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 24 September 2009 and 19 July 2012. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturers of the active substance

CSL Behring GmbH
Emil-von-Behring-Straße 76
35041 Marburg
Germany

CSL Behring GmbH
Goerzhaeuser Hof 1
35041 Marburg (Stadtteil Michelbach)
Germany

CSL Behring L.L.C.
50 Armour Road,
Bradley, IL 60915
United States

Manufacturer responsible for batch release

Nova Laboratories Limited
Martin House, Gloucester Crescent, Wigston,
Leicester, Leicestershire, LE18 4YL,
United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Greg Markey Co-Rapporteur: Piotr Fiedor

- The application was received by the EMA on 28 October 2013.

- The procedure started on 20 November 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 February 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 6 February 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 6 March 2014.
- During the meeting on 20 March 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 March 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 September 2014.
- The summary report of the inspection carried out at the following site: " commercial manufacturing site" on 16/10/2014 was issued on 20/11/2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 24 October 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 6 November 2014.
- During the CHMP meeting on 20 November 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 December 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 January 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 9 January 2015.
- During the meeting on 22 January 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Raplixa.

2. Scientific discussion

2.1. Introduction

Haemostasis is an essential and often challenging part of surgical procedures. As first line, surgeons need to apply conventional haemostatic methods i.e. meticulous surgical techniques such as sutures, ligatures, or cautery. Topical haemostatic agents (gelatine, collagen, or oxidized regenerated cellulose) are widely used as an adjunct to these methods.

Haemostatic agents fall into three broad categories: Mechanical haemostatic agents, such as gauze pads, collagen/gelatin sponges, and cellulose sponges; Active haemostatic agents such as topical thrombins (bovine/human/recombinant) - these agents are approved in the US as "general aids/adjuncts to haemostasis" but are not yet approved in the EU; Active haemostatic agents like fibrin sealants and "flow-ables" (i.e throbin+gelatins). Fibrin sealants consisting of the biological components human fibrinogen and human thrombin directly apply a fibrin layer on the tissue, either by dripping or by spraying. Individual parameters like the anatomic conditions, bleeding patterns, or tissue properties affect the choice of the appropriate haemostatic

method or product. The availability of a further haemostatic option for the adjunctive treatment of surgical bleeding could provide clinically relevant benefit in the surgical setting.

Raplixa is a human plasma–derived fibrin sealant consisting of fibrinogen and thrombin powder, which is supplied as a single strength 79 mg human fibrinogen and 726 IU human thrombin per gram of powder.

Raplixa was originally proposed for the indication of "Supportive treatment where standard surgical techniques are insufficient: Fibrocaps (human plasma-derived fibrinogen and thrombin) is used as an adjunct to haemostasis in patients undergoing surgical procedures when control of mild or moderate bleeding by conventional surgical techniques including suture, ligature and cautery is ineffective or impractical and as suture support for haemostasis in vascular surgery". The indication granted by the CHMP is: Supportive treatment where standard surgical techniques are insufficient for improvement of haemostasis. Raplixa must be used in combination with an approved gelatin sponge. Raplixa is indicated in adults over 18 years of age.

Raplixa is intended for epilesional use only. Application of the product must be individualised by the treating surgeon. It is proposed that the required dose of Raplixa based on the size of the bleeding surface area to be treated is as in table 1:

Table 1: Required Dose of Raplixa

Maximum Surface Area Direct Application from Vial	**Maximum Surface Area Application Using RaplixaSpray**	**Raplixa Package Size**
25 cm^2	50 cm^2	0.5 g
50 cm^2	100 cm^2	1.0 g

The need for paediatric studies has been deferred by the PDCO.

Formal CHMP scientific advice was provided on non-clinical and clinical aspects (EMEA/CPMP/SAWP/451467 and EMEA/CHMP/SAWP/572876).

2.2. Quality aspects

2.2.1. Introduction

Raplixa is supplied as a ready to use dry-powder formulation of a fibrin sealant which is a combination of two known active substances - human fibrinogen and human thrombin.

Raplixa dissolves readily on contact with aqueous fluids (e.g., blood) activating thrombin that enzymatically converts fibrinogen into fibrin monomers that aggregate to form a fibrin clot. The serine protease thrombin is a coagulation protein that has many effects in the coagulation cascade. It is the final proteolytic enzyme of the coagulation process and converts soluble fibrinogen into insoluble strands of fibrin, as well as catalyzing many other coagulation-related reactions. The thrombin also activates Factor XIII from the patient's blood into Factor XIIIa that crosslinks the fibrin monomers, which stabilize the clot.

2.2.2. Active Substance

Human Fibrinogen

General information

Fibrinogen is a soluble plasma glycoprotein with a molecular weight of approximately 340 kD and circulates in plasma as a precursor of fibrin. The native molecule is a homo-dimer, in which both subunits consist of three different polypeptide chains (Aα, Bβ, and γ). All three polypeptide chains of the subunits as well as the dimer are linked with disulfide bonds. The genes coding for the three different polypeptide chains of fibrinogen are located on the long arm of chromosome 4. The three pairs of polypeptide chains named Aα, Bβ, and γ are composed of 610, 461, and 411 amino acids, respectively. Each arm of the fibrinogen molecule contains single Aα, Bβ, and γ chains from each of the three pairs of polypeptide chains. The central domain is a dimeric structure in which both subunits contain the three amino terminals of the individual arms. The slightly thickened amino terminal ends of the Aα and Bβ chains represent fibrinopeptides A (FPA) and B (FPB), respectively, which are not present in fibrin. The dimeric halves of the central domain are held together by three of 11 disulfide bonds, the rest of which are located between the Aα and Bβ chains and in the junctions between the central domain and the coiled-helices. These coiled-helices are composed of the single Aα, Bβ, and γ chains supercoiled as α -helices. Six disulfide bonds in each coiled-helix are responsible for the supercoil structure and for the attachment to the central and lateral domains in the form of disulfide rings. The basic structure consists of three pairs of polypeptide chains: Aα, Bβ, and γ, arranged in a mirror image.

Manufacture

The manufacture of fibrinogen starts from cryoprecipitate. Cryoprecipitate is obtained from the starting material human plasma for fractionation or purchased from third parties.

The purification is mainly based on precipitating techniques in the presence of glycine. Residual prothrombin complex proteins are removed by aluminium hydroxide adsorption. The active ingredient paste is concentrated via ultrafiltration and subsequently dialyzed followed by 0.2µm filtration. The final bulk is prepared by adding human albumin as stabilizer followed by a sterilizing filtration. After filling, the drug substance is lyophilized.

Control of materials

Human fibrinogen is produced from human plasma for fractionation which is collected, tested, stored and transported in accordance with the information given in the currently valid CSL Behring Plasma Master File (PMF). Also human plasma used for manufacture of purchased cryoprecipitate (alternative starting material) complies with the current version of CSL Behring's PMF. The latest EMA approval certificate of the PMF has been provided.

All reagents that have a relevant Ph. Eur. monograph are complied with and this includes the antithrombin III and the sodium heparin. Regarding the two additional plasma-derived medicinal products used in manufacture – antithrombin III and albumin relevant information has been provided in line with the Chapter 10 of the current version of the guideline on plasma-derived medicinal products.

Non-compendial materials are assayed and controlled adequately before use.

Process validation and/or evaluation

From retrospective analyses of routine manufacture of human fibrinogen and from the results of formal studies, the criticality of operating parameters was evaluated and summarized in risk assessment reports that reflect the available information about the active substance process steps and their function, in addition to the process

control parameters (PCPs) and their effect on the corresponding product quality attributes. Based on the risk assessments, the active substance production process was validated at full-scale. All critical PCPs and IPCs (in-process controls) were provided and evaluated.

Overall, the results of the process validation and investigation studies at down-scale and full-scale indicate that the fibrinogen manufacturing process has been successfully validated from the starting material human plasma to the bulk solution after sterilizing filtration at full production scale. In conclusion, the process assessed in these studies reliably and reproducibly manufactures an active substance complying with the relevant quality standards.

Characterisation

Impurities

Human fibrinogen active substance is a concentrate of fibrinogen. Specific plasma derived proteins and process related non-proteins impurities were analysed throughout the production process in relevant impurity studies. The analytical methods used are appropriate and have been adequately validated.

The results of these impurity studies have thoroughly characterised the presence of product and process related impurities and indicate that both protein and non-protein impurities are consistently eliminated or reduced throughout the process resulting in an acceptable and reproducible impurity profile. The production process for human fibrinogen is therefore capable of reliably and reproducibly purifying fibrinogen and removing impurities.

Specification

Human fibrinogen active substance is obtained after blending, final adjustment and sterilizing filtration of the bulk solution. The active substance specifications are considered acceptable.

Stability

Sufficient stability data was provided and supports the proposed shelf life for human fibrinogen.

Active Substance

Thrombin

General information

Thrombin is a glycoprotein with a molecular weight of approximately 39,000 Dalton. It is formed by two peptide chains of 36 and 259 amino acids respectively, linked by disulphide bonds. Three important sites have been identified on the surface of the enzyme: the catalytic site that confers to the molecule its serine protease activity; the exosite I responsible for the binding of the substrate (fibrinogen or thrombin receptor) and the exosite II responsible for the binding of antithrombin III and inactivation of thrombin. The active site residues involved in catalysis are histidine (43), aspartic acid (99) and serine (205) of the heavy chain.

The earliest identified function of thrombin is the cleavage of fibrinogen into fibrin monomers and the activation of the fibrin-stabilizing factor (factor XIII) and protein C. Thrombin generates fibrin monomers by cleaving fibrinopeptides A (FPA) and B (FPB) from fibrinogen. Fibrin monomers spontaneously polymerize to form a soluble fibrin clot, which is then rendered insoluble by the action of factor XIII. Clotted blood is a meshwork of insoluble fibrin threads that traps blood cells and serum. Thrombin has the property of activating factor XIII to act as a transaminase and form covalent links between the carboxyl and amino groups of two different fibrin monomers, enhancing the strength of the clot.

Human thrombin active substance is presented as a white lyophilized powder and does not contain any preservatives. After reconstitution with 5 mL water for injection, the solution contains 10,000 IU thrombin per mL.

Overall, the general information provided for the active substance including structure and general properties is acceptable.

Manufacture

The manufacturing process of human thrombin active substance consists of the following steps:

- Separation of plasma into cryoprecipitate and cryo-depleted plasma.
- Adsorption of prothrombin complex on ion exchanger chromatography followed by washing and elution of loaded chromatography gel, stabilization, pasteurization, purification by ammonium sulfate precipitation and calcium phosphate adsorption, elution, activation of prothrombin to thrombin.
- Clarifying filtration, concentration and dialysis.
- Adjustment of bulk solution clarifying and 0.2 µm filtration, filling (50000 IU thrombin/injection vial), lyophilization and packaging.

Control of materials

Human thrombin active substance is produced from human plasma for fractionation which is collected, tested, stored and transported in accordance with the information given in the currently valid Master File (PMF). The latest EMA approval certificate of the PMF has been provided.

Process validation and/or evaluation

Risk analyses for the manufacturing process of human thrombin active substance have been conducted. The objective of these risk assessments was the identification of process control parameters (PCPs) affecting the product quality attributes (PQA) of the active substance. A risk assessment covered all production steps of the basic fractionation process. A process validation study involved the manufacture of three consecutive batches at full scale from cryodepleted plasma to lyophilized active substance. The results demonstrated that the manufacturing process of human thrombin is reproducible and provides a product of consistent quality.

Characterisation

Impurities

Process related impurities have been minimised and their presence does not appear to vary between batches. Overall, thrombin has been adequately characterised.

Specification

The active substance specifications, which have been set following regulatory requirements or based on batch history, are considered acceptable. Justification for the parameters listed in the specification is mainly based on Ph. Eur. requirements. The proposed ranges reflect process and assay variability and were based on historical data.

Stability

All stability data presented are within the specification and supports the claimed shelf-life for human thrombin.

2.2.3. Finished Medicinal Product

Description of the product

Raplixa is a dry-powder formulation of a fibrin sealant that is made of a single blend of premixed dry powder containing both human fibrinogen and human thrombin. Raplixa is supplied as a single strength 79 mg human fibrinogen and 726 IU human thrombin per gram of powder, in three different presentations: 0.5 grams, 1.0 grams, and 2.0 grams.

The finished product does not require reconstitution. Raplixa can be applied with the RaplixaSpray delivery device (CE marked) or from the vial depending on the bleeding surface area, whether applied directly or using the spray. Raplixa should be used in combination with an approved gelatin sponge.

Manufacture of the product

The finished product manufacturing process is well described and the process validation data is overall acceptable. A full overview of the critical process parameters, the affected CQA (critical quality attributes), the proven and normal operating ranges (including hold times), and the control strategies have been provided. Results for IPCs, CPPs (critical process parameters) and additional monitored parameters were presented. Major deviations did occur, nevertheless these were found not to affect product quality and corrective actions implemented were considered acceptable.

For the manufacturing of the finished product the active substances fibrinogen and thrombin are supplied by a licensed plasma fractionating company. The final finished product is manufactured under aseptic conditions by the commercial manufacturing site.

Human plasma derived fibrinogen and thrombin are separately spray dried. The spray dried fibrinogen and spray dried thrombin powders are blended in a 1:1 weight ratio, and filled in 0.5,1 or 2.0 gram labelled glass vial. Each vial is placed in an aluminium pouch and carton box.

Product specification

The finished product is controlled for appearance, potency, identity, content uniformity, protein analysis for fibrinogen and thrombin, moisture content, particle size distribution, total protein, albumin content, endotoxin and sterility. Adequate release and shelf life specifications have been set to ensure the product quality and consistency.

Container closure system

The container closure system for Raplixa Finished Product consists of type I (Ph. Eur.) clear glass vials with a rubber stopper and a crimp cap.

The container closure system is satisfactorily described providing sufficient detailed information confirming compliance with Ph. Eur. requirements.

Medical device

RaplixaSpray is a dedicated spray device for Raplixa and is classified as a Class IIa CE marked medical device. The RaplixaSpray delivery device is packed and supplied separately from the Raplixa finished product.

Stability of the product

Based on the data provided, a shelf-life of 18 months for the finished product when stored between +2°C to +25°C is considered acceptable.

Adventitious agents

The active substances are human plasma derived fibrinogen and human plasma derived thrombin. In the manufacturing process of fibrinogen, human albumin is also used. Two other materials from biological origin are used in the human fibrinogen concentrate and human thrombin manufacturing processes. The selection of viruses for validation studies included both enveloped and non-enveloped viruses with a wide range of physico-chemical characteristics and in general follows the recommendations of the available guidance documents. The validation strategy and choice of viruses are considered acceptable.

The submitted validation studies (control of bioburden, viruses and TSE agents) and overall information provided are sufficient to demonstrate acceptable adventitious agents control.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information about the active substances was of acceptable quality. Overall the analytical methods were satisfactorily validated.

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. A range of methods have been used to characterise the finished product. Results confirmed that there are no large scale changes in content following spray drying. A satisfactory analysis of the particle size distribution following spray drying was undertaken and demonstrated the reproducibility of the process.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the Company has provided sufficiently detailed data and documents indicating that the quality of the active substances and finished product are well controlled.

Sufficient evidence regarding the manufacturing process of the active substances has been provided. The manufacturing process of the finished product is described in sufficient detail and has been satisfactorily validated. The IPC tests are described and deemed suitable for controlling and monitoring the manufacturing processes. The results indicate that the active substances as well as the finished product can be reproducibly manufactured.

The stability program is in general considered satisfactory. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.3. Non-clinical aspects

2.3.1. Introduction

In primary pharmacodynamic studies Raplixa was tested with haemostatic agents to evaluate its haemostatic effect and its contribution to reducing blood loss. The primary pharmacology of Raplixa was studied in rabbit,

swine, mice, guinea pig, and sheep and different bleeding wounds/tissues that were representative of indications in the clinical program.

The non-clinical studies were conducted in accordance with ICH S6 Preclinical Safety Evaluation for Biotechnology-Derived Pharmaceuticals and the S6 Addendum where appropriate and ISO 10993 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing. All toxicology studies were performed under Good Laboratory Practices (GLP) with the exception of the bony implant study.

Scientific advice on this product was provided by the CHMP (ref: EMEA/CPMP/SAWP/451467 and EMEA/CHMP/SAWP/572876) which included advice on the non-clinical programme, in defining the scope of the non–clinical toxicology package, in the design of the non–clinical immunogenicity studies and the scope of the non–clinical pharmacology package.

2.3.2. Pharmacology

Non-clinical models of mild to moderate bleeding were developed to assess the effect of Raplixa on haemostasis and included wounds made in soft tissues (liver and spleen) and vascular models (AV graft) and in general, spanned from mild to moderate bleeds (< 5 g/mL to >20 g/mL, respectively); comparisons with gauze or other "mechanical" haemostatic controls as well as "active" topical haemostatic agents were also tested.

Primary pharmacodynamic studies

Four primary pharmacodynamic studies comparing Raplixa's ability to reduce time-to-haemostasis (TTH) and blood loss to that of other commonly used haemostatic agents were submitted. In order to assess these main pharmacological endpoints a model of mild to moderate bleeding was developed using the spleen or liver of anaesthetised animals.

The results of the studies are summarised in Table 2.

Table 2: Evaluation of Raplixa haemostatic efficacy

Study	Aim	Treatment	Results		
				TTH (hr:min:sec)	**Blood Loss (g)**
1698-001/SR-FC-P006 Swine spleen	Evaluate the haemostatic efficacy of Raplixa in a large animal model with mild to moderate bleeds compared to commercially available control material.	Surgicel (NuKnit) (thin, oxidized cellulose sponge)	**Mean**	0:06:16	2.527
			SD	0:01:47	0.807
		Raplixa (applied by a device at 1bar)+Ultrafoam (collagen sponge pre-wetted with saline)	**Mean**	0:02:31	0.788
			SD	0:00:49	0.288
		Surgicel (oxidized	**Mean**	0:09:53	5.580

Study	Aim	Treatment	Results		
		cellulose sponge)	**SD**	0:00:11	3.977
		Gelfoam (soaked in thrombin)	**Mean**	0:01:15	0.365
			SD	0:00:16	0.242
		Raplixa (applied by a device at 1 bar)+Dukal (non-stick gauze pad)	**Mean**	0:01:00	0.128
			SD	0:00:00	0.067
1698-002/SR-FC-P011 Swine spleen	Evaluated the haemostatic activity of Raplixa.	Wet application			
		Control (gauze only)	**Mean**	0:10:00	31.832
			SD	0:00:00	19.024
		Raplixa+Surgifoam (pre-soaked in saline)	**Mean**	0:02:45	0.511
			SD	0:00:32	0.335
		Surgifoam	**Mean**	0:02:35	0.698
			SD	0:01:07	0.756
		Raplixa+Gelfoam (pre-soaked in saline)	**Mean**	0:02:30	0.822
			SD	0:00:42	0.424
		Gelfoam (pre-soaked in saline)	**Mean**	0:02:00	0.798
			SD	0:00:33	1.228
		Dry application			
		Control (gauze only)	**Mean**	0:05:00	24.668
			SD	0:00:00	10.509
		Raplixa+Surgifoam	**Mean**	0:02:10	0.375
			SD	0:00:31	0.277
		Surgifoam	**Mean**	0:03:00	0.949
			SD	0:01:52	1.156
		Raplixa+Gelfoam	**Mean**	0:02:25	0.387
			SD	0:00:48	0.197
		Gelfoam	**Mean**	0:02:20	0.653
			SD	0:01:02	0.779
1698-003/SR-FC-P013 Swine spleen	Evaluated the haemostatic activity of Raplixa.				
		Control (gauze only)	**Mean**	0:05:00	5.989
			SD	0:00:00	3.121
		Raplixa+Surgicel	**Mean**	0:03:30	2.131
			SD	0:00:57	3.393
		Surgicel (oxidized cellulose sponge)	**Mean**	0:05:00	6.402
			SD	0:00:01	4.115
1698-004/SR-FC-P016 Swine spleen	Compare haemostatic efficacy of Raplixa with human plasma derived thrombin				

Study	Aim	Treatment	Results		
	(Floaseal) and recombinant human thrombin (Recothrom)	Control (gauze only)	**Mean**	0:05:00	29.091
			SD	0:00:00	12.208
		Raplixa+Gelfoam (wet in saline)	**Mean**	0:02:52	1.080
			SD	0:00:44	0.366
		FloSeal (gelatin+human thrombin)	**Mean**	0:01:50	1.054
			SD	0:00:31	0.369
		Recothrom+Gelfoam (wet in Recothrom)	**Mean**	0:01:45	0.866
			SD	0:00:16	0.363

The *in-vivo* non-clinical pharmacology program also evaluated the dose response aiming to select the final ratio of thrombin to fibrinogen, haemostatic efficacy of both non-irradiated and e-beam treated Raplixa as well as an evaluation of the user requirements for the Raplixa spray device. Results showed that Raplixa reduced TTH and blood loss better than mechanical agents such as gauze, gelfoam and surgical and similar to marketed products containing active biologics.

Study 1698-009/SR-FC-P054

Study 1698-009/SR-FC-P054 aiming to evaluate the topical haemostatic efficacy of Raplixa manufactured aseptically compared to Raplixa sterilized with β – irradiation showed similar results in terms of TTH and measured blood loss.

Study No. SR – FC – P014

The goal of this study was to compare the haemostatic efficacy of Raplixa/Raplixa fibrin sealant in combination with a gelatin sponge (Spongostan) as a pressure sheet to that of human thrombin in combination with a gelatin sponge in a swine liver model yielding bleeding rates that are in general, 5-fold higher than those observed in the swine spleen model. Raplixa was applied to the wound by means of the Fibrospray device prior to using gelatin to apply light manual pressure to the bleeding wound thereby evaluating as well the handling characteristics and usability of the device in combination with Raplixa. Similar results were obtained with FC+Spongostan vs Spongostan vs thrombin + spongostan in terms of bleeding rates. Similar levels of reduction of TTH with FC+ Gelatin and thrombin + gelatin were achieved.

Study SR-FC-P0004

Study SR-FC-P0004 done in rabbits that were assigned to one of the three treatment groups (Table 3) was submitted aiming to assess the haemostatic effectiveness of Raplixa fibrin sealant in combination with collagen sponge (Avitene) versus conventional therapy [Avitene alone and oxidized cellulose (Surgicel)] in mild to moderate bleeding model.

Table 3: Model Control Endpoints

Treatment	Average Bleeding Rate (g/min ± Std Dev)[1]	Excised Liver (g ± Std Dev)
Avitene®	1.6 (1.38)	0.21 (0.06)
Surgicel®	0.92 (0.43)	0.31 (0.11)
Fibrocaps™	1.49 (1.47)	0.32 (0.09)

[1] Calculated by measuring the amount of blood loss on a single gauze sponge in 30 seconds. The value had 1.41 subtracted (the average weight of a gauze sponge) and multiplied by 2 to yield the g/min rate.

The results are summarised in Figure 1 and 2 below.

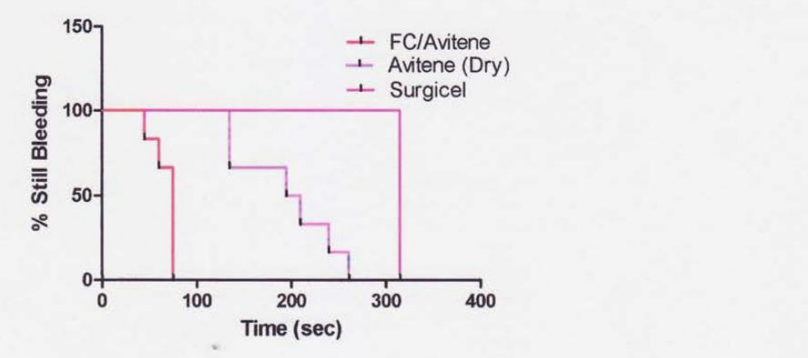


Figure 1 Fibrocaps™ with Avitene® reduces TTH compared to Avitene® alone or Surgicel® (n=6 lesions treated/group)

Figure 2 Fibrocaps™ and Avitene® reduce blood loss compared to Surgicel®.

Study SR-FC-P114

Study SR-FC-P114 aiming to provide evidence for the activity of Raplixa used on its own was submitted in which Raplixa's effect alone without the use of gelatin sponge was tested in a swine spleen model. Raplixa alone resulted in rapid TTH and reduced blood loss in all treated wounds similarly to the control group of Raplixa plus gelatin sponge.

Study PF-2007-1002

In order to establish the amounts of fibrinogen and thrombin in the product, a dose-response study (study PF-2007-1002) was performed in a pilot swine liver bleeding model using three different target concentrations of fibrinogen (50, 75, and 100 mg/g) and two different target concentrations of thrombin (200 and 500 IU/g). The results suggested that the intermediate target concentration of fibrinogen (75 mg/g) and the high concentration of thrombin (500 IU/g) were most effective at reducing TTH suggesting that the optimal amounts of each component were at least 6% w/w fibrinogen (> 60 mg/g) and at least 300 IU thrombin/g.

Study SR-FC-0015

A veterinary clinical case report (study SR-FC-0015) in sheep with the intent to study effects of use of Raplixa at sites of vascular anastomosis was submitted. In particular the objectives of this study were to:

a) determine whether Raplixa can achieve haemostasis by adequately adhering to the polytetrafluoroethylene graft material;

b) explore the time to haemostasis in this experimental system;

c) determine whether the device used with Raplixa is suitable for use with arterio-venous anastomoses;

d) gather the opinion of the end-user on use of Raplixa with the device.

The study showed that when 0.25mg of Raplixa powder (lot VEC0110) were applied directly onto the anastomosis site, either as one or two applications at each site of suturing (i.e up to 4 sites of application) via a device activated on the site of anastomosis at a pressure of 1-1.5 bar adhered to the graft and stopped bleeding for at least 30 seconds in less than 2 minutes at all sites of its application. The anastomosis site was checked and no further bleeding was seen. The medicinal product appeared more effective in controlling bleeding prior to release of the vascular loops than after release of the loops, when blood flow had already been established. The suitability of the device used to administer Raplixa in clinical use was also confirmed.

Secondary pharmacodynamic studies

For the secondary pharmacodynamics two studies aimed at testing the swelling of Gelfoam and Surgifoam in the presence of Raplixa powder were submitted. No impact on swelling was observed.

Study SR-FC-0037

Study SR-FC-0037 aimed at evaluating the *in vitro* effect of Raplixa on the swelling capacity of Gelfoam, Gelfoam Compressed and Surgifoam tested dry or wet after Raplixa being "pre-activated" for 15 minutes. Table 4 summarises the treatments and in Figure 5 and 6 the results can be seen.

Table 4 – Experimental Design

Group[1]	Name	Material [2]	Treatment
1	GF Control-Dry	Gelfoam 50	None
2	GF Control- Wet	Gelfoam 50	Saline[3]
3	GFC- Control – Dry	Gelfoam Compressed	None
4	GFC- Control – Wet	Gelfoam Compressed	Saline[3]
5	SF Control - Dry	Surgifoam	None
6	SF Control -Wet	Surgifoam	Saline[3]
7	GF + FC- Dry	Gelfoam 50	0.20 g FC
8	GF + FC - Wet	Gelfoam 50	Saline[3] + 0.20 g FC
9	GFC- + FC – Dry	Gelfoam Compressed	0.20 g FC
10	GFC +FC – Wet	Gelfoam Compressed	Saline[3] + 0.20 g FC
11	SF + FC - Dry	Surgifoam	0.20 g FC
12	SF + FC - Wet	Surgifoam	Saline[3] + 0.20 g FC

[1] each group will have 6 individually prepared/treated pieces
[2] 2 x 2 cm^2 piece (surface 4 cm^2)
[3] amount of saline needed to be saturating; see Appendix 1 for details.

Figure 3 **Fibrocaps in combination with dry gelatin sponges does not increase swelling based on volume**

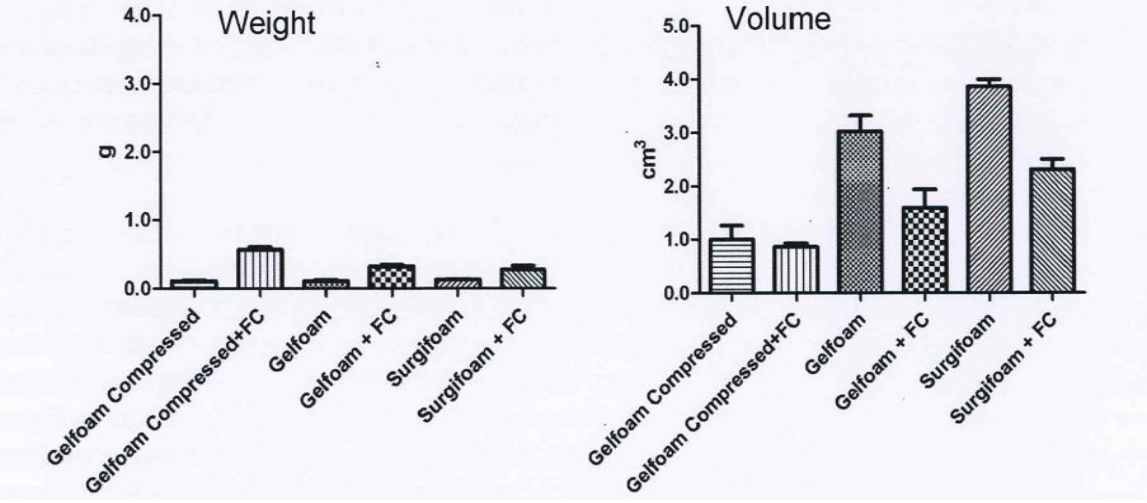
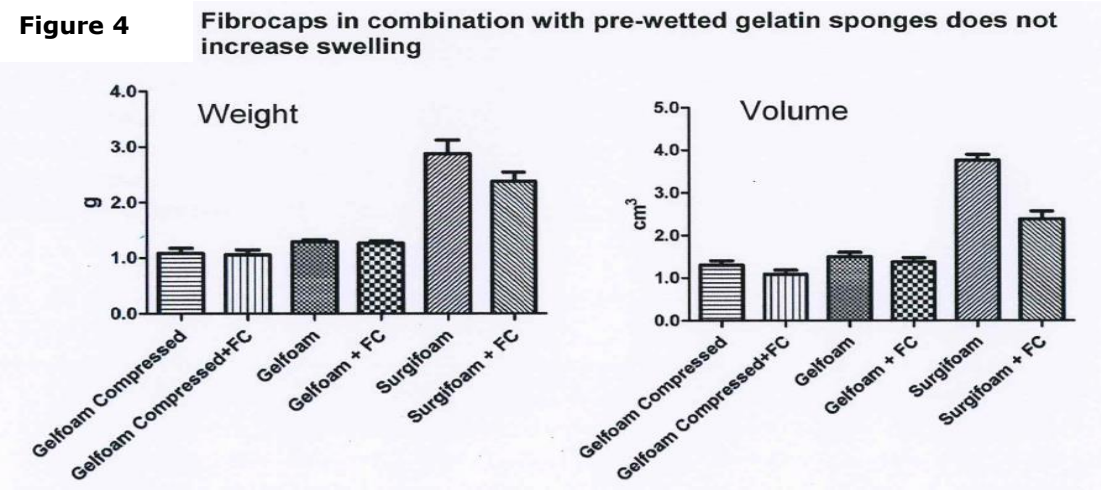


Figure 4 **Fibrocaps in combination with pre-wetted gelatin sponges does not increase swelling**



Study SR-FC-044

Study SR-FC-044 was carried out in order to:

1) evaluate gelatin sponges in combination with Raplixa at the time of Raplixa activation.

2) evaluate gelatin sponges in combination with Raplixa after 4 hours of contact period between the sponge and Raplixa.

Table 5 below details the comparisons made; each group contained six 2x2 cm^2 pieces of each sponge and was tested with and without use of Raplixa.

Table 5 – Experimental Design

Group[1]	Name	Material [2]	Treatment[3],	Time Evaluated
1	Dry GF ± FC	Gelfoam 50	0.20 g FC	4 hrs
2	Pre-wetted GF ± FC	Gelfoam 50	0.20 g FC	4 hrs
3	Dry GFC- ± FC	Gelfoam Compressed	0.20 g FC	4 hrs
4	Pre-wetted GFC±FC	Gelfoam Compressed	0.20 g FC	4 hrs
5	Dry SF ± FC	Surgifoam	0.20 g FC	4 hrs
6	Pre-wetted SF ± FC	Surgifoam	0.20 g FC	4 hrs

[1] n=3/group
[2] 2 x 2 cm^2 piece (surface 4 cm^2)
[3] see Appendix 1 for details

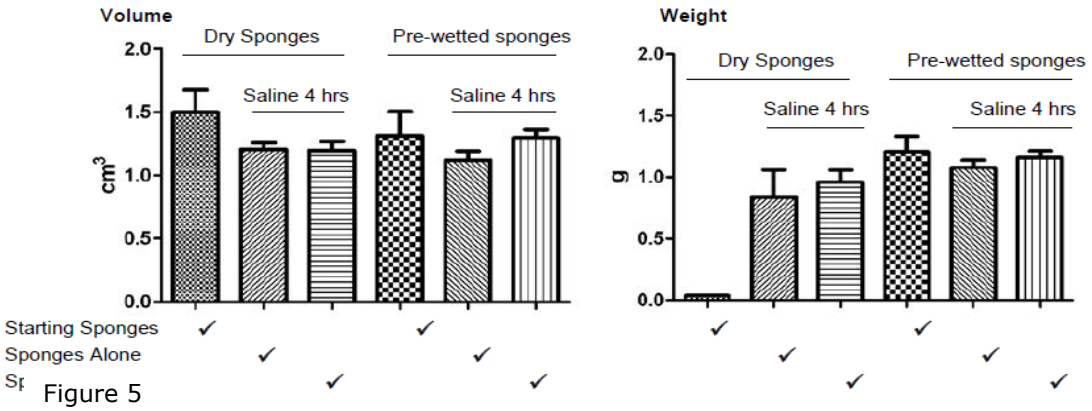


Figure 5

Figure 3 No impact on swelling potential of Gelfoam 100 after incubation with Fibrocaps for 4 hours

Safety pharmacology programme

Dedicated safety pharmacology studies have not been submitted. See toxicity studies.

Pharmacodynamic drug interactions

Non-clinical studies on pharmacodynamic drug interaction have not been submitted.

2.3.3. Pharmacokinetics

No pharmacokinetic studies have been submitted. See discussion.

2.3.4. Toxicology

Single dose toxicity

Six single dose toxicity studies were submitted (see tables 6 and 7).

Table 6 Single dose toxicity studies for Raplixa fibrin sealant

Species / strain GLP compliance	Method of administration	Doses Duration of dosing	Results

Species / strain GLP compliance	Method of administration	Doses Duration of dosing	Results
Mouse (Mus musculus) OFI Ico (IOPS Caw) GLP: Yes	Single dose IV Single dose IP	0 5 g/kg extracts 10 g/kg extracts Acute	no differences between the Raplixa extract and control. Body weight gains same across both groups. No mortality was observed; animals appeared clinically normal
Rabbit NZW White GLP: No	topical	0.04 g/wound Single dose implantation into bone	Raplixa did not interfere with bone healing cascade at 4 and 8 weeks; no macroscopic adverse reactions, tissue reactions and inflammatory and foreign body reactions at the histological level: Raplixa was biocompatibile and was completely absorbed at 4 weeks from implantation. No unscheduled deaths; surgery and recovery was uneventful with no rabbits developing post-operative infections.
Rabbit NZW White Hra NZW SPF GLP: Yes	topical	0.125 g/liver wound 0.215 g/abdominal cavity Single dose implantation in liver and abdominal cavity	transient body weight loss following surgery but no difference between groups ; clinical observations of abrasions and scabbing were also unremarkable. Scores for assessment of adhesions were similar (primarily in the liver and omentum but were not found on the bowels). No other findings of concern at macroscopic examination. No unscheduled deaths.
Rabbit NZW White Hra NZW SPF GLP: Yes	topical	4.5 g/ animal Single dose implantation in liver; safety of Fibrospray device	haemostasis under all conditions tested; no unscheduled deaths; no differences in post-surgery weight loss. Use of the device was not associated with any clinical signs of air embolism such as death, tachycardia, hypotension, shock or tachypnea or any indication or cardiovascular or respiratory difficulty.

Table 7 Single dose toxicity for device components

Type of study/	species	Device / parts used	Method of	Outcome

Study number			administration	
Singe- dose toxicity	mice	device lot 32228 (8940-350) parts: cap for the vial holder, sieve, engine and nozzle	iv injection (for saline extracts) or ip injection (for sesame oil extracts)	Mice appeared normal, no evidence of systemic toxicity
Singe- dose toxicity	mice	device lot 32228 (8940-350) parts: cap for the vial holder, sieve, engine and nozzle	iv injection (for saline extracts) or ip injection (for sesame oil extracts)	Mice appeared normal, no evidence of systemic toxicity

Repeat dose toxicity

One repeat dose study was submitted. The aim of this study was to evaluate the local tolerance and characterize the toxicological and histological profile, including the evaluation of thrombogenicity, of Raplixa medicinal product, after multiple applications of a single dose, to soft tissue organ such as the spleen in swine. For this study time to initial haemostasis, coagulation time, clinical observations, body weight, food intake and clinical pathology parameters were measured.

Measures of coagulation were not affected. Regarding coagulation times administration of Raplixa with or without the gelatin sponge did not result in any significant alteration in either sex at any interval. In all treatment groups (including the sham surgery), there were up to 1.3-fold elevations in Activated Partial Thromboplastin Time (APTT) up to day 7 in males, and up to day 2 in females. APTT times were similar to baseline pretest values by the following interval in both sexes. All individual and mean values were within an acceptable range for biologic and procedure-related variation.

The most common findings from the physical examinations included lacrimation, swelling, abrasions, and scabbed areas. These findings were not considered to be test article related as the observations were present across all treatment groups. An evaluation of body weight data found all animals to have gained weight at a normal rate over the course of the study.

In this study, there were no unscheduled deaths and there were no indications of toxicity in clinical observations body weight or in clinical pathology parameters.

Genotoxicity

One genotoxicity study was submitted. The objective of this study was to determine *in vitro* whether leachables extracted from the test material would cause mutagenic changes to *S. typhimurium* LT2 tested strains TA98, TA100, TA1535 and TA1537 and in *E.coli* strain WP2 urvA with or without metabolic activation, to simulate the usual metabolic process. Revertant colonies were counted as an indicator of mutagenic potential and cytotoxicity. Under the conditions of this study, the test article extracted in 0.9% NaCl and DMSO was not toxic nor mutagenic in the tested species.

Carcinogenicity

No carcinogenicity studies have been submitted (see discussion).

Reproduction Toxicity

No reproduction toxicity studies have been submitted (see discussion).

Toxicokinetic data

N/A

Local Tolerance

Two studies testing the local tolerance were submitted.

Study 87970

Liver implantation study in swine was performed in order to assess the systemic and local tolerance. Each of 22 pigs had 4 liver wounds made during the surgical procedure. Each wound was treated with either a collagen sponge alone, gelatine sponge alone (control 1 and 2 respectively) or test article in combination of each control article.

Swelling, adhesion to the wound site, secondary detachment of the test and control treatments was considered equivalent.

The TTH of Raplixa with collagen or collagen alone was not significantly different whereas Raplixa in combination with gelatin was significantly faster than gelatine alone. Macroscopic evaluation conducted at weeks 3 and 12 showed no differences in adhesions, inflammation or fibrosis between treatments. In histological evaluation of peripheral liver parenchyma no degenerative change at any group at any time point was noted. Granulomatous reactions of the foreign body type was noted in all groups. No difference in the inflammatory pattern compared to test or control specimens was noted.

Study 13374

A liver implantation test in swine was performed in order to evaluate the systemic and local tolerance of Raplixa drug manufactured by Nova Laboratories-used in Phase III to Raplixa manufactured by Vectura-used in Phase II clinical studies. Raplixa was applied using the spray device at 1.5 bar ~5 cm from the inflicted wounds.

Each pig had 5 standardized surgically created wounds of the liver. Each wound was treated with either a gelatine sponge or gelatine sponge in combination with:

- Nova Laboratories Raplixa non-irradiated - thrombin 602 IU/g and 74 fibrinogen mg/g;
- Nova Laboratories Raplixa e-beam irradiated - thrombin 501 IU/g and 73 fibrinogen mg/g;
- Vectura Raplixa non-irradiated - thrombin 640 IU/g and 73 fibrinogen mg/g;
- Vectura Raplixa irradiated – e-beam treated- thrombin 480 IU/g and 76 fibrinogen mg/g;

Treatments were evaluated at implantation and at 3 and 8 weeks following implantation by means of macroscopic and histological analyses. The mean blood loss after wounding was similar across groups (7.93 to 10.68 g/ml) although higher than in study 87970. All haemostatic treatments were able to result in haemostasis at the 3 minute landmark time point.

Almost all (11 out of 12) pigs showed intrahepatic and general adhesions at week 3. Similarly, at 8 weeks, all pigs had intra-hepatic adhesions and 5 out of 8 pigs had general adhesions in various peritoneal organs. No significant differences were seen across any of the treatment groups.

Histological examination at 3 weeks control treatment was characterized by infiltrate resulting from granulomatous reaction and in surrounding tissue there was evidence of fibroplasia, fibrosis and fibrocytes of moderate grade. No necrosis was observed in the control group. Sites from Raplixa and gelatin treatment groups had a granulomatous reaction infiltrate with more marked to severe presence of macrophages and giant cells and with marked grade lymphocytes, and plasma cells and slight to moderate grade polymorphonuclear cells compared with the control treated sites. There was no difference in the infiltrating cell types or severity at 3 weeks across any of the Raplixa treatment groups. Fibrosis, fibroplasia and evidence of fibrocytes was similar across all groups regardless of treatment, however the control group did not show evidence of necrosis as observed in the Raplixa treatment groups. The presence of Raplixa did not alter the nature of the inflammatory cells in the infiltrate but was associated with an increased density as compared to control.

Histological examination at 8 weeks revealed some differences between the Raplixa treatment groups. Test treatment 1 induced lower grade of granulomatous type of infiltrate than other test groups. This inflammatory reaction was of a higher grade than with the control treatment. There were no differences in fibroplasia or evidence of fibrocytes between Test treatment 1 and the control treatment. However, more fibrosis was observed with treatment 1 (mean grade 2.5) versus control (mean grade 1.7). The remaining Raplixa test treatments 2, 3 and 4 showed increased evidence of infiltrate and slightly higher evidence of fibrosis, fibroplasia and fibrocyes as compared to Treatment 1 and control treatment.

A higher incidence of granulomatous inflammation could be observed between Raplixa test treatments compared to control treatment at 3 weeks and 8 weeks. However at 8 weeks test treatment 1 induced only slightly more inflamation locally than control treatment. Other Raplixa test treatments 2, 3 and 4 still showed moderate to marked signs of granulomatous types of reaction at 8 weeks. The presence of Raplixa did not change the nature if the inflammatory cells infiltrate after treatment as compared to gelatin alone, but was responsible for an increase if the different cell type local density.

Other toxicity studies

Study 90064

The aim of this study was to evaluate the potential of extracts from the material to produce irritation and delayed-type hypersensitivity following intradermal injection of 0,9% NaCl or sesame oil Raplixa extract to rabbits. The results showed that both test extracts produced slightly more erythema and oedema than the control.

Study 90065

The aim of this study was to evaluate the potential for delayed dermal contact sensitization in guinea pigs following intradermal and topical application. A range of concentrations (100%, 50%, 25%, 0%) of Raplixa extracted in 0,9% NaCl or sesame oil at a final concentration of 0,2 g/ml were used. The results showed that there was no evidence of sensitization by topical route application with either vehicle; but there was evidence of sensitization by intradermal route with the 0.9% NaCl extract.

Neither of the vehicles, 0.9% nor sesame oil, was an irritant when applied ID (preliminary study) or topically. No evidence of sensitization was observed for Raplixa extracts, regardless of vehicle, when applied topically. There were no clinical observations in either group.

Studies 157672, 157788, 157673, 157789

Additional studies aiming at testing the potential of the material to produce irritation following intradermal injection or topically applied of 0.9% NaCl or sesame oil test article extracts in the rabbit (first two studies) and

guinea pigs (last two studies) using rigid and flexible nozzle on the device for the delivery of Raplixa, were submitted. The results showed that under the conditions of the studies extracts of the test article with either vehicle did not induce any erythema or edema reaction as indicated by examination after 24 48, and 72 hours.

Study 162282

The purpose of this study was to determine whether the Raplixa delivery kit would cause haemolysis *in vitro* by direct contact or extraction. The results showed that under the conditions of the study the mean haemolytic index for the test article by direct contact was of 0.85% and the mean haemolytic index for the test article extract was 0.44% ; therefore the test article was considered not-haemolytic.

Table 8: Results of the haemolysis test by extract

	Negative control extract			Positive control extract			Test article extract		
	Assay 1	Assay 2	Assay 3	Assay 1	Assay 2	Assay 3	Assay 1	Assay 2	Assay 3
Free hemoglobin (g/l)	0.0029	0.0046	0.0026	1.1761	1.2173	1.2233	0.0075	0.0049	0.0039
Hemolytic index (%)	0.23%	0.37%	0.21%	95.17%	98.51%	98.99%	0.61%	0.40%	0.32%
Mean hemolytic index (%)	0.27%			97.56%			0.44%		
Hemolytic grade	Not hemolytic			Hemolytic			Not hemolytic		

Table 9: Results of the haemolysis test by direct contact

	Negative control			Positive control			Test article		
	Assay 1	Assay 2	Assay 3	Assay 1	Assay 2	Assay 3	Assay 1	Assay 2	Assay 3
Free hemoglobin (g/l)	0.0033	0.0048	0.0049	1.1476	1.1449	1.1615	0.0123	0.0073	0.0119
Hemolytic index (%)	0.27%	0.39%	0.40%	92.87%	92.65%	93.99%	1.00%	0.59%	0.96%
Mean hemolytic index (%)	0.35%			93.17%			0.85%		
Hemolytic grade	Not hemolytic			Hemolytic			Not hemolytic		

Study 162286

The purpose of this study was to determine whether a biomaterial or a medical device by direct contact and on extract can cause haemolysis. The results are summarised in the tables below. These results show that the test article extract was not haemolytic.

Table 10: Results of the haemolysis test by extract

	Negative control extract			Positive control extract			Test article extract		
	Assay 1	Assay 2	Assay 3	Assay 1	Assay 2	Assay 3	Assay 1	Assay 2	Assay 3
Free hemoglobin (g/l)	0.008	0.0086	0.0088	1.2404	1.2464	1.2764	0.0121	0.01	0.0126
Hemolytic index (%)	0.64%	0.69%	0.70%	99.35%	99.83%	102.24%	0.97%	0.80%	1.01%
Mean hemolytic index (%)	0.68%			100.48%			0.93%		
Hemolytic grade	Not hemolytic			Hemolytic			Not hemolytic		

Table 11: Results of the haemolysis test by direct contact

	Negative control			Positive control			Test article		
	Assay 1	Assay 2	Assay 3	Assay 1	Assay 2	Assay 3	Assay 1	Assay 2	Assay 3
Free hemoglobin (g/l)	0.0104	0.0092	0.0159	1.2519	1.2541	1.2355	0.0078	0.011	0.0155
Hemolytic index (%)	0.83%	0.74%	1.27%	100.28%	100.45%	98.96%	0.62%	0.88%	1.24%
Mean hemolytic index (%)	0.95%			99.90%			0.92%		
Hemolytic grade	Not hemolytic			Hemolytic			Not hemolytic		

Study 149307

The purpose of this study was to evaluate the biocompatibility of the test article using *in vitro* mammalian cell culture test (potential for cytotoxicity). The results showed that under the conditions of the study, the extract of the test article showed no evidence of causing cell lysis or toxicity.

Study 149306

The purpose of this study was to test the potential for cytotoxicity of extract on Raplixa delivery device. Under the conditions of this study, the extract of the test article showed no evidence of causing cell lysis or toxicity.

2.3.5. Ecotoxicity/environmental risk assessment

No ecotoxicity / ERA studies were submitted. See discussion.

2.3.6. Discussion on non-clinical aspects

The aim of the pharmacodynamic studies was to characterize the potential of Raplixa to promote rapid haemostasis at the site of bleeding when used in conjunction with gelatin- or collagen- containing sponges. To that end, several non-clinical models of mild to moderate bleeding were developed to assess the effect of Raplixa on haemostasis. The pharmacology models included wounds made in soft tissues (liver and spleen) and vascular models (AV graft) and in general, spanned from mild to moderate bleeds (< 5 g/mL to >20 g/mL, respectively). Several of these studies also included gauze or other "mechanical" haemostatic controls as well as "active" topical haemostatic agents like human thrombin and FloSeal such that comparison could be made to Raplixa.

The main non-clinical species rabbit and swine are considered suitable species for pharmacological assessment.

In all pharmacological studies a single application of the Raplixa fibrin sealant was sufficient to control the bleeding in terms of time to haemostasis and total blood loss.

Study SR-FC-P0004 carried out in rabbits was submitted to assess the haemostatic effectiveness of Raplixa compared to conventional therapy. Avitene is a collagen sponge used clinically as a topical haemostatic agent and Surgicel is a haemostatic agent that contains a polyanhydroglucuronic acid polymer lacking thrombin and fibrin. In this study, Raplixa was given together with Avitene. The results showed a statistically significant shorter time to haemostasis and reduced blood loss for the Raplixa/Avitene group ($p<0.0004$ by log rank Mantel Cox testing) as compared to Avitene alone or to Surgicel thanks to the addition of thrombin and fibrin contained in Raplixa.

Raplixa's haemostatic effect when used alone was questioned. At the request of the CHMP study SR-FC-P114 was submitted in which the effect without the use of gelatin sponge was evaluated in swine spleen bleed model. The results showed that Raplixa is pharmacologically active and able to promote haemostasis in the absence of gelatin sponge. However, the proposed indication is in combination with an approved haemostatic sponge.

Furthermore, the applicant was requested to justify the amounts of fibrinogen and thrombin chosen. In that regard an empiric approach was taken at the time of initial product formulation and the appropriate concentrations in Raplixa of thrombin and fibrinogen were established, using different concentrations of these in a pilot swine liver bleeding model. The results suggested that all combinations had at least some haemostatic activity, but that the intermediate target concentration of fibrinogen (75 mg/g) and the high concentration of thrombin (500 IU/g) were most effective at reducing TTH (study PF-2007-1002). No additional preclinical dose-ranging studies were completed prior to the Phase 1 clinical study.

The product is applied topically, acts locally and does not distribute, appreciably to distal tissues or organs, therefore pharmacokinetic studies are not applicable. As regards metabolism, this was explored in the general toxicity studies and breakdown was consistent with normal fibrinolysis and clot dissolution.
The absence of safety pharmacology studies and drug-drug interaction studies is acceptable given the localised use of the product. Toxicity studies suffice to support the expectation for safety of the product in clinical use. Single and repeated dose toxicity studies submitted showed no evidence of systemic toxicity arising from the active substances of Raplixa or from the device components.

No carcinogenicity studies have been submitted. This is justified on the basis of absence of carcinogenicity associated with the class of fibrin sealants or clinical case reports of such risk, short duration of use of the product with no systemic exposure expected. The justification provided is in compliance with ICHS6 Guidance on the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals Development.

No reproduction toxicity studies have been submitted, which is justified with reference to absence of reports for such harm caused by fibrin sealants, the topical use of the product and its breakdown being the same manner as an endogenous clot. In the SmPC section 4.6 it is stated that "Animal reproduction studies have not been conducted with Raplixa. The safety of Raplixa for use in human pregnancy or during breast-feeding has not been established in controlled clinical trials. The product should not be administered to pregnant and breast-feeding women. Fertility studies have not been conducted". Studies have not been done in juvenile animals. The product is not indicated for use in patients aged <18.

Exemption from the need for an environmental risk assessment is justified with reference to the Guideline on Environmental Risk Assessment of Medicinal Products for Human use CHMP/SWP/4447/00, of 1 June 2006 – as proteins are exempted from the need for an environmental risk assessment. The product is sourced from human plasma. It is applied topically with expected no systemic bioavailability and its degradation route is expected to be the same as that of an endogenous clot. Toxicity studies indicate no special reason for concern and it is unlikely that the product will result in a significant risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. The information is included in SmPC sections 5.3 and 4.6.

The non-clinical programme submitted in support of the application for a Marketing Authorisation for Raplixa is adequate.

2.4. Clinical aspects

2.4.1. Introduction

The efficacy and safety of Raplixa as currently developed has been evaluated in three clinical studies: two phase II studies (proof of concept) FC-002 NL and FC-002 US, and one phase III (confirmatory) FC-004 (Table 12). In addition, a first-in-human, Phase 2 trial was conducted in 29 subjects undergoing liver resection at four hospitals in the Netherlands (FC-001) (the Fibrocaps used in FC-001 was made from drug substances (human plasma-derived thrombin and fibrinogen) sourced from a different source than the current product and for this reason safety and efficacy data from FC-001 were not used for this submission.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

  Table 12 – Summary of Fibrocaps Clinical Trials

Phase	Study No.	Subject Population	Objectives	Treatments Studied	N
2	FC-002 NL	Hepatic resection	Efficacy and safety	Fibrocaps + gelatin sponge	39
				Gelatin sponge alone	17
				Total:	56
2	FC-002 US	Spinal surgery, peripheral vascular surgery, and general surgery	Efficacy and safety	Fibrocaps + gelatin sponge	47
				Gelatin sponge alone	23
				Total	70
3	FC-004	Spinal surgery, hepatic resection, vascular surgery, and soft tissue dissection	Efficacy and safety	Fibrocaps + gelatin sponge	480
				Gelatin sponge alone	239
				Total	719
				Fibrocaps + gelatin sponge	566
				Gelatin sponge alone	279
				Total:	845

2.4.2. Pharmacokinetics

Pharmacokinetic studies have not been submitted (see discussion).

2.4.3. Pharmacodynamics

Studies on Mechanism of action, primary and secondary pharmacology on fibrinogen and thrombin components of Raplixa have not been submitted (see discussion).

2.4.4. Discussion on clinical pharmacology

Raplixa is intended for epilesional use only. Intravascular administration is contraindicated and as a consequence intravascular pharmacokinetic studies in man were not performed.
Specific clinical pharmacology studies have not been performed as Raplixa is applied topically, acts locally and as such there is little to no biodistribution to other tissues / sites.

Further, the fibrinogen and thrombin components of Raplixa are indistinguishable from endogenously expressed fibrinogen / thrombin. Fibrin Sealants/haemostatics are metabolised in the same way as endogenous fibrin by fibrinolysis and phagocytosis.

Immunogenicity of the current product was investigated and is assessed under clinical safety.

2.4.5. Conclusions on clinical pharmacology

The CHMP considers the justification for the omission of studies related to pharmacology acceptable.

2.5. Clinical efficacy

2.5.1. Dose response studies

Dose response studies have not been submitted (see discussion).

2.5.2. Main study

Study FC-004: **A Phase 3, Randomised, Single-blind, controlled trial of topical RAPLIXA™ in intraoperative surgical hemostasis (FINISH-3)**

This was a Phase 3, international, multi-centre, randomised, single-blind, controlled trial in subjects undergoing surgery in four separate surgical indications (spinal surgery, vascular surgery, hepatic resection, and soft tissue dissection surgery), which were run in parallel as four independently-powered trials. This trial was conducted at 28 study sites in the United States and 29 sites in the EU. The study period was: from May 21, 2012 to April 24, 2013.

Methods

Study Participants

The study included male and female subjects ≥18 years of age undergoing one of the following surgical procedures:

1. Spinal surgery: Cervical, thoracic, or lumbar discectomy, corpectomy, laminectomy, lateral or interbody fusion. The target bleeding site may not have been within a bony cavity or other confined area.

2. Vascular Surgery:

All subjects undergoing vascular surgery were to be systemically heparinized according to standard procedures. The clamp(s) were to be removed to determine if an appropriate target bleeding site with mild to moderate bleeding was present. The clamps were to remain off once a target bleeding site was identified and during the treatment and assessment of TTH. If protamine reversal was indicated, it was to occur after the 5-minute TTH assessment period was completed, unless a safety concern dictated that it should happen earlier.

a. Arterial bypass surgery: Arterial bypass with an artificial graft (i.e., polytetrafluoroethylene [PTFE] or Dacron) including patching and revision procedures, and abdominal aorta aneurysm (AAA) repair. Anastomotic sites at the proximal end of the graft, the distal end of the graft (AAA repair ONLY) or on the suture line of the patch were

to be available for TTH measurement. The allowed vessels included those of the extremities and the abdominal aorta.

b. Arteriovenous graft formation for haemodialysis access: Artificial graft (i.e., PTFE or Dacron) for haemodialysis access, including revision procedures. Anastomotic sites only at the arterial end of the graft were to be available for TTH measurement.

c. Carotid endarterectomy: Carotid endarterectomy requiring a Dacron patch, where the suture line of the patch was used for TTH assessment.

3. Hepatic resection: Hepatic wedge resection or anatomic resection of 1 to 5 contiguous hepatic segments, which may have been combined with surgical procedures involving the pancreas, gall bladder, bile duct or intestines. Subjects undergoing living-related liver donation were also eligible.

4. Soft tissue dissection: The target bleeding site was to be identified during the soft tissue dissection related to the primary operative procedure. Primary operative procedures included but were not limited to: abdominoplasty, lower anterior resections, abdominal perineal resections, distal pancreatectomy, esophagectomy, donor skin graft site in limited burn patients, and mastectomy.

Appropriate soft tissue types included but were not be limited to: loose areolar tissue, fat, lymphatic tissue/lymph node beds, and muscle. The TBS was not to involve parenchymal, vascular (anastomotic or vascular repair sites), gastrointestinal or genitourinary soft tissue.

Main inclusion criteria during surgery were:

- Subject has not received blood transfusion between screening and study treatment
- Presence of mild or moderate bleeding/oozing when control by conventional surgical techniques, including but not limited to suture, ligature, and cautery is ineffective or impractical
- Absence of intra-operative complications other than bleeding which, in the opinion of the Investigator, may interfere with the assessment of efficacy or safety
- No intra-operative use of a topical hemostat containing thrombin prior to study treatment
- Approximate TBS surface area of ≤ 100 cm2
- All participants were ≥18yrs of age

Exclusion Criteria were any of the following:

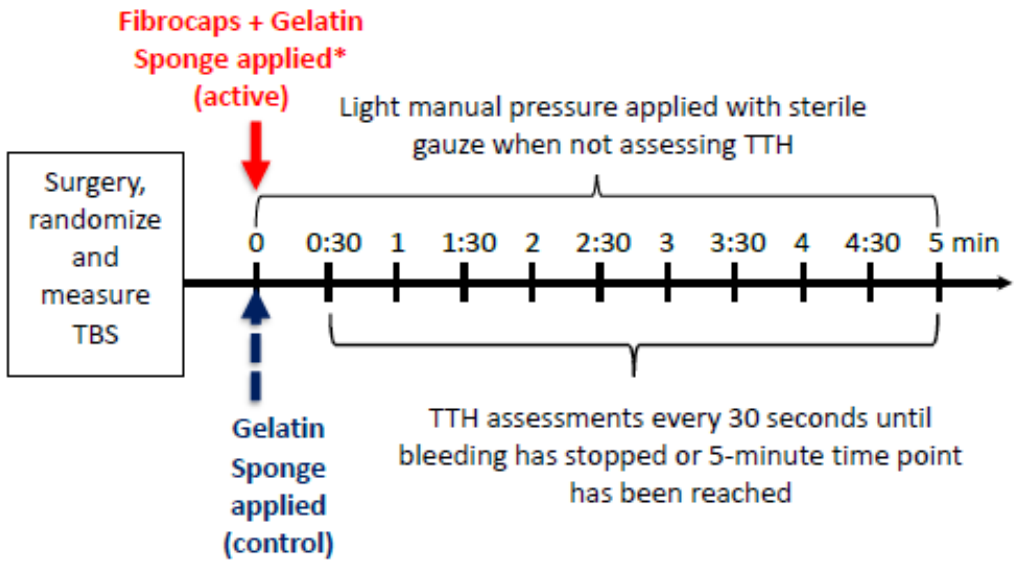
- Subject has known antibodies or hypersensitivity to thrombin or other coagulation factors
- Subject has history of heparin-induced thrombocytopenia (only for vascular subjects where heparin use is required)
- Subject has known allergy to porcine gelatin
- Subject is unwilling to receive blood products
- Has any clinically-significant coagulation disorder that may interfere with the assessment of efficacy or pose a safety risk to the subject according to the Investigator, or baseline abnormalities of INR > 2.5 or aPTT > 100 seconds during screening that are not explained by current drug treatment (e.g., warfarin, heparin)

- Aspartate aminotransferase or alanine aminotransferase > 3 x upper limit normal range during screening, except for subjects undergoing liver resection surgery or with a diagnosis of liver metastases where there is no upper limit for these analytes due to the nature of their disease
- Platelets < 100 $x10^9$ cells/L during screening

Treatments

Subjects were randomised to receive treatment with either Raplixa, administered with or without the use of the Fibrospray device, in combination with a gelatin sponge or gelatin sponge alone. A schematic view of the surgery, treatment and time to haemostasis events are shown in the following figure:

Figure 6 **TTH Assessment Schema**



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

Dose selection was based on powder volume used in the Phase 2 trials (FC-002 US and FC-002 NL) and laboratory testing. Raplixa was supplied as a 1.0 g vial which can cover about 100 cm^2 when applied using the Fibrospray delivery device.

During a surgical procedure on Day 1, subjects were treated with up to one vial of Raplixa (1 g) plus gelatin sponge or gelatin sponge alone at the target bleeding site and the time to haemostasis assessed every 30 seconds for up to 5 minutes.

The time to haemostasis clock started as soon as the application of the assigned treatment began. Assessment of haemostasis was done by carefully lifting the sterile gauze pad and checking for bleeding through or around the Gelatin sponge starting at 30 seconds and then every 30 seconds until haemostasis had been achieved or 5 minutes had elapsed, whichever came first. In case application took longer than 30 seconds, the first time-to-haemostasis assessment started at the next scheduled time point (i.e. 1 min).

Subjects were re-treated with their assigned treatment as necessary during the 5-minute time to haemostasis assessment period, with up to a maximum of 3 vials of Raplixa (3 g) in total.

Subjects who did not achieve haemostasis within 5 minutes were considered treatment failures and were treated with an alternative topical haemostatic agent or device of the surgeon's choosing provided it did not contain thrombin.

Subjects who achieved haemostasis within 5 minutes but experienced a re-bleeding before the 5 minute time to haemostasis assessment period had ended were considered haemostatic failures and were treated with the assigned treatment or an alternative topical haemostatic agent or device of the surgeon's choosing provided it did not contain thrombin.

Objectives

Primary objective: to demonstrate the superiority of Raplixa plus gelatin sponge, as compared to gelatin sponge alone, for achieving haemostasis 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 study 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.

Exploratory Objectives were to evaluate the health economics and outcomes data by analysing the utilization of selected medical resources by treatment group.

Outcomes/endpoints

Primary efficacy endpoint was: time to haemostasis within the 5-minute TTH assessment period.

Secondary endpoints were:

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

Exploratory endpoints consisted on description of performance parameters of the Fibrospray device and health economics and outcomes data including:

– Duration of surgical procedure from incision to closure

– Total hospital length of stay through Day 29

– Use of blood products other than RBCs

– Need for re-operation at TBS for complications other than bleeding

– TTH and treatment success rate in subjects with baseline coagulation lab values of international normalized ratio (INR) >2.0 and/or activated partial thromboplastin time (aPTT) >100 seconds compared to subjects with normal coagulation labs

– Treatment success rate of subjects taking anticoagulants and/or anti-platelet agents compared to subjects not taking these medications.

Outcomes/endpoints

Sample size

Based on the Phase 2 data in vascular subjects, the proportion of subjects who achieved haemostasis within the 5-minute assessment period was expected to be about 80% in the gelatin sponge alone arm and 90% in the Raplixa plus gelatin sponge arm.

The FC-004 trial was powered for a minimally clinically-relevant increase of 70% in the hazard for haemostasis (hazard ratio of 1.70). Under an assumed constant hazard ratio of 1.70, the FC-004 trial (with 2:1 randomisation) would require 144 events (subjects achieving haemostasis within 5 minutes) to attain 85% power for detecting a difference between treatment arms using a 2-sided level 0.05 test (1-sided level 0.025).

Randomisation

Randomization was done in a 2:1 ratio (active: control).

Subjects were randomised to the following groups:

a. Raplixa & gelatin sponge group: rapidly apply Raplixa using one of the following three methods:

   i. Sprinkle a thin layer of Raplixa directly from the vial onto the target bleeding site followed by application of a gelatin sponge (wet or dry)

   ii. Spray a thin layer of Raplixa onto the target bleeding site using the Fibrospray device followed by application of a gelatin sponge (wet or dry)

   iii. Apply Raplixa onto a moistened absorbable gelatin sponge that is then applied to the target bleeding site.

Light manual pressure using sterile gauze should follow for all three application methods.

b. Gelatin sponge group: Apply gelatin sponge followed by light manual pressure using sterile gauze.

Blinding (masking)

The trial was designed as a single-blind comparative trial because it was not considered ethical to have a double-blind trial requiring the application of a placebo powder onto the bleeding site.

Statistical methods

All statistical analyses were performed using SAS, Version 9.1.3. Unless otherwise specified, all continuous endpoints were summarised using descriptive statistics, which included the number of subjects, mean, standard deviation, median, minimum, and maximum. All categorical endpoints were summarized using frequencies and percentages.

The following populations were specified for this study:

Efficacy Population: All subjects who were randomised, received study intervention, and had a time to haemostasis assessment recorded regardless of whether the measurement was censored. All efficacy analyses were performed using this population. Subjects were analysed in treatment groups as randomised.

Intent-to-Treat Population: All subjects randomised, regardless of whether they were treated, were used in a sensitivity analysis of the primary efficacy endpoint and the time to haemostasis -related secondary efficacy endpoints. Subjects were grouped by assigned treatment.

Safety Population: All subjects who were randomised and received study intervention. All safety analyses were performed using this population. Subjects were analysed in treatment groups according to treatment received.

In the primary analysis, the difference in the time to haemostasis survival curves comparing Raplixa plus gelatin sponge to gelatin sponge alone in each surgery type was tested using the log-rank statistic while ensuring an overall 2-sided significance level of 0.05 for each surgical setting. The Cox proportional hazards model was used to estimate the relative difference in the hazard for haemostasis comparing treatment arms. Estimates of the distribution of time to haemostasis were computed using the Kaplan-Meier method. Median time to haemostasis and the associated 2-sided 95% confidence interval were calculated using the Kaplan-Meier method.

In a secondary analysis of the primary endpoint of time to haemostasis, sensitivity to missing data was assessed by treating missing time to haemostasis values as treatment failures. The same analyses performed for the primary endpoint were performed for the sensitivity analysis.

Analyses of the secondary efficacy endpoints used a 2-sided significance level of 0.05. The difference in restricted mean time to haemostasis over 5 minutes was computed using Irwin's estimator. The difference in the probability of time to haemostasis over 3 and 5 minutes was tested using a 2-sample binomial test of proportions. The normal approximation was used along with a continuity correction for testing. Wald-based 95% confidence intervals for the difference in probability of time to haemostasis were computed using the normal approximation.

Secondary efficacy endpoints related to time to haemostasis were tested using a hierarchical, step-down procedure for pairwise comparisons.

Adverse event terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary with the relationship to Raplixa, the Fibrospray device and/or the gelatin sponge determined by the Investigator.

Independent Data Monitoring Committee

An Independent Data Monitoring Committee comprising external experts in surgery, haematology, and statistics were charged with monitoring the trial for safety.

Two Independent Data Monitoring Committee meetings were planned and completed: the first after 100 subjects had been treated and followed for 4 weeks for safety and the second after 50% of the total subjects had been treated and followed for 4 weeks for safety.

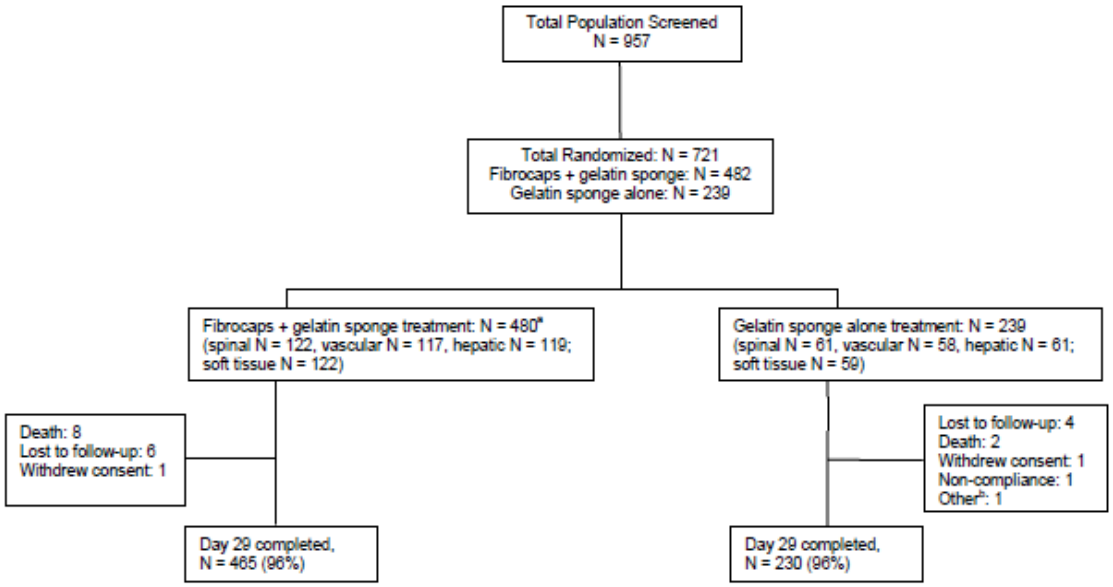
The Independent Data Monitoring Committee was provided with unblinded safety data to review prior to each meeting. No safety signals were identified by the Independent Data Monitoring Committee during their reviews and they recommended that the trial continue as planned.

Results

Participant flow

The disposition of all subjects is summarized in Figure 8 below.

Figure 7 **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)

Enrolment

957 subjects were screened and 721 were randomised.

Of the 721 randomised subjects, 482 (67%) were randomised to the Raplixa plus gelatin sponge group and 239 (33%) were randomised to the gelatin sponge only group.

Allocation

Among the 480 subjects treated with Raplixa plus gelatin sponge, 122 underwent spinal surgery, 117 underwent vascular surgery, 119 underwent hepatic resection, and 122 underwent soft tissue dissection.

Among the 239 subjects treated with gelatin sponge alone, 61 underwent spinal surgery, 58 underwent vascular surgery, 61 underwent hepatic resection, and 59 underwent soft tissue dissection.

Two subjects randomised to the Raplixa plus gelatin sponge group were discontinued from the trial before receiving treatment (one because of lack of an appropriate target bleeding site and the other for receiving blood product after randomization, which was a protocol violation): these two subjects are part of the 721 subjects in the intent-to-treat population.

Follow-up

Most subjects (695/719; 96%) completed the Day 29 safety assessments.

Of the 24 subjects who prematurely discontinued from the trial after receiving treatment, 15 were in the Raplixa plus gelatin sponge group and nine were in the gelatin sponge alone group. Reasons for premature discontinuation were death (10 subjects: eight Raplixa plus gelatin sponge, two gelatin sponge alone), lost to follow-up (10 subjects: six Raplixa plus gelatin sponge, four gelatin sponge alone), withdrawal of consent (two subjects: one Raplixa plus gelatin sponge, one gelatin sponge alone), "other" (one subject: gelatin sponge alone; subject did not return for their final follow-up visit), and non-compliance (one subject; gelatin sponge alone).

Analysis

The safety population (defined as all subjects who were randomised and received study treatment) and efficacy population (defined as all subjects who were randomised, received study treatment, and had a time to haemostasis assessment) were identical and consisted of 719 subjects

Protocol deviations

There were 82 major protocol deviations reported for 68 subjects, as summarised in the following table:

Table 13 – Major Protocol Deviations

Deviation Category	Number of Subjects[a]
Informed consent	29
SAE not reported/reported out of window	14
Randomization error	9
Day of surgery/TTH	8
Inclusion/exclusion	6
Prohibited medication	6
Laboratory assessment	5
Other[b]	3
Assessment not completed	1
Investigational product	1

[a] Subjects could have more than one type of deviation

[b] "Other" included: Fibrocaps application done by Investigator not listed on the task and delegation log; >1 vial of Fibrocaps used for initial application; and sub-Investigator signed AE form and eligibility criteria.

The major deviations were identified by clinical monitors at routine site visits and immediately brought to the attention of the site staff, Investigator and sponsor.

In 29 cases of informed consent, the form used was not the up-to-date version, 9 subjects were randomised out of order according to the randomisation schedule (all of these subjects received the correct treatment assignment), 8 subjects had deviations on surgery technique and timing method, 6 subjects received prohibited thrombin-containing concomitant medication.

Recruitment

957 potential subjects were screened for this study; of these, 721 subjects (75%) were enrolled and randomised at 28 sites in the US and 29 sites in the EU (the Netherlands, Belgium, and the United Kingdom).

Date first patient enrolled: May 21, 2012.
Date last patient completed: April 24, 2013.

Database lock: June 2013; Follow-up occurred at the day 29 safety assessment.

Conduct of the study

Subject enrollment in the US, Belgium, and the Netherlands commenced under protocol version 1.2, while subject enrollment in the UK commenced under protocol version 2. (Protocol version 4.3 was submitted in the UK only; however subject enrollment was complete at this time and no subjects were enrolled under this amendment).

There were no substantive changes to the study conduct. Two changes were made to the planned analyses for the trial: n exploratory analysis of time to haemostasis and treatment success rate in subjects with baseline coagulation values of INR > 2.0 and/or aPTT > 100 seconds compared to subjects with normal coagulation values was specified in the SAP. However, because only six subjects had baseline coagulation values of INR > 2.0 and/or aPTT > 100 seconds, a meaningful subgroup analysis was not possible; An additional ad hoc statistical analysis was conducted using Fisher's exact test to compare the incidence of adverse events between the two treatment arms

Baseline data

Demographics for all 721 subjects enrolled and randomised in this trial are summarized in Table 26. The overall study population was generally balanced with regard to sex (female = 46%) and the majority were white (88%). Median age at enrollment was 59.0 years (range, 19–91 years). The majority of subjects were < 65 years (461/721; 64%), 260/721 subjects (36%) were ≥ 65 years, and 79/721 (11%) were ≥ 75 years. The number and percentage of subjects who underwent each type of surgical procedure is summarized in table 14.

Table 14 – Demographics of Study Subjects

	Fibrocaps plus Gelatin Sponge (N=482)	Gelatin Sponge Alone (N=239)	All Subjects (N=721)
Sex [n (%)]			
Male	268 (56)	124 (52)	392 (54)
Female	214 (44)	115 (48)	329 (46)
Age at Consent (years)			
Mean (SD)	57.4 (14.44)	58.1 (14.12)	57.6 (14.33)
Median	59.0	59.0	59.0
Min, Max	19, 88	22, 91	19, 91
Race [n (%)]			
White	422 (88)	210 (88)	632 (88)
Black/African American	42 (9)	20 (8)	62 (9)
Asian	8 (2)	3 (1)	11 (2)
American Indian/ Alaskan Native	1 (<1)	1 (<1)	2 (<1)
Other	7 (1)	4 (2)	11 (2)
Not Reported	2 (<1)	1 (<1)	3 (<1)

Table 15 – Enrollment by Surgical Procedure

	Fibrocaps plus Gelatin Sponge (N=482)	Gelatin Sponge Alone (N=239)	All Subjects (N=721)
Surgery Type [n (%)]			
Spinal Surgery	122 (25)	61 (26)	183 (25)
Vascular Surgery	118 (24)[a]	58 (24)	176 (24)
Arterial bypass surgery	92 (19)	51 (21)	143 (20)
Arteriovenous graft formation for hemodialysis access	13 (3)	3 (1)	16 (2)
Carotid endarterectomy	11 (2)	4 (2)	15 (2)
Hepatic Resection	120 (25)[a]	61 (26)	181 (25)
Soft Tissue Dissection	122 (25)	59 (25)	181 (25)

[a] Two subjects randomized but not treated (one vascular subject, one hepatic resection subject)
Source: Appendix Section 14: Table 4.1

Males comprised most subjects undergoing hepatic resection and vascular surgery; 64%% and 69%, respectively. In contrast, females comprised the majority of subjects undergoing soft tissue dissection; 70%. Approximately equal proportions of males and females were undergoing spinal surgery (44% female). The median age was relatively similar for the four different surgery types: 56 years, 66 years, 63 years, and 49 years for spine, vascular, hepatic, and soft tissue surgeries, respectively

Concurrent medical conditions were relatively balanced between the Raplixa plus gelatin sponge and gelatin sponge alone groups and were consistent with the subjects' age (mean = 57.6 years) and the types of surgery being performed.

Prior and concomitant medication use was relatively balanced between the Raplixa plus gelatin sponge and gelatin sponge alone groups and was consistent with the types of surgery being performed.

Use of anticoagulants and/or antiplatelet agents at baseline varied among surgery types. Use of these agents was documented in 7/183 subjects (38%) for spinal surgery, 141/175 subjects (80%) for vascular surgery, 116/180 subjects (64%) for hepatic resection, and 52/181 subjects (29%) for soft tissue dissection surgery.

Numbers analysed

721 subjects were enrolled and randomised in this trial.

The safety population (defined as all subjects who were randomised and received study treatment) and efficacy population (defined as all subjects who were randomised, received study treatment, and had a time to haemostasis assessment) were identical and consisted of 719 subjects. 695 subjects (96%) completed the Day 29 safety assessments.

Outcomes and estimation

The primary efficacy endpoint measured in this trial was the time to haemostasis (TTH) within the 5-minute time to haemostasis assessment period. The following table presents the median time to haemostasis with Raplixa plus gelatin sponge versus gelatin sponge alone in each of the four surgical settings evaluated in this study:

Table 16 – Time to Hemostasis by Surgery Type and Treatment

	Fibrocaps 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: Appendix Section 14: Tables 12.2, 12.3, 12.4, and 12.5

Using the Cox proportional hazards model, the relative difference in the hazard of haemostasis for Raplixa plus gelatin sponge versus gelatin sponge alone was 3.3 for spinal surgery, 2.1 for vascular surgery, 2.3 for hepatic resection, and 3.4 for soft tissue dissection. By log-rank test, the median time to haemostasis for each surgery type was significantly shorter with Raplixa plus gelatin sponge than with gelatin sponge alone ($p<0.0001$).

Kaplan-Meier survival curves comparing the percentage of subjects who achieved haemostasis over time in the Raplixa plus gelatin sponge versus gelatin sponge alone groups are presented by surgery type:

Figure 8 TTH: Spinal Surgery

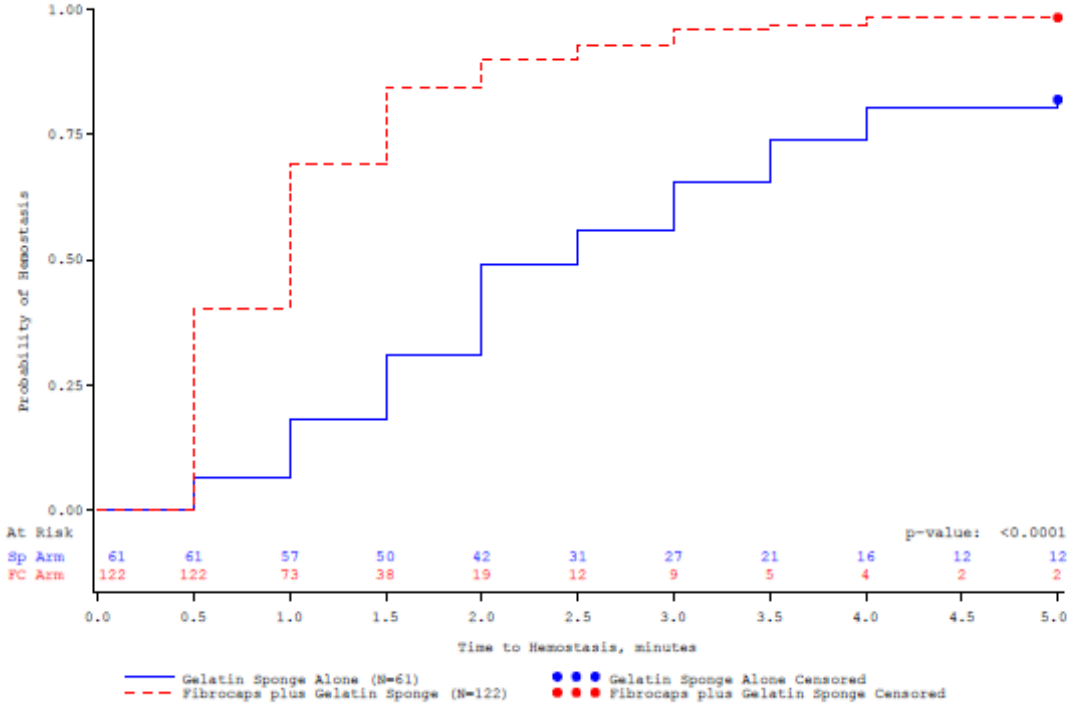


Figure 9 TTH: Vascular Surgery

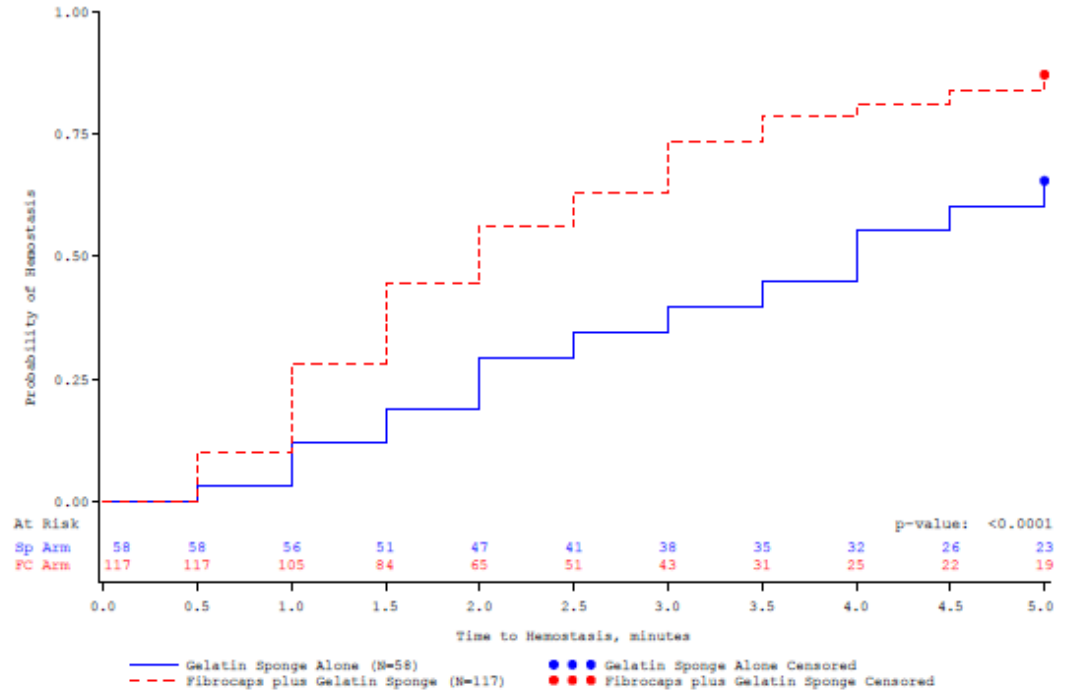


Figure 10 TTH: Hepatic Resection

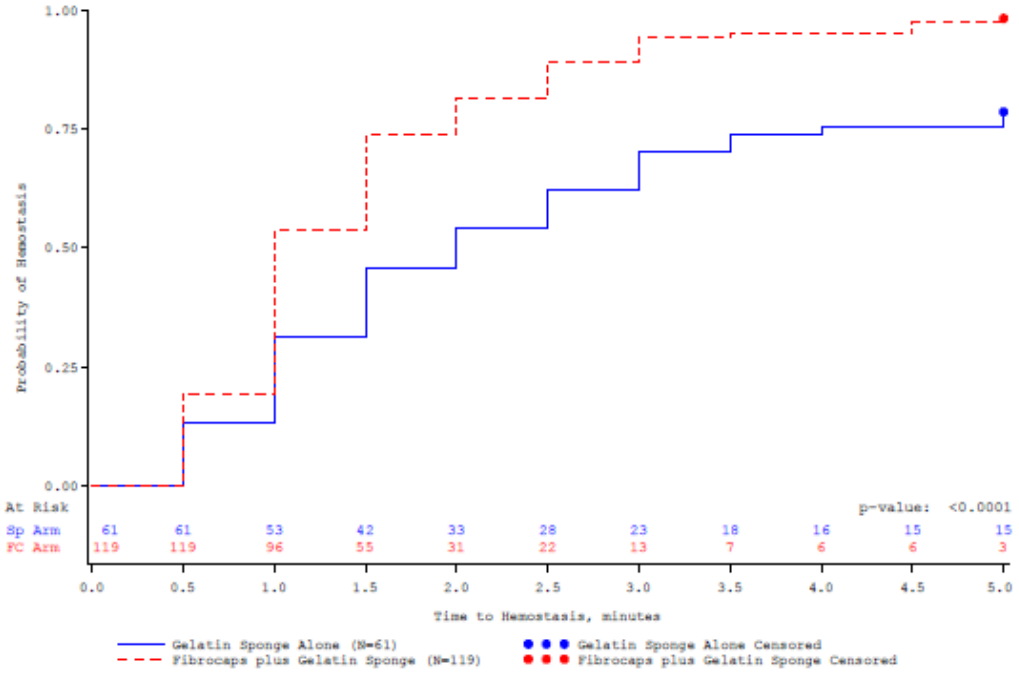
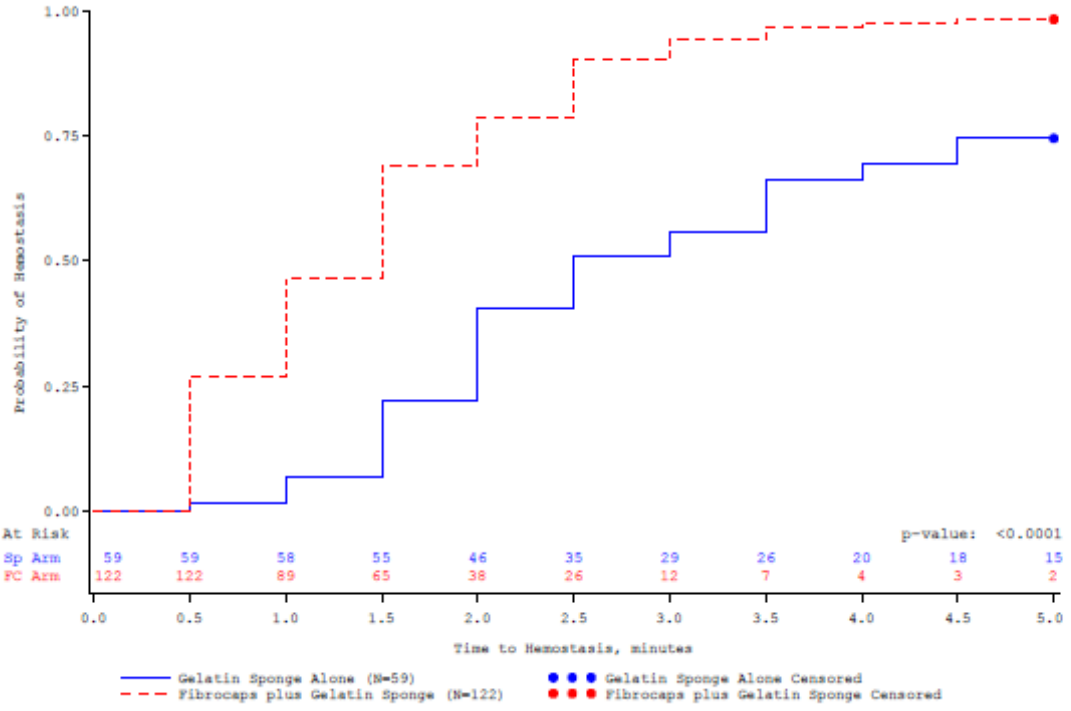


Figure 11 TTH: Soft Tissue Dissection



Secondary Efficacy endpoints Analysis

Restricted mean time to haemostasis

The difference in restricted mean time to haemostasis over 5 minutes as computed using Irwin's estimator is presented by surgery type in the following:

Table 17 **Restricted Mean TTH by Surgery Type and Treatment**

	Fibrocaps 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: Appendix Section 14: Tables 12.2, 12.3, 12.4, and 12.5

For all surgery types, a statistically significant difference in restricted mean time to haemostasis was observed between Raplixa plus gelatin sponge versus gelatin sponge alone ($p<0.0001$).

Proportion of Subjects Achieving Haemostasis at 3 and 5 Minutes

The following table summarises the proportion of subjects who achieved haemostasis with Raplixa plus gelatin sponge or with gelatin sponge alone at 3 and 5 minutes after application:

Table 18 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				
Fibrocaps 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				
Fibrocaps 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: Appendix Section 14: Tables 12.2, 12.3, 12.4, and 12.5

At both time points and in all four surgery types, a significantly higher proportion of subjects achieved haemostasis with Raplixa plus gelatin sponge than with gelatin sponge alone.

Use of alternative haemostatic agents at the target bleeding site

Across all surgery types, six of 480 subjects (1%) treated with Raplixa plus gelatin sponge and seven of 239 subjects (3%) treated with gelatin sponge alone required intervention with an alternative haemostatic agent. Alternative haemostatic agents included thrombin, epinephrine, oxidized cellulose and Tisseel.

Transfusion requirements up to day 29

Across all surgery types, red blood cells were administered to forty of 480 subjects (8%) in the Raplixa plus gelatin sponge arm and 22 of 239 subjects (9%) in the gelatin sponge alone arm.

Usage was similar across each of the surgery types with the exception of hepatic resection for which red blood cells were more frequently administered to subjects in the gelatin sponge alone arm (14 of 61 subjects [23%]) compared with 18 of 119 subjects (15%) in the Raplixa plus gelatin sponge arm.

Re-operation at the target bleeding site for bleeding

One subject undergoing vascular surgery in the gelatin sponge alone treatment arm required re-operation at the target bleeding site for an adverse event of bleeding.

Ancillary analyses

Subgroup Analyses

Demographics

Raplixa plus gelatin sponge was associated with a shorter median and restricted mean time to haemostasis than gelatin sponge alone for both females and males and for subjects <65 years and ≥65 years.

Similar results were obtained in all surgical settings. Evaluation of the impact of race on efficacy data was limited by the fact that most (88%) of subjects enrolled in FC-004 were white.

Baseline anticoagulation / antiplatelet usage

For spinal surgery, vascular surgery, and soft tissue dissection, Raplixa plus gelatin sponge was associated with shorter median and restricted mean time to haemostasis than gelatin sponge alone regardless of whether subjects were or were not taking these medications. The median time to haemostasis with Raplixa plus gelatin sponge, however, was identical to that with gelatin sponge alone for subjects who were undergoing hepatic resection and taking anticoagulation/antiplatelet agents (For subjects undergoing hepatic resection, Raplixa plus gelatin sponge was associated with a shorter restricted mean time to haemostasis than gelatin sponge alone regardless of whether subjects were or were not taking these medications.).

Fibrospray device usage

The Fibrospray device was used extensively in both hepatic resection (93%) and soft tissue dissection surgeries (95%). In addition, almost one quarter of spinal surgeons used the Fibrospray device,

Vascular surgery subtypes

Of the 175 subjects undergoing vascular surgery, 142 (81%) had arterial bypass surgery, 16 (9%) had AV graft formation for haemodialysis access and 15 (9%) had carotid endarterectomy.

Raplixa plus gelatin sponge was associated with a shorter median time to haemostasis than gelatin sponge alone for each of these vascular surgery subgroups (hazard ratios of 2.24, 2.09, and 1.32 for arterial bypass, AV graft formation, and carotid endarterectomy, respectively).

Sensitivity analyses

Three sensitivity analyses were conducted.

- In the first analysis, subjects who had missing time to haemostasis values were handled as treatment failures.
- The second sensitivity analysis considered a "worst case" scenario in which patients with missing values in the Raplixa plus gelatin sponge arm prior to achieving haemostasis had time to haemostasis imputed to failure at 5 minutes with censoring, while patients in the gelatin sponge alone arm had a time to haemostasis time imputed that was the minimum missing assessment.
- In the final sensitivity analysis, time to haemostasis was evaluated in the ITT population which consisted of all 721 subjects randomised in the trial.

Results of these sensitivity analyses did not change the finding that Raplixa plus gelatin sponge was superior to gelatin sponge alone at achieving haemostasis in all four surgical settings.

Results of the ITT analyses are shown in the following tables:

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 19: summary of efficacy for trial FC-004

Title: A phase 3, randomised, single-blind, controlled trial of topical Raplixa in intra-operative surgical haemostasis			
Study identifier	FC-004		
Design	Multi-centre, randomised, single-blind, controlled		
	During a surgical procedure on Day 1 (Visit 2), subjects were initially treated with up to one vial of Raplixa (1 g) plus gelatin sponge or gelatin sponge alone at the target bleeding site and the time to haemostasis assessed every 30 seconds for up to 5 minutes.		
Hypothesis	Superiority of Raplixa plus gelatin sponge, as compared to gelatin sponge alone, for achieving haemostasis 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.		
Treatments groups	Spinal surgery		n = 183
	Vascular surgery		n = 175
	Hepatic resection		n = 180
	Soft tissue dissection		n = 181
Endpoints and definitions	Primary endpoint	efficacy	The restricted mean time to haemostasis within the 5-minute time to haemostasis assessment period by treatment group within each surgical indication.
	Secondary	efficacy	The proportion of subjects achieving haemostasis within 3 and 5 minutes by treatment group within each surgical indication
	Secondary	safety	Overall safety, as determined by the incidence, severity and relationship of adverse events, clinical laboratory abnormalities and post-surgery bleeding complications.
Database lock	June 2013 (trial start date May 2012)		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Efficacy Population: all subjects who were randomised, received study intervention, and had a time to haemostasis assessment recorded regardless of whether the measurement was censored (times were censored at 5 mins). All efficacy analyses were performed using this population. Subjects were analysed in treatment groups as randomised. The difference between the time-to-haemostasis survival curve comparing Raplixa plus gelatin to gelatin alone in each surgical setting was tested using the log-rank statistic Estimates of the distribution of time-to-haemostasis were computed using the Kaplan-Meier method. Median time-to-haemostasis and the associated 2-sided 95% CI were calculated using the Kaplan-Meier Method.				
Efficacy measure Time to Haemostasis 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 Log-rank test
	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
.					
Analysis description	**Sensitivity analysis**				
	Intent-to-Treat Population: all subjects randomised, regardless of whether they were treated, were used in a sensitivity analysis of the primary efficacy endpoint and the time to haemostasis-related secondary efficacy endpoints. Subjects were grouped by assigned treatment.				
Efficacy measure Restricted Mean TTH by Surgery Type and Treatment Restricted mean based on Irwin estimator and tested		Raplixa Plus Gelatin Sponge Restricted Mean TTH, min. (SEM)	Gelatin Sponge Alone Restricted Mean TTH, min. (SEM)	Difference in Means	p-value
	Spinal (n=183)	1.2 (0.08)	2.7 (0.19)	-1.5	<0.0001

using normal approximation	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
	.				
Efficacy measure 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 haemostasis 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 (Wald-based normal approximation of binomial with continuity correction)	<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 (Wald-based normal approximation of binomial with continuity correction)	0.0012	0.0019	0.0003	<0.0001

Supportive studies

Study FC-002 NL: A Phase 2, Randomised, Single-Blind, Controlled, Comparative Efficacy and Safety Study of Topical Raplixa™ and Gelatin Sponge in Surgical Haemostasis in the Netherlands

This is a multi-centre, prospective, randomised (2:1), single-blind, controlled, comparative efficacy and safety study in subjects underwent open hepatic resection at study centres 5 sites in the Netherlands.

Study Objectives were: To characterize the efficacy of topical Raplixa plus gelatin sponge (i.e. Spongostan™), as compared to gelatin sponge alone in surgical subjects when control of mild to moderate bleeding by standard surgical techniques is ineffective and/or impractical; To characterize the safety of topical Raplixa plus gelatin sponge, as compared to gelatin sponge alone, in surgical subjects when control of mild to moderate bleeding by standard surgical techniques is ineffective and/or impractical

The study population included adult subjects who were undergoing open hepatic resection (wedge resection or anatomic resection of 1 to 5 contiguous hepatic segments) and had an appropriately sized target bleeding site with mild or moderate bleeding.

Main intra-operative inclusion criteria were:

1. Presence of mild or moderate bleeding/oozing, in which control by conventional surgical techniques, including but not limited to suture, ligature and cautery, was ineffective or impractical

2. Absence of intra-operative complications other than bleeding at the resection site that could, in the opinion of the Investigator, interfere with assessment of efficacy or safety;

3. No intra-operative use of a topical haemostat containing thrombin

4. Approximate target bleeding site surface area of ≤ 100 cm2

Main exclusion criteria were:

1. Any clinically-significant coagulation disorder that could interfere with the assessment of efficacy or pose a safety risk to the subject according to the Investigator

2. Platelets < 100 $x10^9$ cells/L at screening

3. aPTT > 100 seconds during screening

4. INR > 2.5 during screening

Primary efficacy endpoint was: Mean Time to Haemostasis. Time to Haemostasis is defined as the absolute time from the start of Raplixa application until haemostasis is achieved. If haemostasis was not achieved within 10 minutes, the patient was considered a treatment failure

Secondary endpoint was: Proportion of subjects achieving haemostasis at 3, 5, and 10 minutes

60 subjects were planned to be evaluable. Randomisation was to be done intra-operatively, using sealed envelopes after the subject was deemed eligible according to the intra-operative inclusion criteria. A block randomization was performed stratified to surgical procedure at each site, using a block size of 3 (2 active, 1 control). Subjects were not informed of the treatment assigned to them (FCGS or GS) and remained blinded during the study.

Statistical methods

The primary efficacy endpoint of time to haemostasis was compared between the treatment arms for all subjects who achieved hemostasis within 10 minutes, using a two-sided t-test.

Subjects with a time to haemostasis > 10 min were censored at 10 min, considered a treatment failure, and included in a time-to-event analysis to determine the proportion of patients achieving hemostasis within 3, 5 and 10 minutes of Raplixa application (secondary efficacy endpoint).

Kaplan-Meier curves for time to haemostasis were compared between the treatment arms using the log rank test, and success rates were compared using the Fisher's Exact test.

The main analysis population for efficacy parameters was the Intent-to-Treat population, defined as all subjects who underwent surgery, had an acceptable target bleeding site and were randomised

A Per Protocol population for efficacy analysis was defined as the Intent-to-Treat population minus subjects not treated or with significant protocol violations

The Safety population was defined as the subjects treated and analysed according to the treatment they actually received.

Results

Numbers analysed

The study started on the 20th December 2010 and completed on the 24th October 2011.

79 subjects were screened; 56 subjects were randomised and analysed; 23 subjects failed screening (22 screen failures occurred intra-operatively because of a lack of a suitable target bleeding site).

39 subjects were randomised to Raplixa plus gelatin sponge (FCGS) and 17 were randomised to gelatin sponge alone (GS). 2 subjects in the FCGS group were lost to follow-up before completing the study: 1 subject died during the study and 1 subject died after completing the study. 1 subject in the GS group was not treated as randomised and did not receive either study treatment. All subjects in the GS group completed the study.

Demographics

Demographics of subjects are summarized in the following table:

Table 20 Demographics, ITT Population

Demographic	FCGS N=39	GS N=17	Total N=56	p-value
Age, years				0.239[1]
Mean ± SD (n)	60.1 ± 13.33 (39)	64.3 ± 8.92 (17)	61.4 ± 12.24 (56)	
Median (range)	63.0 (25,82)	62.0 (49,80)	62.5 (25,82)	
Sex, % (n/N)				1.00[2]
Male	64.1% (25/39)	64.7% (11/17)	64.3% (36/56)	
Female	35.9% (14/39)	35.3% (6/17)	35.7% (20/56)	
Race, % (n/N)				0.519[2]
Asian	2.6% (1/39)	5.9% (1/17)	3.6% (2/56)	
White	97.4% (38/39)	94.1% (16/17)	96.4% (54/56)	

[1] Two-sample t-test
[2] Fisher's Exact test
Source: Table 14.2.1.A.

Most subjects were male, Caucasian and over 60yrs of age.

Medical history

The most common medical history was neoplasm, which was reported by 45 (80.4%) subjects in the ITT population, followed by vascular and cardiac disorders, reported by 14 (25.0%) and 9 (16.1%) subjects, respectively. Subjects' medical history are summarised in the following table:

All subjects in the safety population received heparin during the study. In addition, 2 (5.1%) subjects in the FCGS group and none in the GS group received non-heparin platelet aggregation inhibitors; 3 (7.7%) in the FCGS group and 4 (25.0%) in the GS group received vitamin K antagonists.

Selection of Doses in the Study

The average dose of Raplixa for liver resection subjects in clinical study FC-001 was about 1.8 g per subject (n=28, range 0.8 to 6.0 g), which included subjects with large bleeding areas (up to approximately 200 cm^2), subjects with re-applications, and subjects treated with and without the Fibrospray device.

Laboratory testing suggested that one vial (1.5 g) can cover approximately 100 to 150 cm^2, which was dependent on the thickness of the Raplixa applied and was considered adequate for the cases in this study.

The initial application of Raplixa was up to a single vial and only applied and assessed on one target bleeding site per subject for time to haemostasis measurement in the FCGS group, with the actual dose used depending on the surface area of the target bleeding site and rate of bleeding.

Up to one additional vial of Raplixa could be applied if haemostasis had not been achieved within 3 minutes.

Following haemostasis or the end of the 10-minute observation period, whichever came first, the remaining third vial of Raplixa from the allotted quantity (3 vials of Raplixa per subject) could be used by the surgeon at surgical bleeding sites other than the TBS that required an adjunct to haemostasis and were part of the original surgical procedure. The amount of Raplixa applied to these sites was recorded.

Efficacy results

Primary efficacy parameter

Results are summarised in the following table:

Table 21 **Time to Hemostasis, ITT Population**

Parameter	FCGS N=39	GS N=17	P-value
TTH, min			
Mean ± SD	2.16 ± 1.18	4.36 ± 3.13	0.004[1]
Median (range)	1.87 (1.0,6.1)	3.00 (1.0,10.0)	

[1] Wilcoxon Mann-Whitney test
[2] Fisher's Exact test
Source: Table 14.9.1.A

Raplixa plus gelatin sponge met the primary efficacy endpoint of a statistically significant reduction in time to haemostasis as compared to control (gelatin sponge alone).

Secondary Efficacy Parameters

Within 3 minutes after application, 30 (76.9%) of the 39 FCGS-treated subjects in the group and 9 (52.9%) of the 17 control subjects had achieved haemostasis. The percentages of subjects achieving haemostasis within 5 and 10 minutes were statistically significantly higher in the FCGS group. Results are summarised in the following table:

Table 22 **Incidence of Hemostasis by 3, 5 and 10 Minutes After Treatment, ITT Population**

Time After T_{start} (min)	FCGS N=39	GS N=17	p-value[1]
3	76.9% (30/39)	52.9% (9/17)	0.113
Time After T_{start} (min)	FCGS N=39	GS N=17	p-value[1]
5	94.9% (37/39)	70.6% (12/17)	0.022
10	100% (39/39)	82.4% (14/17)	0.025

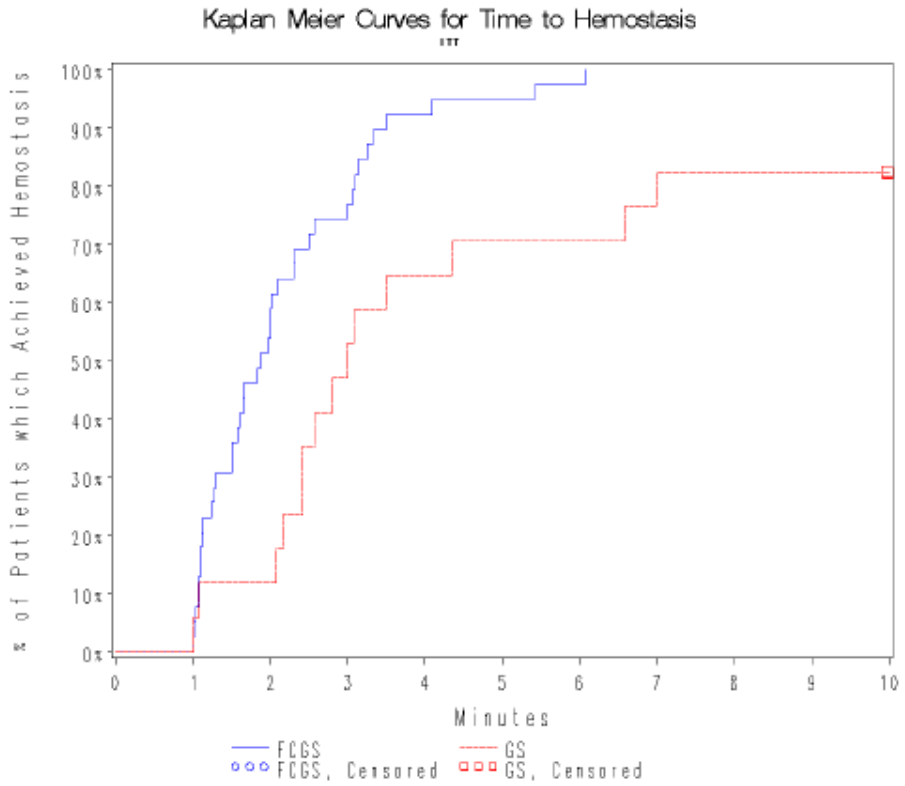
[1] Fisher's Exact test

Source: Table 14.9.1.A

None of the subjects in either treatment group who achieved hemostasis within 10 minutes experienced re-bleeding at the target bleeding site.

The following figure presents the Kaplan-Meier curves of the percentages of subjects achieving haemostasis over time in the two treatment groups. Using the log rank test, the difference between the two curves was statistically significant (p<0.0001), which supports the primary and secondary efficacy endpoints.

Figure 12 **Kaplan-Meier Curves for Time to Hemostasis, ITT Population**



Raplixa met secondary efficacy endpoints of higher incidence of haemostasis achieved at 5 and 10 minutes (difference was non-significant at 3 minutes).

Study FC-002 US: A U.S. Phase 2, Randomised, Single-Blind, Controlled, Comparative Efficacy and Safety Study of Topical Raplixa™ and Gelatin Sponge (USP) in Surgical Haemostasis

This is a multi-centre, prospective, randomised (2:1), single-blind, controlled, comparative efficacy and safety study in subjects who underwent one of the following open surgical procedures: spinal, peripheral vascular, liver resection, and soft tissue dissection. Study centres were at 8 sites in the USA.

The objectives were: To characterize the efficacy of topical Raplixa plus gelatin sponge (i.e. Spongostan), as compared to gelatin sponge alone in surgical subjects when control of mild to moderate bleeding by standard surgical techniques is ineffective and/or impractical; To characterize the safety of topical Raplixa plus gelatin sponge, as compared to gelatin sponge alone, in surgical subjects when control of mild to moderate bleeding by standard surgical techniques is ineffective and/or impractical.

Inclusion criteria

The study population included adult subjects who were undergoing

- spinal surgery (cervical, thoracic, or lumbar discectomy, corpectomy, laminectomy and lateral or inter-body fusion)
- peripheral vascular surgery (bypass surgery or AV graft formation for haemodialysis access)
- open hepatic resection (wedge resection or anatomic resection of 1 to 5 contiguous hepatic segments)
- soft tissue dissection (including skin graft, abdominal, oesophageal surgery etc.)

and had an appropriate target bleeding site with mild or moderate bleeding requiring the use of an adjunct to haemostasis.

Intra-operative inclusion criteria were:

1. Presence of mild or moderate bleeding/oozing, in which control by conventional surgical techniques, including but not limited to suture, ligature and cautery, was ineffective or impractical

2. Absence of intra-operative complications other than bleeding at the resection site that could, in the opinion of the Investigator, interfere with assessment of efficacy or safety;

3. No intra-operative use of a topical haemostat containing thrombin

4. Approximate target bleeding site surface area of ≤ 100 cm2

Exclusion criteria included the following:

1. Had any clinically-significant coagulation disorder that could interfere with the assessment of efficacy or pose a safety risk to the subject according to the Investigator

2. Platelets < 100 $x10^9$ cells/L at screening

3. aPTT > 100 seconds during screening

4. INR > 2.5 during screening

Endpoints

Primary efficacy endpoint was: Mean Time to Haemostasis; Time to Haemostasis is defined as the absolute time from the start of Raplixa application until haemostasis is achieved at the target bleeding site. If haemostasis was not achieved within 10 minutes, the patient was considered a treatment failure.

Secondary endpoint was the proportion of subjects achieving haemostasis at 3, 5, and 10 minutes.

Subjects were to be randomised in a 2:1 ratio to the FCGS group or the GS group. A block randomization was performed stratified to surgical procedure at each site, using a block size of 6 (4 active, 2 control). To reduce selection bias, randomization was done intra-operatively, using sealed envelopes, after the subject was deemed eligible according to the intra-operative inclusion criteria.

Sample size and statistical methods

90 subjects were planned to be evaluable.

The primary efficacy endpoint of time to haemostasis was compared between the treatment arms for all subjects who achieved hemostasis within 10 minutes, using a two-sided t-test.

Subjects with a time to haemostasis > 10 min were censored at 10 min, considered a treatment failure, and included in a time-to-event analysis to determine the proportion of patients achieving hemostasis within 3, 5 and 10 minutes of Raplixa application (secondary efficacy endpoint).

Kaplan-Meier curves for time to haemostasis were compared between the treatment arms using the log rank test, and success rates were compared using the Fisher's Exact test.

The main analysis population for efficacy parameters was the Intent-to-Treat population, defined as all subjects who underwent surgery, had an acceptable target bleeding site and were randomised.

A Per Protocol population for efficacy analysis was defined as the Intent-to-Treat population minus subjects not treated or with significant protocol violations.

The Safety population was defined as the subjects treated and analysed according to the treatment they actually received.

Numbers analysed

83 subjects were screened; 70 subjects were randomised and analysed; 13 subjects failed screening (11 were found to be not eligible at the time of surgery). 47 subjects were randomised to Raplixa plus gelatin sponge (FCGS): 24 underwent spinal surgery, 20 underwent vascular surgery, and 3 underwent general surgery (hepatic resection and soft tissue dissection). 23 were randomised to gelatin sponge alone (GS): 13 underwent spinal surgery, 10 underwent vascular surgery, and none underwent general surgery.

The study started on 1st February 2011 and ended on the 14th October 2011.

Demographics

Demographics of study subjects are summarised in the following table:

Table 23 – Demographics of Study Subjects

		FCGS N = 47	GS N = 23	Total N = 70	p-value
Age (yrs)					0.499[1]
	Mean ± SD (N)	59.0 ± 13.97	61.3 ± 10.48	59.8 ± 12.89	
	Median (range)	61.0 (26-81)	61.0 (35-81)	61.0 (26-81)	
Sex					0.315[2]
Male	% (n)	53.2% (25)	39.1% (9)	48.6% (34)	
Female	% (n)	46.8% (22)	60.9% (14)	51.4% (36)	
Ethnicity					0.132[2]
Asian	% (n)	0.0% (0)	8.7% (2)	2.9% (2)	
Black	% (n)	2.1% (1)	4.3% (1)	2.9% (2)	
White	% (n)	95.7% (45)	87.0% (20)	92.9% (65)	
Other	% (n)	2.1% (1)	0.0% (0)	1.4% (1)	

Source: Table 14.2.1.A.
SD = standard deviation.
[1] Two-sample t-test.
[2] Fisher's Exact test.

The number and percentage of subjects who underwent each type of surgical procedure in the study are summarised in the following table:

Table 24 – Percentage (number of Subjects) by Surgical Procedures

	FCGS N = 47	GS N = 23
Surgical Procedure		
Spinal surgery	51.1% (24)	56.5% (13)
Hepatic Resection	4.3% (2)	0.0% (0)
Peripheral arterial bypass surgery	31.9% (15)	34.8% (8)
Arteriovenous graft formation for hemodialysis access	10.6% (5)	8.7% (2)
Soft tissue dissection	2.1% (1)	0.0% (0)
Primary Operative Procedure		
Cervical	13.0% (6)	18.2% (4)
Lumbar discectomy	15.2% (7)	9.1% (2)
Laminectomy	21.7% (10)	18.2% (4)
Lateral or interbody fusion	2.2% (1)	13.6% (3)
Hepatic wedge resection	2.2% (1)	0.0% (0)
Anatomic resection of 1 to 5 contiguous hepatic segments	2.2% (1)	0.0% (0)
Peripheral artery bypass with PTFE graft	15.2% (7)	22.7% (5)
PTFE graft for hemodialysis access	6.5% (3)	0.0% (0)
Peripheral artery bypass with native graft	17.4% (8)	13.6% (3)
Native graft for hemodialysis access	4.3% (2)	4.5% (1)
Missing	1	1

Source: Table 14.08.01

The hepatic resection and soft tissue dissection groups included only 3 subjects, all of whom were randomised to the FCGS group, thus precluding any efficacy analysis.

Medical history

Two (4.3%) subjects in the FCGS group had a bleeding history, including 1 subject with anti-phospholipid syndrome and 1 subject with a history of receiving transfusion; 44 subjects (93.6%) in the FCGS group and 22 subjects (95.7%) in the GS group had a history of surgery. One (2.1%) subject in the FCGS group and 2 (8.7%) subjects in the GS group had a history of using topical haemostatic products. Anticoagulant concomitant medications were used by 25 (53.2%) subjects in the FCGS group and 13 (56.5%) in the GS group. The anticoagulants used were mostly heparin and non-heparin platelet aggregation inhibitors. Overall, medical histories were balanced between the FCGS and GS groups and consistent with the study subjects' age (average 60 years) and the types of surgery (spinal, vascular, and general) required for enrolment.*Selection of Doses in the Study*

The average dose of Raplixa for hepatic resection subjects in the previous clinical study FC-001 was about 1.8 g per subject (n=28, range 0.8 to 6.0 g) which included subjects with large bleeding areas (up to approximately 200 cm^2), subjects with re-applications, and subjects treated with and without the Fibrospray device.

Laboratory testing suggested that one vial (1.5 g) can cover approximately 100 to 150 cm2, depending the thickness of the Raplixa applied, and was believed adequate for this study.

The initial application of Raplixa was up to a single vial, which was only applied and assessed on one target bleeding site per subject for time to haemostasis measurement in the FCGS group, with the actual dose used depending on the surface area of the target bleeding site and rate of bleeding.

Up to one additional vial of Raplixa (1.5 g) could be applied to the target bleeding site if haemostasis had not been achieved within 3 minutes.

Following haemostasis or the end of the 10-minute observation period, whichever came first, the remaining Raplixa from the allotted quantity (3 vials of Raplixa per subject) could be used by the surgeon at surgical bleeding sites other than the TBS that required an adjunct to haemostasis and were part of the original surgical procedure. The amount of Raplixa applied to these sites was recorded.

Outcomes and estimations

Primary efficacy parameter

The primary efficacy endpoint measured in this study was the mean time to haemostasis. Results are shown in the following table:

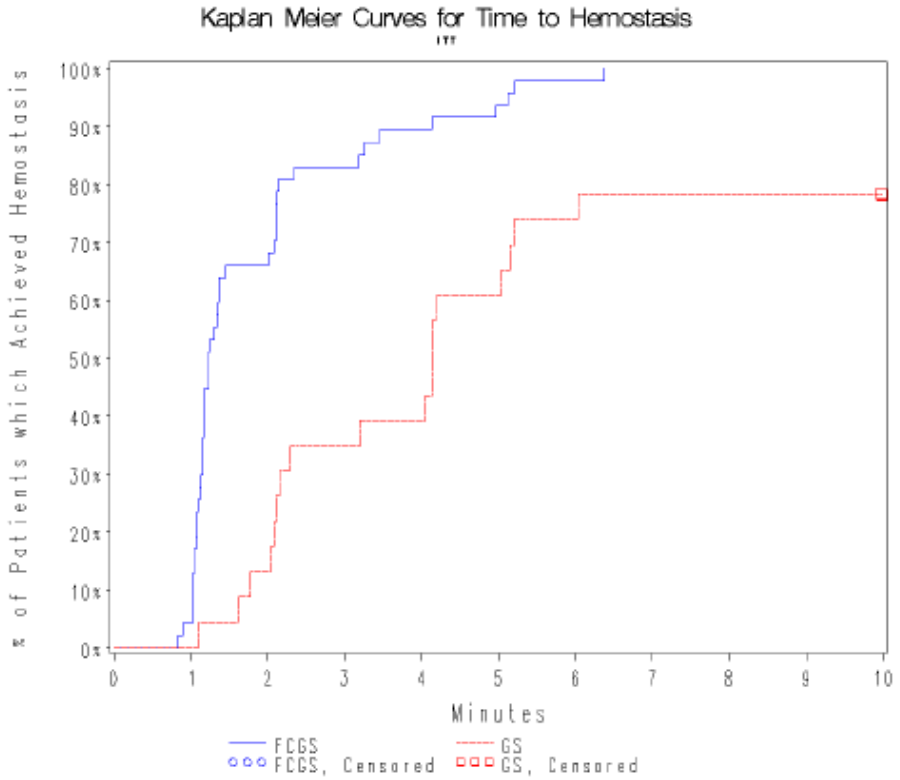
Table 25 – Time to Hemostasis (TTH) and Treatment Success

Parameter	FCGS N=47	GS N=23	p-value
TTH, min			<0.001[1]
Mean ± SD	1.9 ± 1.3	4.8 ± 3.1	
Median (range)	1.2 (0.8, 6.4)	4.2 (1.1, 10.0)	
Treatment Success, % (n)			0.003[2]
Yes	100% (47)	78.3% (18)	
No	0% (0)	21.7% (5)	

Source: Tables 14.09.01.A and 14.09.02.A.
[1] Wilcoxon-Mann-Whitney test.
[2] Fisher's Exact test.

The Kaplan-Meier curves comparing the percentages of subjects in the FCGS and GS groups achieving haemostasis over time. All subjects in the FCGS group reached haemostasis in less than 7 minutes.

Figure 13 **Kaplan-Meier Curves for Time to Hemostasis (ITT)**



A statistically significant difference on a time-to-event analysis using the Kaplan-Meier curves of time to haemostasis data was observed using the Log-Rank test (p<0.0001).

Secondary Efficacy Parameters

The cumulative percentages of subjects achieving haemostasis by 3, 5, and 10 minutes after T-start are summarised in the following table.

Table 26 – Cumulative Percentages of Subjects Achieving haemostasis by 3, 5 and 10 minutes after treatment start

Time After T_{start} (min)	FCGS N=47	GS N=23	p-value[1]
3	83.0% (39)	34.8% (8)	<0.001
5	93.6% (44)	60.9% (14)	0.001
10	100% (47)	78.3% (18)	0.003

Source: Table 14.09.01.A.
[1] Fisher's Exact test.

The percentages of subjects achieving haemostasis were significantly higher in the FCGS group than in the GS group within all 3 time intervals.

2.5.3. Discussion on clinical efficacy

Due to the mechanism of action, the dose solely depends on the size of the tissue to be treated. Dose-response studies were therefore not applicable.

Design and conduct of clinical studies

The main study submitted in support of the current application was study FC-004, a phase III randomised, single-blind, controlled trial of Raplixa in the management of haemostasis during open surgery (spinal surgery, vascular surgery, hepatic surgery and soft tissue surgery).

The active comparator was a gelatin sponge (CE marked Spongostan in EU and Gelfoam in the USA); both are intended for haemostasis in surgical procedures "when control of capillary, venous or arteriolar bleeding by pressure, ligature and other conventional procedures is either ineffective or impractical". Both sponges may be used "with or without thrombin to obtain haemostasis". The choice of comparator is appropriate and is in accordance with CHMP scientific advice received. Gelatin sponge alone was used as a comparator across all of the surgical indications evaluated in the Phase 3 trial. Use of gauze pressure would have presented an ethical dilemma if used as the control comparator because it is regarded as an inferior method to achieve haemostasis.

Raplixa was applied to the target bleeding site in one of three ways: (i) apply direct to bleeding site and then apply the gelatin sponge, (ii) apply to gelatin sponge and then apply sponge to bleeding site or (iii) use the Fibrospray medical device to apply (the Raplixa device required connection to a pressure regulator and a medical CO_2 gas supply) and then apply a gelatin sponge. Raplixa was not used without a gelatin sponge.

The patient population was adequately selected and reflected a population undergoing either spinal, vascular, hepatic or soft tissue surgery. Although carried out as one trial, each surgery type was adequately powered to report on efficacy.

The primary endpoint of "time to haemostasis within the 5-minute time to haemostasis assessment period" is appropriate (and was decided upon after consultation with regulatory agencies). Secondary endpoints such as "overall safety", "transfusion requirements" and "re-operation at the target bleeding site" complement the primary endpoint and are appropriate.

Neither the surgeon carrying out the operation nor the assistant handling the Raplixa or the data analyser were blinded during the study and so potential bias in the study analysis that resulted in lower timing being recorded for use of Raplixa cannot be excluded, however it is acknowledged that blinding of the surgeon and assistant would not have been feasible.

The two treatment groups did not differ significantly in the distribution of age, sex or race. About equal numbers of subjects were enrolled in each surgical setting. The overall duration of the study for 29 days after surgery allowed collection of safety data including an analysis of the development of antibodies to the active substances of Raplixa.

Efficacy data and additional analyses

In the pivotal trial FC-004, 719 patients were studied in the settings of spinal surgery (183 patients), vascular surgery (175 patients), hepatic surgery (180 patients) and soft tissue surgery (181 patients). Raplixa was used in combination with a gelatin sponge to achieve haemostasis in cases of mild or moderate bleeding when conventional surgical techniques such as suture, ligature and cautery were ineffective or impractical. The control

group was exposed to the gelatin sponge only. 480 patients were exposed to Raplixa with a gelatin sponge and 239 patients were in the control group. Each type of surgery in study FC-004 was adequately powered to return statistically significant results.

The primary end-point in the surgeries studied was time taken to achieve haemostasis within a 5-minute assessment period. Using the Cox proportional hazards model, the relative difference in the hazard of haemostasis for Raplixa plus gelatin sponge versus gelatin sponge alone was 3.3 for spinal surgery, 2.1 for vascular surgery, 2.3 for hepatic resection, and 3.4 for soft tissue dissection. By log-rank test, the median time to haemostasis for each surgery type was significantly shorter (by up to 2.5mins) with Raplixa plus gelatin sponge than with gelatin sponge alone ($p<0.0001$).

The key finding is reduction in the time to stop bleeding during the open surgeries described. Haemostasis is achieved within 3 minutes in 90% of patients using Raplixa (compared to ~60% if a gelatin sponge alone is used). The [up to] 2 minute difference observed between Raplixa and gelatin sponge alone is reproducible across very different surgery types performed, and across clinical sites. By log-rank test, the median time to haemostasis for each surgery type was significantly shorter with Raplixa plus gelatin sponge than with gelatin sponge alone ($p<0.0001$). The median time to haemostasis was reduced by between 1 and 2 minutes when Raplixa was used. Ancillary analysis of restricted mean time to haemostasis confirmed a reduction in mean time to haemostasis by between 1.0 to 1.6 minutes. Similar reduction in the time to stop bleeding during surgery was demonstrated for all four types of surgery studied: spinal, vascular, hepatic and open surgery.

Secondary endpoints included (i) restricted mean time to haemostasis (reduced by up to 1.6 mins, $p<0.0001$ in all surgery groups studied) and (ii) the proportion of subjects achieving haemostasis within 3 (or 5) minutes. Haemostasis was achieved within 3 minutes in 90% of patients using Raplixa compared to ~60% if a gelatin sponge alone was used. The reduction in time taken to achieve haemostasis was apparent irrespective of age or sex of the patient.

Three age groups of adults were studied: <65yrs, >65yrs and >75yrs. Results submitted suggest that the reduction in time to stop bleeding was not affected by age of the recipient.

Children were not studied: the Applicant has received a deferral from the Paediatric Committee (EMA) for studies in children. The current status of lack of information in children is reflected in the SmPC.

Patients with chronic renal impairment and / or chronic hepatic impairment and pregnant women were not studied. Section 4.6 of the SPC recommends that Raplixa should not be used in pregnant or lactating women.

Both Gelfoam and Spongostan may be used without Raplixa and are intended for haemostasis during surgical procedures when control of bleeding by conventional means is ineffective or impractical. It is acknowledged that, within the context of an operation that may last several hours, a reduction in time to haemostasis of (about) 2 minutes may seem small yet is clinically relevant.

The lack of clinical pharmacology investigations of Raplixa is justified of the nature of the active substances.

Raplixa is intended to be applied topically to a bleeding site during surgery to reduce the time taken to stop bleeding. Raplixa may be applied either (i) directly on to tissue followed by application of a gelatin sponge or (ii) on to a gelatin sponge which is then applied to tissue or (iii) by using the spray medical device (designed specifically for use with Raplixa) in combination with a gelatin sponge. The gelatin sponges used by the Applicant during the clinical development programme were Gelfoam and Spongostan. Raplixa spray medical device has obtained a CE mark.

The small reduction in time to haemostasis observed (approximately 2 minutes) is translated in a relevant clinical benefit as a few minutes of bleeding can result in enough blood loss to trigger a requirement for

transfusion or complicate the surgery with a resulting increased risk to the patient. Surgical procedures may encounter multiple bleeding sites and so a 2-minute reduction in time to haemostasis at each bleeding site multiplied by several bleeding sites can result in a substantial saving. In the FC-004 clinical trial Raplixa was used to control bleeding at sites other than the primary target bleeding site in 25% of subjects (and >6% percent of subjects had more than three non-target bleeding sites treated). In subjects undergoing hepatic resection, a surgical indication associated with a high risk for blood loss, the 2-minute difference in time-to-haemostasis resulted in a decreased need for transfusion.

The use of fibrinogen and thrombin to assist in the formation of a clot to stop bleeding in the surgical setting is not novel. However, Raplixa is presented as being capable of direct use to the bleeding site or to sponges that will commonly be used to soak up blood in surgery and in this, it has potential to offer an alternative to existing products that require some form of manipulation prior to their use. It is, of course, recognised that the medical use will be in conjunction with sponges and that the nature of experimentation is such that it may be difficult to reliably induce an experimental injury that can consistently show the additional benefit of a product used, as Raplixa is, in addition to sponges. However, sole use of Raplixa may not be achievable at all clinically and testing animals is the only practical means of exploring the effects of sole use of this product.

Raplixa does not need to be thawed, reconstituted or mixed which is time-saving for a critical part of the surgery. The in-use shelf life of 2 hours makes it easier for the surgeon to use Raplixa on multiple bleeding sites.

Overall, there is a potential clinical benefit of reduced time to achieve haemostasis in cases of mild or moderate bleeding during surgical procedures when conventional surgical techniques such as suture, ligature and cautery were ineffective or impractical.

2.5.4. Conclusions on the clinical efficacy

The Applicant has submitted results of studies to support that Raplixa, when used in conjunction with a gelatin sponge in open surgery (spinal surgery, vascular surgery, hepatic surgery and soft tissue surgery), significantly reduces the time to achieve haemostasis in cases of mild or moderate bleeding during surgical procedures when conventional surgical techniques such as suture, ligature and cautery were ineffective or impractical.

2.6. Clinical safety

Patient exposure

The trials constituting the Raplixa clinical safety program consisted of two randomised, single blind, controlled Phase 2 trials (FC-002 US and FC-002 NL) and one randomised, single-blind, controlled Phase 3 trial (FC-004).

An additional first-in-human, open-label study (FC-001) was conducted using first-generation Raplixa material, manufactured with human plasma-derived fibrinogen and thrombin from a different supplier than that used in the subsequent Phase 2 and 3 trials. For this reason, safety data from FC-001 have not been integrated with data from FC-002 US, FC-002 NL, and FC-004

Each of the trials evaluated the safety and immunogenicity of Raplixa topically applied with a gelatin sponge to study subjects for surgical haemostasis, with and without the use of the Fibrospray device.

Surgical settings were: spinal surgery, vascular surgery, hepatic resection and soft tissue dissection.

The studies compared the safety of Raplixa (applied directly from the vial or with the use of the air-powered Fibrospray delivery device) plus gelatin sponge versus gelatin sponge alone. (see table 27)

Table 27 – Description of Fibrocaps Clinical Trials included in the integrated Analysis of Safety

Study ID. (Phase)	Number of Trial Centers & Country	Trial, Dates [a]	Design (Control Type)	Primary/ Secondary Objectives	Surgical Indications	Subjects Randomized[b]/ Planned	Subjects Treated with Fibrocaps plus Gelatin Sponge	Subjects Treated with Gelatin Sponge Alone	Gender M/F Mean age (± SD)
FC-004 (Phase 3)	6 BE 11 NL 12 UK 28 US	May 12–Jun 13	Randomized, single-blind, controlled (gelatin sponge)	Efficacy/ safety	Hepatic resection, spinal, vascular, and soft tissue dissection	721[c]/672	480	239	392/329 58 ± 14.3
FC-002 US (Phase 2)	7/US	Feb 11–Oct 11	Randomized, single-blind, controlled (gelatin sponge)	Efficacy/ safety	Spinal, peripheral vascular, and general surgery	70/90	47	23	34/36 59.8 ± 12. 9
FC-002 NL (Phase 2)	5/NL	Dec 10–Oct 11	Randomized, single-blind, controlled (gelatin sponge)	Efficacy/ safety	Hepatic resection	56[d]/60	39	16	36/20 61.4 ± 12.24

[a] Start-end date and database lock
[b] Total randomized in both treatment arms
[c] Two subjects randomized to Fibrocaps plus gelatin sponge did not receive treatment
[d] One subject randomized to gelatin sponge did not receive treatment

566 subjects were treated with Raplixa plus a gelatin sponge during the three clinical trials. 86 subjects were treated with Raplixa in the Phase 2 program and 480 subjects were treated with Raplixa in Phase 3.

For all trials, each subject received Raplixa during a single surgical procedure although multiple sites of bleeding could be treated. For most subjects (532/566; 94%) one vial of Raplixa was used at the target bleeding site with two vials used for 31/566 subjects (5%) and three vials used for 3/566 subjects (<1%).

Across all surgery types, Raplixa was used at non-target bleeding site in 134/566 subjects (24%), with a single vial used for the majority of subjects 107/566 (19%), two vials used for 23/566 subjects (4%), and three vials used for 4/566 subjects (<1 %). Raplixa was applied using the spray device in 42/86 subjects (48.8%) in FC-002 NL and FC- 002 US and 260/480 subjects (54%) in FC-004. As expected, more vials of Raplixa were used during hepatic resection than were used for the other surgery types.

The following table summarises the demographic profile of subjects enrolled in the Phase 2 and Phase 3 trials:

Table 28 – Demographic characteristics in the Phase 2 and Phase 3 trials (all surgery types)

	Phase 2		Phase 3		Total	
	Fibrocaps Plus Gelatin Sponge (N=86)	Gelatin Sponge Alone (N=39)	Fibrocaps Plus Gelatin Sponge (N=480)	Gelatin Sponge Alone (N=239)	Fibrocaps Plus Gelatin Sponge (N=566)	Gelatin Sponge Alone (N=278)
Sex, n (%)						
Male	50 (58)	19 (49)	266 (55)	124 (52)	316 (56)	143 (51)
Female	36 (42)	20 (51)	214 (45)	115 (48)	250 (44)	135 (49)
Age at Consent (years)						
Mean (SD)	59.5 (13.6)	62.1 (9.5)	57.4 (14.5)	58.1 (14.1)	57.7 (14.3)	58.7 (13.6)
Median	62.5	61.0	59.0	59.0	60.0	60.0
Min, Max	25, 82	35, 81	19, 88	22, 91	19, 88	22, 91
Age >= 65 yrs, n (%)	37 (43)	15 (38)	170 (35)	89 (37)	207 (37)	104 (37)
Age >= 75 yrs, n (%)	8 (9)	3 (8)	55 (11)	24 (10)	63 (11)	27 (10)
Race, n (%)						
White	83 (97)	35 (90)	420 (88)	210 (88)	503 (89)	245 (88)
Black or African American	1 (1)	1 (3)	42 (9)	20 (8)	43 (8)	21 (8)
Asian	1 (1)	3 (8)	8 (2)	3 (1)	9 (2)	6 (2)
American Indian or Alaska Native	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Other	1 (1)	0	7 (1)	4 (2)	8 (1)	4 (1)
Not Reported	0	0	2 (<1)	1 (<1)	2 (<1)	1 (<1)

Source: ISS Appendix Table 3

459 of the total 844 subjects (54%) were male: most subjects were white (748/844; 89%): the median age was 60 years (range, 19, 91): 403/844 subjects were < 65 years old: 311/844 subjects (37%) were >65 years and 90/844 subjects (11%) were ≥75 years.

The following table presents a summary of subject demographics by surgery type:

Table 29 – Demographic characteristics in Phase 2 and 3 by Surgery Type

Parameter	Category/ Statistic	Spine (N=220)	Hepatic (N=237)	Vascular (N=205)	Soft Tissue (N=182)	Total (N=844)
Gender, n (%)	Female	101 (46)	88 (37)	68 (33)	128 (70)	385 (46)
	Male	119 (54)	149 (63)	137 (67)	54 (30)	459 (54)
Age, yr	Mean (SD)	55.1 (13.72)	60.7 (13.18)	65.7 (10.09)	49.5 (14.11)	58.0 (14.11)
	Median	56.0	63.0	66.0	49.0	60.0
	Min, Max	23, 86	21, 91	36, 88	19, 83	19, 91
	≥65 years, n (%)	60 (27)	103 (43)	121 (59)	27 (15)	311 (37)
	≥75 years, n (%)	16 (7)	29 (12)	36 (18)	9 (5)	90 (11)
Race, n (%)	White	203 (92)	226 (95)	184 (90)	135 (74)	748 (89)
	Black/African American	8 (4)	4 (2)	12 (6)	40 (22)	64 (8)
	Asian	5 (2)	4 (2)	2 (<1)	4 (2)	15 (2)
	American Indian/Alaskan Native	1 (<1)	0	0	1 (<1)	2 (<1)
	Other	3 (1)	2 (<1)	5 (2)	2 (1)	12 (1)
	Not Reported	0	1 (<1)	2 (<1)	0	3 (<1)

Source: ISS Appendix Table 4

Males comprised most subjects undergoing spinal surgery, hepatic resection and vascular surgery: 54%, 63% and 67%, respectively. In contrast, females comprised most subjects undergoing soft tissue dissection; 70%.

The proportion of subjects who were ≥65 years old was higher in both hepatic resection and vascular surgery (43% and 59%, respectively) as compared to spinal surgery and soft tissue dissection (27% and 15%, respectively). A similar pattern was observed in the ≥75 year old age category.

Most subjects in all surgery types were white. Concurrent medical conditions were relatively balanced between the Raplixa and gelatin sponge alone groups and were consistent with the study subjects' age (mean = 57.6 years) and the types of surgery being performed. Concomitant medication use was relatively balanced between the Raplixa plus gelatin sponge and gelatin sponge alone groups and was consistent with the types of surgeries being performed and diseases states of the subjects in each surgical indication.

Study FC-004

480 subjects were treated with Raplixa in combination with a gelatin sponge.

For most subjects (448/480; 93%) one vial of Raplixa was used at the target bleeding site

Two vials were used for 29/480 subjects (6%) and three vials used for 3/480 subjects (<1%).

For each surgery type, most subjects were treated with a single vial of Raplixa (>99%, 91%, 90%, and 93% of spinal, vascular, hepatic, and soft tissue dissection subjects, respectively).

The three subjects who were treated with three vials of Raplixa were undergoing vascular surgery (two subjects) and hepatic resection (one subject).

The median percentage of Raplixa used per vial was similar across vascular surgery, hepatic resection, and soft tissue dissection surgeries (100%, 100%, and 90%, respectively), but lower in spinal surgery (20%).

Across all surgery types, Raplixa was used at non-target bleeding site in 122/480 subjects (25%), with a single vial used for the majority of subjects (96/122; 79%), two vials used for 22/122 subjects (18%), and three vials used for 4/122 subjects (3%).

Overall, the Fibrospray device was used in 260 surgeries (54%). For most subjects treated using the Fibrospray device, (242/260; 93%) one vial of Raplixa was used, with two vials used for 17/260 subjects (7%) and three vials used for 1/260 subjects (<1%). The device was used for almost all hepatic and soft tissue dissection surgeries performed with Raplixa (97% and 94%, respectively) but for a lower proportion of spinal or vascular surgeries (24% and 1%, respectively).

Adverse events

All adverse events

All adverse events were coded according to MedDRA, Version 15.0 by system organ class and preferred term. The following table summarises the overall adverse event profile of Raplixa in the Phase 2 and Phase 3 trials:

Table 30 **Overall Summary of Adverse Events in the Phase 2 and Phase 3 Trials (All Surgery Types)**

	Phase 2		Phase 3		Total (Phase 2 + Phase 3)	
n(%)	Fibrocaps+ Gelatin Sponge (N=86)	Gelatin Sponge (N=39)	Fibrocaps+ Gelatin Sponge (N=480)	Gelatin Sponge (N=239)	Fibrocaps+ Gelatin Sponge (N=566)	Gelatin Sponge (N=278)
Any TEAE	79 (92)	32 (82)	426 (89)	214 (90)	505 (89)	246 (88)
Any Serious TEAE	18 (21)	5 (13)	81 (17)	29 (12)	99 (17)	34 (12)
Any TEAE related to treatment[a]	1 (1)	0	2 (<1)	4 (2)	3 (<1)	4 (1)
Any Serious TEAE related to treatment	1 (1)	0	0	0	1 (<1)	0
Any TEAE related to Fibrospray device	0	0	0	0	0	0
Any Serious TEAE related to Fibrospray device	0	0	0	0	0	0
Any Grade 3, 4 or 5 TEAE	16 (19)	6 (15)	105 (22)	44 (18)	121 (21)	50 (18)
Any Grade 3, 4 or 5 TEAE related to treatment	1 (1)	0	0	0	1 (<1)	0
Any Grade 3, 4 or 5 TEAE related to Fibrospray device	0	0	0	0	0	0
Any TEAE leading to discontinuation of treatment	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)

[a] defined as "related", "probably related", or "possibly related"
Source: ISS Appendix Table 5

Subjects experienced at least one treatment-emergent adverse event (89% in the Raplixa plus gelatin sponge group and 88% in the gelatin sponge alone group) as would be expected for subjects undergoing surgery. The percentage of subjects who had treatment-emergent adverse events considered related to study treatment was extremely low in the two treatment groups; 0.5% in the Raplixa plus gelatin sponge group and 1.4% in the gelatin sponge alone group.

The proportion of subjects who experienced a serious treatment-emergent adverse event was similar between the two treatment groups and consistent with the surgical populations included in this trial and the variety of chronic baseline diseases reported.

Study FC-004

A total of 426/480 subjects (89%) in the Raplixa plus gelatin sponge group and 214/239 subjects (90%) in the gelatin sponge alone group experienced at least one treatment-emergent adverse event.

Two subjects in the Raplixa plus gelatin sponge group (<1%) and four subjects in the gelatin sponge alone group (2%) had adverse events that were considered by the Investigator to be at least possibly related to study treatment. No adverse events were considered related to the Fibrospray device.

No serious adverse events were considered by the Investigator to be at least possibly related to study treatment.

Common adverse events

The following table presents a summary of treatment-emergent adverse events reported in ≥5% of subjects in either treatment group by overall descending order of incidence.

Table 31 Adverse Events Occurring in ≥5% of Subjects Overall by Preferred Term (Safety Population; All Surgery Types)

	Phase 2		Phase 3		Total	
N (%) of Patients Preferred Term	Fibrocaps+ Gelatin Sponge (N=86)	Gelatin Sponge (N=39)	Fibrocaps+ Gelatin Sponge (N=480)	Gelatin Sponge (N=239)	Fibrocaps+ Gelatin Sponge (N=566)[a]	Gelatin Sponge (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)
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)

[a] Sort order based on Fibrocaps plus gelatin sponge
Source: ISS Appendix Table 6

In the Phase 2 and Phase 3 trials combined, the most frequently reported adverse events (in ≥10% of subjects) with Raplixa plus gelatin sponge and with gelatin sponge alone were procedural pain, nausea, constipation, and nausea. These events each occurred at a similar frequency in both treatment arms and in Phase 2 versus Phase 3, and were consistent with events usually reported in subjects undergoing the surgical procedures evaluated in these studies.

The most noteworthy difference in the incidence of adverse events in subjects exposed to Raplixa plus gelatin sponge as compared to subjects exposed to gelatin sponge alone was for insomnia and pruritus: the disparate frequency of these events between treatment groups was only evident in the Phase 3 trial.

Study FC-004

Pruritus was reported in 36/566 subjects (6%) treated with Raplixa plus gelatin sponge versus 9/278 subjects (3%) treated with gelatin sponge alone. While pruritus can be a symptom of an allergic-type reaction, it tended to occur without any associated signs or symptoms typical of allergic reactions (e.g. rash, difficulty breathing, and hypotension) that might suggest a risk of an allergic reaction.

Insomnia was reported in 46/566 subjects (8%) treated with Raplixa plus gelatin sponge versus 12/278 subjects (4%) treated with gelatin sponge alone. The lack of a mechanistic or scientific relationship coupled with the lack of consistency across surgery types suggests that insomnia may be at least partially due to random statistical chance. The issue was discussed by the Independent Data Monitor Committee.

None of the insomnia (or pruritus) events was considered related to Raplixa, gelatin sponge or the Fibrospray device, and are difficult to connect with the mode of administration of Raplixa (applied topically to a bleeding site) or the mechanism of action (rapid, localized clot formation).

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

Treatment-Related Adverse Events

In the Phase 2 and Phase 3 trials combined, 3/566 subjects (0.5%) in the Raplixa plus gelatin sponge group and 4/278 subjects (1.4%) in the gelatin sponge alone group had adverse events that investigators considered to be at least possibly related to treatment.

In the Phase 2 trials, the only adverse events that was considered at least possibly related to treatment was Grade 3 stroke in a subject treated with Raplixa plus gelatin sponge in FC-002 NL.

Study FC-004

Of the 480 subjects treated with Raplixa plus gelatin sponge, 2 (<1%) experienced adverse events that Investigators considered to be possibly related study treatment. Both subjects were undergoing hepatic resection; one subject experienced decreased haemoglobin and the other experienced pyrexia. No subjects experienced adverse events that Investigators considered related to the Fibrospray device.

Of the 239 subjects treated with gelatin sponge alone, four (2%) experienced adverse events that were considered possibly or definitely related to study treatment. All four subjects were undergoing hepatic resection. One of the subjects experienced thrombocytopenia and decreased white blood cell count that were both considered possibly related to study treatment. Events in the other three subjects were post-procedural haemorrhage, pulmonary embolism, and anaemia. The adverse event of post-procedural haemorrhage was considered definitely related to study treatment, while the other two adverse events were considered possibly related.

No treatment-related effects or trends were observed for any vital signs.

Serious adverse event/deaths/other significant events

Deaths

12 subjects died during the Phase 2 and Phase 3 trials.

Studies FC-002US and FC-002NL

There were two deaths in the Phase 2 trials; one subject died of ventilator-associated pneumonia and one subject died of aspiration. Both subjects were treated with Raplixa plus gelatin sponge. Neither death was considered related to study treatment; prior medical conditions were considered contributory.

Study FC-004

Ten subjects died during the 30-day safety follow-up period: eight subjects treated with Raplixa plus gelatin sponge and two subjects treated with gelatin sponge alone (see Table 46).

Four cardiac deaths occurred in subjects known to have cardiac disease: one death was caused by a ruptured aortic aneurysm: one death was caused by malignancy: one death occurred in a subject with liver failure and one death had cause unknown, autopsy not performed.

None of the deaths were considered by Investigators or the Sponsor to be related to study treatment.

Serious adverse events

In the Phase 2 and Phase 3 trials combined, serious adverse events were reported for 99/556 subjects (18%) treated with Raplixa plus gelatin sponge and 34/278 subjects (12%) treated with gelatin sponge alone. No preferred term was reported in >5 subjects in either treatment group and the frequencies and the types of events were similar between the two treatment groups. The only serious adverse event considered at least possibly related to treatment by the Investigator was a stroke in the right hemisphere in a subject treated with Raplixa plus gelatin sponge in FC-002 NL (the subject later died).

Study FC-004

Treatment-emergent serious adverse events are presented for all surgery types and by surgery type.

110/719 subjects (15%) experienced a serious adverse event: 81/480 subjects (17%) treated with Raplixa and 29/239 subjects (12%) treated with gelatin sponge alone.

All serious adverse events were reported in <5% of subjects in either treatment group within each surgical setting and the frequencies and the types of events were similar between the two treatment groups. Serious adverse events for all surgeries are shown in the following table 32:

N (%) of Patients

System Organ Class Preferred Term	Fibrocaps plus Gelatin Sponge (N=480)	Gelatin Sponge Alone (N=239)	All Patients (N=719)
Patients With at Least One Serious TEAE	81 (17)	29 (12)	110 (15)
Infections And Infestations	23 (5)	8 (3)	31 (4)
Pneumonia	4 (<1)	2 (<1)	6 (<1)
Abdominal abscess	4 (<1)	1 (<1)	5 (<1)
Postoperative wound infection	4 (<1)	0	4 (<1)
Sepsis	3 (<1)	0	3 (<1)
Wound infection	2 (<1)	1 (<1)	3 (<1)
Abdominal sepsis	1 (<1)	0	1 (<1)
Cellulitis	1 (<1)	0	1 (<1)
Infectious peritonitis	1 (<1)	0	1 (<1)
Liver abscess	1 (<1)	0	1 (<1)
Lower respiratory tract infection	0	1 (<1)	1 (<1)
Lung infection	1 (<1)	0	1 (<1)
Osteomyelitis	0	1 (<1)	1 (<1)
Peritonitis	0	1 (<1)	1 (<1)
Psoas abscess	0	1 (<1)	1 (<1)
Rectal abscess	0	1 (<1)	1 (<1)
Septic shock	1 (<1)	0	1 (<1)

N (%) of Patients

System Organ Class Preferred Term	Fibrocaps plus Gelatin Sponge (N=480)	Gelatin Sponge Alone (N=239)	All Patients (N=719)
Subcutaneous abscess	1 (<1)	0	1 (<1)
Subdiaphragmatic abscess	1 (<1)	0	1 (<1)
Urinary tract infection	0	1 (<1)	1 (<1)
Urosepsis	1 (<1)	0	1 (<1)
Injury, Poisoning And Procedural Complications	23 (5)	6 (3)	29 (4)
Gastrointestinal anastomotic leak	3 (<1)	1 (<1)	4 (<1)
Post procedural bile leak	2 (<1)	2 (<1)	4 (<1)
Seroma	2 (<1)	2 (<1)	4 (<1)
Anastomotic leak	2 (<1)	0	2 (<1)
Post procedural haematoma	2 (<1)	0	2 (<1)
Post procedural haemorrhage	2 (<1)	0	2 (<1)
Small-for-size liver syndrome	2 (<1)	0	2 (<1)
Vascular graft thrombosis	1 (<1)	1 (<1)	2 (<1)
Anaesthetic complication	1 (<1)	0	1 (<1)
Anastomotic haemorrhage	1 (<1)	0	1 (<1)
Arteriovenous fistula thrombosis	1 (<1)	0	1 (<1)
Fall	1 (<1)	0	1 (<1)
Gastrointestinal disorder postoperative	1 (<1)	0	1 (<1)
Pancreatic leak	1 (<1)	0	1 (<1)
Postoperative fever	1 (<1)	0	1 (<1)
Procedural pain	0	1 (<1)	1 (<1)
Pseudomeningocele	1 (<1)	0	1 (<1)
Vascular pseudoaneurysm	1 (<1)	0	1 (<1)
Gastrointestinal Disorders	12 (3)	7 (3)	19 (3)
Ileus	3 (<1)	2 (<1)	5 (<1)
Gastrointestinal haemorrhage	1 (<1)	1 (<1)	2 (<1)
Impaired gastric emptying	1 (<1)	1 (<1)	2 (<1)
Small intestinal obstruction	1 (<1)	1 (<1)	2 (<1)
Abdominal pain lower	1 (<1)	0	1 (<1)
Anal haemorrhage	1 (<1)	0	1 (<1)
Gastric perforation	1 (<1)	0	1 (<1)
Gastroduodenal haemorrhage	1 (<1)	0	1 (<1)
Ileus paralytic	1 (<1)	0	1 (<1)
Intestinal ischaemia	0	1 (<1)	1 (<1)
Localised intraabdominal fluid collection	0	1 (<1)	1 (<1)
Pancreatitis acute	1 (<1)	0	1 (<1)
Small intestinal ulcer haemorrhage	1 (<1)	0	1 (<1)
Respiratory, Thoracic And Mediastinal Disorders	6 (1)	7 (3)	13 (2)
Pulmonary embolism	2 (<1)	1 (<1)	3 (<1)
Respiratory failure	0	3 (1)	3 (<1)
Acute respiratory distress syndrome	2 (<1)	0	2 (<1)
Respiratory depression	1 (<1)	1 (<1)	2 (<1)
Chylothorax	1 (<1)	0	1 (<1)
Dyspnoea	0	1 (<1)	1 (<1)
Hypercapnia	1 (<1)	0	1 (<1)
Pleural effusion	1 (<1)	0	1 (<1)
Pulmonary oedema	0	1 (<1)	1 (<1)
Vascular Disorders	9 (2)	3 (1)	12 (2)
Lymphorrhoea	3 (<1)	0	3 (<1)
Peripheral ischaemia	2 (<1)	1 (<1)	3 (<1)
Deep vein thrombosis	1 (<1)	1 (<1)	2 (<1)
Aortic aneurysm rupture	1 (<1)	0	1 (<1)
Arterial haemorrhage	0	1 (<1)	1 (<1)
Hypotension	1 (<1)	0	1 (<1)
Vena cava thrombosis	1 (<1)	0	1 (<1)
Cardiac Disorders	7 (1)	1 (<1)	8 (1)

N (%) of Patients

System Organ Class Preferred Term	Fibrocaps plus Gelatin Sponge (N=480)	Gelatin Sponge Alone (N=239)	All Patients (N=719)
Atrial fibrillation	2 (<1)	0	2 (<1)
Cardiac arrest	2 (<1)	0	2 (<1)
Myocardial infarction	1 (<1)	1 (<1)	2 (<1)
Myocardial ischaemia	2 (<1)	0	2 (<1)
Cardiac failure	0	1 (<1)	1 (<1)
Silent myocardial infarction	1 (<1)	0	1 (<1)
General Disorders And Administration Site Conditions	5 (1)	2 (<1)	7 (<1)
Cardiac death	1 (<1)	0	1 (<1)
Chest pain	0	1 (<1)	1 (<1)
Death	1 (<1)	0	1 (<1)
Hernia obstructive	0	1 (<1)	1 (<1)
Malaise	1 (<1)	0	1 (<1)
Pyrexia	1 (<1)	0	1 (<1)
Unintentional medical device removal by patient	1 (<1)	0	1 (<1)
Blood And Lymphatic System Disorders	5 (1)	1 (<1)	6 (<1)
Anaemia	4 (<1)	0	4 (<1)
Leukocytosis	1 (<1)	0	1 (<1)
Thrombocytopenia	0	1 (<1)	1 (<1)
Metabolism And Nutrition Disorders	5 (1)	1 (<1)	6 (<1)
Hypovolaemia	2 (<1)	1 (<1)	3 (<1)
Dehydration	2 (<1)	0	2 (<1)
Electrolyte imbalance	1 (<1)	0	1 (<1)
Hyperglycaemia	1 (<1)	0	1 (<1)
Hepatobiliary Disorders	2 (<1)	1 (<1)	3 (<1)
Gallbladder perforation	1 (<1)	0	1 (<1)
Hepatic failure	0	1 (<1)	1 (<1)
Hepatic function abnormal	1 (<1)	0	1 (<1)
Musculoskeletal And Connective Tissue Disorders	2 (<1)	1 (<1)	3 (<1)
Back pain	1 (<1)	1 (<1)	2 (<1)
Intervertebral disc protrusion	1 (<1)	0	1 (<1)
Nervous System Disorders	3 (<1)	0	3 (<1)
Cerebral infarction	1 (<1)	0	1 (<1)
Paraplegia	1 (<1)	0	1 (<1)
Transient ischaemic attack	1 (<1)	0	1 (<1)
Investigations	1 (<1)	1 (<1)	2 (<1)
Hepatitis C antibody positive	1 (<1)	1 (<1)	2 (<1)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	2 (<1)	0	2 (<1)
Meningioma	1 (<1)	0	1 (<1)
Small intestine carcinoma	1 (<1)	0	1 (<1)
Psychiatric Disorders	1 (<1)	1 (<1)	2 (<1)
Delirium	0	1 (<1)	1 (<1)
Mental status changes	1 (<1)	0	1 (<1)
Renal And Urinary Disorders	1 (<1)	0	1 (<1)
Renal failure acute	1 (<1)	0	1 (<1)

No serious adverse events were considered by Investigators or the Sponsor to be related to study treatment.

Adverse Events of Interest

Adverse events of interest were those that were biologically plausibly associated with Raplixa exposure, have been historically associated with the class of topical haemostatic agents, or have been historically associated with drug application using air or gas-pressurized sprayers.

The following table provides a summary of adverse events of interest reported in ≥5% of subjects in the Phase 2 and Phase 3 trials:

Table 33 Adverse Events of Interest Occurring in ≥5 % of Subjects Overall (Safety

	Phase 2		Phase 3		Total	
N (%) of Patients	Fibrocaps (N=86)	Gelatin Sponge (N=39)	Fibrocaps (N=480)	Gelatin Sponge (N=239)	Fibrocaps (N=566)	Gelatin Sponge (N=278)
Any	79 (92)	32 (82)	426 (89)	214 (90)	505 (89)	246 (88)
Thromboembolic Events	**5 (5.8)**	**3 (8)**	**14 (3)**	**8 (3)**	**19 (3)**	**11 (4)**
Pulmonary Embolism	1 (1)	1 (3)	2 (<1)	2 (<1)	3 (<1)	3 (1)
Deep Vein Thrombosis	1 (1)	0	2 (<1)	2 (<1)	3 (<1)	2 (<1)
Cardiac Arrest	1 (1)	0	2 (<1)	0	3 (<1)	0
Vascular Graft Thrombosis	0	0	2 (<1)	1 (<1)	2 (<1)	1 (<1)
Arteriovenous Fistula Thrombosis	0	1 (3)	1 (<1)	0	1 (<1)	1 (<1)
Cerebrovascular Accident	1 (1)	1 (3)	0	0	1 (<1)	1 (<1)
Myocardial Infarction	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Myocardial Ischaemia	0	0	2 (<1)	0	2 (<1)	0
Acute Coronary Syndrome	1 (1)	0	0	0	1 (<1)	0
Arterial Thrombosis Limb	0	0	1 (<1)	0	1 (<1)	0
Cerebral Infarction	0	0	1 (<1)	0	1 (<1)	0
Femoral Artery Occlusion	0	0	0	1 (<1)	0	1 (<1)
Intestinal Ischaemia	0	0	0	1 (<1)	0	1 (<1)
Silent Myocardial Infarction	0	0	1 (<1)	0	1 (<1)	0
Thrombosis	0	0	0	1 (<1)	0	1 (<1)
Vena Cava Thrombosis	0	0	1 (<1)	0	1 (<1)	0
Surgical Site-related AE	9 (10)	5 (13)	72 (15)	34 (14)	81 (14)	39 (14)
Incision Site Pain	5 (6)	3 (8)	63 (13)	32 (13)	68 (12)	35 (13)
Postoperative Wound Infection	2 (2)	1 (3)	4 (<1)	3 (1)	6 (1)	4 (1)
Incision Site Erythema	2 (2)	0	4 (<1)	1 (<1)	6 (1)	1 (<1)
Incision Site Complication	0	0	3 (<1)	0	3 (<1)	0
Incision Site Cellulitis	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Incision Site Infection	1 (1)	0	1 (<1)	0	2 (<1)	0
Incision Site Pruritus	1 (1)	0	0	1 (<1)	1 (<1)	1 (<1)
Postoperative Wound Complication	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Incision Site Blister	0	1 (3)	0	0	0	1 (<1)
Incision Site Haemorrhage	0	1 (3)	0	0	0	1 (<1)

	Phase 2		Phase 3		Total	
N (%) of Patients	Fibrocaps (N=86)	Gelatin Sponge (N=39)	Fibrocaps (N=480)	Gelatin Sponge (N=239)	Fibrocaps (N=566)	Gelatin Sponge (N=278)
Suspected air/gas emboli[a]	**0 (0)**	**0 (0)**	**14 (3)**	**6 (3)**	**14 (2)**	**6 (2)**
Procedural Hypotension	0	0	9 (2)	2 (<1)	9 (2)	2 (<1)
Respiratory Failure	0	0	4 (<1)	4 (2)	4 (<1)	4 (1)
Respiratory Distress	0	0	1 (<1)	0	1 (<1)	0
Re-bleeding from the surgical site	**5 (6)**	**0 (0)**	**9 (2)**	**8 (3)**	**14 (2)**	**8 (3)**
Post Procedural Haemorrhage	1 (1)	0	2 (<1)	4 (2)	3 (<1)	4 (1)
Haemorrhage	3 (3)	0	1 (<1)	2 (<1)	4 (<1)	2 (<1)
Haematoma	0	0	2 (<1)	1 (<1)	2 (<1)	1 (<1)
Post Procedural Haematoma	1 (1)	0	2 (<1)	0	3 (<1)	0
Arterial Haemorrhage	0	0	0	1 (<1)	0	1 (<1)
Wound Haematoma	0	0	1 (<1)	0	1 (<1)	0
Wound Haemorrhage	0	0	1 (<1)	0	1 (<1)	0
Hepatitis	**0 (0)**	**0 (0)**	**1 (<1)**	**1 (<1)**	**1 (<1)**	**1 (<1)**
Hepatitis C Antibody Positive[b]	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)

[a] the use of the Fibrospray device with Fibrocaps was not associated with any increased risk of events suggestive of air emboli; see text below in Section 2.1.5.3

[b] There were no TEAE for Hepatitis B or HIV observed in either treatment arm. There were two adverse events of positive hepatitis C antibody test results from a single site, one in the control arm and one in the Fibrocaps arm, which suggests that this may be a site-related finding (e.g., high risk patient population).

Source: ISS Appendix Table 13

There were no imbalances on any of the adverse events of interest as described.

Adverse events were:

- Surgical site-related events, including pain and infection suggestive of a higher complication rate. No difference in the incidence of surgical site-related events, including hematoma, haemorrhage or wound complications was observed in subjects who received Raplixa plus gelatin compared with those who received gelatin sponge alone. Incision site pain was the only event of interest reported above 5%, with 12% and 13% reported for the Raplixa plus gelatin sponge and gelatin sponge alone arms, respectively.
- Thromboembolic events, including acute ischaemic events like myocardial infarction, deep vein thrombosis and stroke. There were 11 (4%) and 19 (3%) thromboembolic events identified for the gelatin sponge alone and Raplixa plus gelatin sponge groups, respectively, with all events classified as unlikely related or unrelated.
- Re-bleeding at the target bleeding site including post-procedural haemorrhage and haematomas. This was reported in 8 (3%) and 14 (2%) subjects for the gelatin sponge alone and Raplixa plus gelatin sponge groups, respectively.
- Air emboli-associated events, including acute respiratory failure or cardiovascular collapse occurring intra-operatively following the use of the Fibrospray device. Events occurred in study FC-004. There were 6 and 14 events identified for the gelatin sponge alone and the Raplixa plus gelatin sponge groups, respectively. Fibrospray was used in 5/14 cases. Three of these five events were procedural hypotension. The remaining 2 events were respiratory failure that occurred one and nine days post-surgery and were considered unrelated to the use of the Fibrospray device.

- Hepatitis / HIV infection suggestive of viral transmission through Raplixa. Overall, there were no reports of hepatitis B or HIV infection post treatment. There were two adverse events of positive hepatitis C antibody test results from a single site, one in the control arm and one in the Raplixa arm, which suggests that this may be a site-related finding (i.e. high risk patient population).
- Drug Interactions
- Drug-drug interactions were not expected as Raplixa is topically applied and not appreciably systemically bioavailable.
- Overdose
- Overdose would be a highly unlikely event for Raplixa. However, the safety margins and safety profile established during the non-clinical studies demonstrated that high concentrations of Raplixa (or mis-use of the Fibrospray device) did not lead to an unwanted toxicities or outcomes.
- Drug Abuse
- As Raplixa is applied in a surgical setting, drug abuse would be unlikely to occur.
- Withdrawal and Rebound
- Withdrawal or rebound symptoms are not anticipated for Raplixa due to its route of administration, lack of systemic bioavailability and mechanism of action.
- Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability
- Not applicable.

Laboratory findings

There were no apparent trends of clinically significant biochemistry or haematology (routine blood count and coagulation tests) abnormalities in either treatment group.

Safety in special populations

Table 34 : AEs in elderly patients

MedDRA Terms	**Age <65** number (percentage)	**Age 65-74** number (percentage)	**Age 75-84** number (percentage)	**Age 85+** number (percentage)
n (%)	Raplixa N=359	Raplixa N=144	Raplixa N=57	Raplixa N=6
Total AEs	324 (90)	130 (90)	45 (79)	6 (100)
Serious AEs – Total[1]	45 (13)	34 (24)	18 (32)	2 (33)
AE leading to Drop Out	1 (<1)	0	0	0
MedDRA Terms				
Psychiatric disorders	40 (11)	30 (21)	11 (19)	2 (33)
Nervous system disorders	36 (10)	16 (11)	6 (11)	2 (33)
Injury, Poisoning And	251 (70)	95 (66)	33 (58)	6 (100)
Procedural Complications				
Cardiac disorders	23 (6)	10 (7)	9 (16)	0
Vascular disorders	37 (10)	27 (19)	12 (21)	3 (50)

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)
n (%)	Raplixa N=359	Raplixa N=144	Raplixa N=57	Raplixa N=6
Cerebrovascular disorders	1 (<1)	0	0	0
Infections and infestations	46 (13)	33 (23)	12 (21)	1 (17)
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	22 (6)	14 (10)	8 (14)	3 (50)
Other AE appearing more frequently in older patients	There were no notable differences in AE profile of Raplixa plus gelatin sponge compared to gelatin sponge alone based on any of these demographic factors (Summary of Clinical Safety Section 5.1.1)[2]			

[1] Note Serious AE were defined using the following criteria: Fatal, Hospitalization/prolong existing hospitalization, Life-threatening, Disability/incapacity, or Other (medically significant); source: TREF15_EMA_ISS.
[2] Age categories assessed were: < 65; ≥ 65; ≥ 75 source: TREF 40.1

There were not any notable differences in adverse event profile of Raplixa plus gelatin sponge compared to gelatin sponge alone based on age, gender or racial origin. Raplixa has not been evaluated during pregnancy or lactation.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions were not specifically studied.

15 subjects had reported adverse events associated with prothrombin time / INR, with seven of those subjects (all from Site 402) having baseline prolongation of prothrombin time that made these findings non-treatment-emergent (five Raplixa plus gelatin sponge subjects and two gelatin sponge alone subjects).

Only one Raplixa-treated subject (Subject 402-020) who underwent soft tissue surgery and received enoxaparin post-surgery was treated for an elevated INR with Vitamin K following the second elevated lab result on Day 10. The INR in this subject returned to baseline by Day 29 without any further treatment.

The other seven treatment-emergent adverse events (six subjects treated with Raplixa plus gelatin sponge and one subject treated with gelatin sponge alone) were transient and mild and typically occurred on Day 2 when subjects may have received heparin/low molecular weight heparin to prevent thromboembolic events in the immediate post-operative period. All of the prothrombin time / INR values in these subjects had returned to normal by Day 29, except Subject 301-015 who was started on warfarin for anticoagulation.

None of the adverse events were considered related to Raplixa or gelatin sponge.

Immunological events

Assays for antibodies

Blood samples from recipients were analysed for antibodies to thrombin and fibrinogen using in-house ELISA and commercially available materials.

Neutralising antibodies (anti-thrombin and anti-fibrinogen) were assayed by adding a specified amount of human thrombin to samples and measuring the time taken to form a fibrin clot. In the presence of neutralising antibodies, the time-to-clot is increased. Each patient's baseline time value was compared to the day 29 value. If a significant difference i.e. >29.78 sec (the mean time to clot + 3SD) was observed when comparing baseline to day 29 time to clot, then the patient was considered to have evidence of neutralising antibodies.Data for neutralisation was reported as 'positive' if a significant difference between baseline and day 29 was observed and 'negative' if there was not a significant difference between baseline and day 29.

Anti-thrombin antibodies were detectable at baseline in 5/440 evaluable Raplixa-treated subjects (1%) and 9/222 evaluable gelatin sponge-treated subjects (4%). Nine of 440 subjects (2%) in the Raplixa plus gelatin sponge group and six of 222 subjects (3%) in the gelatin sponge alone group developed anti-thrombin antibodies during the trial.

Of the nine Raplixa-treated subjects who developed anti-thrombin antibodies, two were undergoing spinal surgery, two were undergoing vascular surgery, two were undergoing hepatic resection, and three were undergoing soft tissue dissection.

Of the six gelatin sponge alone-treated subjects who developed anti-thrombin antibodies, three were undergoing soft tissue dissection, two were undergoing spinal surgery, and one was undergoing hepatic resection. Results are summarised in the following table:

Table 35 Overall Anti-Thrombin Antibody Results for FC-004

	Anti-Thrombin Abs n/N (%): FC + gelatin Treated Subjects	Anti-Thrombin Abs n/N (%): Gelatin Alone Treated Subjects
Antibody Positive[a]	9/440 (2%)	6/222 (3%)
Seroconversion[b]	9/440 (2%)	6/222 (3%)
≥ 1.0 unit Titer Change[c]	0/440 (0%)	0/222 (0%)

[a] Patients with a specific confirmatory assay result and measurable titer at baseline
[b] Patients with a non-reactive or non-specific assay result at baseline but with a specific and measurable titer at Day 29 (i.e., titer >= 1.0)
[c] Patients with a specific and measurable titer at baseline who had a >= 1.0 unit titer increase from baseline to Day 29

None of the antibody positive subjects had neutralizing antibodies to thrombin. None of the patients with baseline positive titres had an increase in titre >1 unit following exposure to Raplixa.

None of the anti-thrombin antibody-positive patients had antibodies to fibrinogen.

There were not any clinical sequelae or evidence of hypersensitivity in subjects with positive anti-thrombin antibody tests.

None of the patients was considered to have evidence of neutralising antibodies with the exception of subject 417014 whose neutralisation status was indeterminable.

The data presented are consistent with those published for related (marketed) products.

Similar results / conclusions were found for the phase 2 studies of the current application.

Discontinuation due to adverse events

None. Two subjects were erroneously described as 'discontinued because of adverse event.

Post marketing experience
N/A

2.6.1. Discussion on clinical safety

In pivotal study FC-004, 719 patients were treated with Raplixa. All subjects were exposed to Raplixa during one surgical procedure: application to multiple bleeding sites during surgery was permitted. Recipients of the current product were followed up for safety analysis at 29 days after exposure. Only insomnia and pruritus appeared to be more common in recipients Raplixa.

Recipients of Raplixa did not appear to develop an immunogenic reaction. Antibodies to the active substances of Raplixa were not detected at day 29 after surgery.

Many treatment-emergent adverse events were reported as would be expected for studies done at the time of a surgical operation. However, most adverse events were considered to be unrelated to Raplixa. Most treatment-emergent adverse events were considered to have arisen from the surgical procedures undertaken; however, it could be possible that surgery-related events may have masked adverse events that were directly related Raplixa.

On review of data, there was concern that cardiac and neurological adverse events were more common in subjects exposed to Raplixa during spinal, vascular and soft-tissue surgery (though not hepatic surgery) and that these events were consequent to gas emboli. It is also considered possible that insomnia may have been one of the more subtle manifestations of gas emboli. It is appreciated that numbers of participants are small and that the number of cardiac and neurological events is correspondingly small and that the surgeries undertaken will have been associated with their own morbidities. The Applicant has been requested to clarify the occurrence of cardiac and neurological events appearing as consequent to use of the Fibrospray device and to ensure that information on use of the Fibrospray device complies with advice issued by the CHMP as per the outcome of the referral procedure in accordance with Article 20 of Regulation (EC) No 726/2004 and Article 31 of Directive 2001/83/EC on the risk of gas embolism of fibrin sealants given by spray application.

Technical reports on the spray device were submitted to support claims that pressure / flow out measurements are comparable for CO2 and air and that surface coverage is also comparable. These reports include "worst case scenarios". In study FC-004, events potentially consistent with air [gas] emboli were reported for 6 subjects in the gelatin sponge alone group and 14 subjects in the Raplixa plus gelatin sponge group. Of the 14 events identified in the Raplixa group, the spray device was only used in 5 of the cases with the other 9 events reported in subjects who had Raplixa sprinkled directly from the vial or applied onto a moistened gelatin sponge prior to application to the target bleeding site. 3/5 events were procedural hypotension which was also observed in 6 subjects treated with Raplixa without the spray device and in two subjects in the control arm.

The remaining 2 events were respiratory failure that occurred 1 and 9 days post-surgery and were considered unrelated to the use of the spray device. Therefore, the use of the spray device with Raplixa was not associated with an increased risk of events suggestive of air [gas] emboli.

Although data with Raplixa are so far reassuring a relevant statement in the SmPC is appropriate as follows: Life threatening air or gas embolism has occurred with the use of spray devices employing a pressure regulator to administer fibrin sealant/haemostatic products. This event appears to be related to the use of spray devices at higher than recommended pressures and/or in close proximity to the tissue surface. The risk appears to be higher when fibrin sealants are sprayed with air, as compared to CO_2 and therefore cannot be excluded with Raplixa.

The potential for abuse or misuse would be minimised by providing education and training for surgeons who intend to use the Raplixa. Such training would need to include training on the use of the Raplixa spray device, the distance to be held from tissue, the pressure of gas to be used and the preference for use of CO2 instead of air, as specified in the educational material (see RMP).

Recipients received exposure to Raplixa only during one surgical procedure. There is no knowledge about safety after repeated use. Immunogenicity may be a concern when the current product is re-administered after an interval, however clinical experience with similar, other, marketed fibrin sealants suggests that immunogenicity may not be clinically significant.

There are not any data from humans on the time taken to absorb the fibrin/thrombin - gelatin sponge combination, however there were no findings in the 29 days follow-up.

Drug-drug reactions were not investigated because of the nature of the current product.

It is understood that the Raplixa spray device has a novel mechanism resulting in a gas pressure similar to venous pressure. The recommendation *"Raplixa is recommended to be sprayed using pressurized CO2 and may be used with medical air"* is therefore appropriate. The product is for epilesional use only. Appropriate warnings that it should not be applied intravascularly have been included in section 4.4 of the SmPC. Life threatening thromboembolic complications may occur if the preparation is unintentionally applied intravascularly.

When spraying Raplixa, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism.

As with any protein product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions may include hives, generalized urticarial, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, the administration should be discontinued immediately.

Warnings have been included in the SmPC section 4.4 to ensure safety with respect to transmissible agents.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV); The measures may be of limited value against non-enveloped viruses such as HAV and parvovirus B19. Parvovirus B19 may be serious for pregnant women (fetal infection) and of individuals with immunodeficiency or increased erythropoiesis (e.g. Haemolytic anaemia).

Raplixa has been studied in patients undergoing spinal surgery, vascular surgery, soft tissue surgery and hepatic resection. There is limited experience of use of Raplixa in vascular surgery when applied with the RaplixaSpray device.

Data are not available to support the use of this product in tissue gluing, neurosurgery, application through a flexible endoscope for treatment of bleeding or in gastrointestinal anastomoses. Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bronchospasm, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in isolated cases in patients treated with fibrin sealants / haemostatics: these reactions have progressed to severe anaphylaxis. Such reactions may especially

be seen, if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to constituents of the product.

Antibodies against components of fibrin sealant/haemostatic products may occur rarely.

Inadvertent intravascular injection could lead to thromboembolic event and disseminated intravascular coagulation (DIC), and there is also a risk of anaphylactic reaction (see section 4.4).

Life threatening air or gas embolism has occurred with the use of spray devices employing pressure regulators to administer the fibrin sealant. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface. The risk appears to be higher when fibrin sealants are sprayed with air, as compared to CO_2 and therefore cannot be excluded with Raplixa.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics section as follows: Insomnia and pruritus are included in the adverse reactions table in section 4.8 as common under "General disorders and administrative site conditions".

2.6.2. Conclusions on the clinical safety

Clinical data have demonstrated the safety of the use of Raplixa in combination with an approved gelatin sponge for the improvement of haemostasis in accordance with the SmPC and the risk minimization measures as agreed in the RMP.
The CHMP considers the following measures necessary to address issues related to safety:

- Educational programme aiming at increasing awareness about the risk of air or gas embolism with the use of Raplixa spray device and providing instructions for the correct usage of pressure regulators.

Key elements of the educational material are included in the Annex II (see also RMP).

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes.

Safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity/ allergic reactions to Raplixa active substances (human thrombin or fibrinogen) or to any of its excipients including known hypersensitivity to blood products
Important potential risks	• • Incorrect application of Raplixa (intra-vascular) since this could lead to a thromboembolic event. (Note : The pharmaceutical form of Raplixa however does not allow for direct intravascular administration). • Air or gas embolism has occurred with the use of spray devices employing a pressure regulator to administer fibrin sealant/haemostatic products. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface Note: The Raplixa spray has been designed incorporating several additional safeguards. The device operate differently as compared to the Evicel spray device. The Raplixa spray device has been designed to reduce the likelihood of air emboli • Viral Infection risk from human plasma
Important missing information	• Adequate safety and efficacy data are not available to support the use in pediatrics and pregnant or lactating women • Safety and efficacy data have not been demonstrated in clinical trials for patients with comorbidities such as renal/ hepatic/ cardiac impairment

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
FC-007 Paediatrics programs in the US A Multi-centre, randomized, single blind, controlled Trial of Raplixa in liver resection, soft tissue dissection, or vascular surgery	To characterize the safety and efficacy of Raplixa administered as an aid to haemostasis in liver resection, soft tissue dissection, or vascular surgery in a paediatric population.	Overall safety, as determined by the incidence, severity and relationship of AEs, clinical laboratory abnormalities and post-surgery bleeding complications, changes on clotting tests, thrombogenicity and antibody formation	Ongoing	Part of the approved PIP
FC-005 : A Phase 3b, Randomized, Single-Blind, Controlled, Comparative Efficacy and Safety Study of Topical Fibrocaps™ (Raplixa™) and	The primary objective of the study is to demonstrate the superiority of Fibrocaps plus gelatin sponge compared to Tachosil and to further evaluate the efficacy and safety of	Overall safety, as determined by the incidence, severity and relationship of AEs, clinical laboratory abnormalities and post-surgery	Ongoing	Q2 2015

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Tachosil® in Surgical Hemostasis During Hepatic Resection	Fibrocaps plus gelatin sponge compared to Tachosil.	bleeding complications, changes on clotting tests, thrombogenicity		
Questionnaire	Conduct targeted follow-up of relevant events which may be indicative of the occurrence of air or gas embolism. A specific questionnaire has been developed for this purpose which will be used as part of the follow-up process for these reports.	Air or gas emboli	planned	At time of MAA approval

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Severe hypersensitivity	< SmPC 4.3 Contraindications> Known hypersensitivity to the Raplixa active substances or to any of the excipients < SmPC 4.4 Warning > *Hypersensitivity Reactions* As with any protein product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions include hives, generalized urticarial, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, the administration has to be discontinued immediately. In case of shock, standard medical treatment for shock should be implemented < SMPC section 4.8 Undesirable effects> As with other protein derivatives, hypersensitivity or allergic reactions may occur in rare cases in patients treated with fibrin sealants. In isolated cases, these reactions may progress to severe anaphylaxis. Such reactions may especially be seen if a fibrin sealant is applied repeatedly. < SmPC Section 4.2 Posology and route of administration Raplixashould only be applied by a	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	surgeon experienced in the administration of haemostatic agents.> <▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions>.	
Trombogenicity	< SmPC 4.3 Contraindications> Raplixa must not be applied intravascularly since this could lead to a thromboembolic event. < SmPC 4.4 Warning > *Thromboembolism* Life threatening thromboembolic complications may occur if the preparation is unintentionally applied intravascularly. < SMPC section 4.8 Undesirable effects> Inadvertent intravascular injection could lead to thromboembolic event and DIC, and there is also a risk of anaphylactic reaction (see section 4.4). < SmPC Section 4.2 Posology and route of administration Raplixa should only be applied by a surgeon experienced in the administration of haemostatic agents.> <▼This medicinal product is subject to additional monitoring.	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions>.	
Air/ gas induced emboli	< SmPC 4.4 Warning > *Air/gas emboli* Air or gas embolism has occurred with the use of spray devices employing a pressure regulator to administer fibrin sealant/haemostatic products. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface. When applying Raplixa using a spray device, the pressure should be within the range recommended by ProFibrix. Spray application of Raplixa should only be done using the provided spray application accessories and the pressure should not exceed 1.5 bars (22 psi). < SMPC section 6.6 Instructions for use and handling> Take the vial and device out of their respective pouches maintaining sterility. When using the Raplixa spray device, connect the Raplixa spray device and air filter to the ProFibrix air regulator and thereby to the medical air supply set to a pressure setting of 1.5 bar (22 psi). Hold the vial upright, shake gently and remove the aluminum cap and rubber stopper. When using the Raplixa spray device, connect the vial to the device by inverting the device over the upright vial and pushing the vial into place. Raplixa should not be sprayed at a distance closer than that recommended by the spray device	All users will be provided with the requested educational material. The RMP section risk minimization was updated (RMP PART V). Additional risk minimization measure were added related to safety concern on air or gas embolism Educational material to make user aware of a) specific information for user that is contained in article 31 procedure for fibrin sealants b) safety events experienced with other spray devices. The educational material comprises of a letter and the SmPC and Quick Reference guide for the device. Educational material will be disseminated with each ProFibrix regulator installation

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	manufacturer and in no case closer than 5 cm from the tissue surface. Application must be within 1 hour after connecting the vial to the device. The Raplixa spray device comes with the fixed nozzle attached, which can be easily removed and the flexible nozzle attached depending on the intended use and surgeon preference. < SmPC Section 4.2 Posology and route of administration Raplixa should only be applied by a surgeon experienced in the administration of haemostatic agents.> <▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions>.	
Viral infections	< SmPC 4.4 Warning > *Infection Risk from Human Plasma* Raplixa is manufactured from human plasma and, therefore, may carry a risk of transmitting infectious agents (e.g., viruses). Standard measures to reduce the risk of transmitting infections include screening of plasma donors, testing plasma pools for specific viral infections and the inclusion of manufacturing steps for the inactivation/ removal of viruses. There is also a possibility that unknown infectious agents may be present in plasma-derived products. The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV. The measures may possible be of	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	limited value against non- enveloped viruses such as HAV and parvovirus B19. Parvovirus B19 may be serious for pregnant women (fetal infection) and of individuals with immunodeficiency or increased erythropoiesis (e.g. Haemolytic anaemia). < SMPC section 4.8 Undesirable effects> < SmPC Section 4.2 Posology and route of administration Raplixa should only be applied by a surgeon experienced in the administration of haemostatic agents.> <▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions>.	

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

In a phase III, randomised, single-blind, controlled trial FC-004 time taken to achieve haemostasis within a 5-minute assessment period in surgeries was studied. The key finding is reduction in the time to stop bleeding during the open surgeries described. Haemostasis is achieved within 3 minutes in 90% of patients using Raplixa (compared to ~60% if a gelatin sponge alone is used). The [up to] 2 minute difference observed between Raplixa and gelatin sponge alone is reproducible across very different surgery types performed, and across

clinical sites, age or sex of the patient. By log-rank test, the median time to haemostasis for each surgery type was significantly shorter with Raplixa plus gelatin sponge than with gelatin sponge alone ($p<0.0001$). The median time to haemostasis was reduced by between 1 and 2 minutes when Raplixa was used. Haemostasis was achieved within 3 minutes in 90% of patients using Raplixa compared to ~60% if a gelatin sponge alone was used.

Uncertainty in the knowledge about the beneficial effects

The Applicant had also claimed the indication "as suture support for haemostasis in vascular surgery" but no data were submitted to justify this claim as the clinical trials were not designed to address this, therefore this part of the indication was withdrawn.

Children were not studied: the Applicant has received a deferral from the Paediatric Committee (EMA) for studies in children. The lack of information in children is reflected in the SmPC. A paediatric study FC-007 is agreed as part of the paediatric investigation plan and will be completed by December 2016.

Furthermore, in order to provide comparative data Study FC 005 is a 3b trial in adults undertaken by the applicant to compare the efficacy and safety of Raplixa to another authorised fibrin sealant in liver patients as there is little head-to-head data in the field of hemostasis. A final report will be available in Q2 2015 (See RMP).

Patients with chronic renal impairment and / or chronic hepatic impairment and pregnant women were not studied. Section 4.6 of the SmPC recommends that Fibrocaps should not be used in pregnant or lactating women.

Neither the surgeon carrying out the operation nor the assistant handling the Raplixa nor the data analyser were blinded during the study; this may be a potential source of bias. It is appreciated, however, that blinding of the surgeon and assistant would not have been feasible.

Risks

Unfavourable effects

Insomnia and pruritus appeared to be more common in recipients of Raplixa. Recipients of Raplixa did not appear to develop an immunogenic reaction.

Uncertainty in the knowledge about the unfavourable effects

Although most treatment-emergent adverse events were considered to have arisen from the surgical procedures undertaken, surgery-related events may have masked adverse events that were directly related to the current product.

Life threatening air or gas embolism has occurred with the use of spray devices employing a pressure regulator to administer fibrin sealant/haemostatic products. This event appears to be related to the use of spray devices at higher than recommended pressures and/or in close proximity to the tissue surface. The potential for abuse / misuse would be minimised by providing education / training for surgeons who intend to use the Raplixa. Such training would need to include training on the use of the Raplixa spray device, the distance to be held from tissue, the pressure of gas to be used and the preference for use of CO_2 instead of air. Educational material will be provided (see RMP, Annex II).

Recipients received exposure to Raplixa only during one surgical procedure. There is no knowledge about safety after repeated use. There are not any data from humans on the time taken to absorb the fibrin/thrombin -

gelatin sponge combination, however no findings have been reported in the follow-up of 29 days. The follow-up performed may have not captured complications occurring in the longer-term. Clinical trials in the post authorisation programme will aim to provide more information on the longer term safety.

Benefit-risk balance

Importance of favourable and unfavourable effects
Haemostasis is an essential part of surgical procedures. Difficulty achieving haemostasis may prolong the procedure and the time exposed to anaesthesia, may promote blood loss and may increase complications in the post-operative period. It is acknowledged that, within the context of an operation that may last several hours, a reduction in time to haemostasis of (about) 2 minutes may be a significant especially in those surgeries where major blood loss can occur such as vascular and hepatic surgeries.

The powder form of Raplixa and the ability to store vials at room temperature are the main innovative aspects of the current product (other marketed fibrin sealants are presented in liquid form and require to be stored in a fridge). Raplixa does not need to be thawed, reconstituted or mixed thereby saving on time. The in-use shelf life of 2 hours makes it easier for the surgeon to use Raplixa on multiple bleeding sites.

The unfavourable effects of insomnia and pruritus may be managed clinically. The consequences of repeat exposure to the proteins found in Raplixa have not been fully evaluated with regards to immunogenicity. Clinical experience with similar, other, marketed fibrin sealants suggests that immunogenicity may not be clinically significant.

Benefit-risk balance
The favourable effect of reduced time to achieve haemostasis in surgery is considered to outweigh the unfavourable effects that may be managed clinically. The risk of gas embolism appears to be low due to the administration of the product as a powder form and can be managed with the educational programme agreed.

Discussion on the benefit-risk balance

Raplixa is a combination of fibrinogen presented in powder form in a vial. The powder form of Raplixa and the ability to store vials at room temperature are the main innovative aspects of the current product. Raplixa does not need to be thawed, reconstituted or mixed thereby saving on time. The in-use shelf life of 2 hours makes it easier for the surgeon to use Raplixa on multiple bleeding sites. The reduction in time to stop bleeding by approximately in cases of mild or moderate bleeding during surgical procedures when conventional surgical techniques such as suture, ligature and cautery were ineffective or impractical is considered clinically relevant. Adherence to the educational material should ensure safe use of the product.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Raplixa in the supportive treatment where standard surgical techniques are insufficient for improvement of haemostasis is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch of Raplixa in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing awareness about the risk of air or gas embolism with the use of Raplixa spray device and providing instructions for the correct usage of pressure regulators.

The MAH shall ensure that in each Member State where Raplixa is marketed, all healthcare professionals who are expected to use Raplixa are provided with the following educational material:

- The Summary of Product Characteristics (SmPC)
- Guide for healthcare professionals

The Guide for healthcare professionals shall inform on the following key elements:

- Risk of life-threatening air or gas embolism if the product is sprayed incorrectly
- Use preferred pressurized CO2 instead of pressurised air

- Use of the Raplixa spray device only in open surgery and not endoscopic surgery
- Use of the correct pressure (not exceed 1.5bars or 22psi) and distance from tissue not closer than 5 cm
- Requirement to dry the wound using standard techniques (e.g., intermittent application of compresses, swabs, use of suction devices) prior to using the product
- Requirement to closely monitor blood pressure, pulse rate, oxygen saturation, and end tidal CO2 when spraying the product, for the occurrence of gas embolism
- Which regulator(s) should be used, in line with manufacturer recommendations and the SmPC instructions for use

These conditions fully reflect the advice received from the PRAC.