27 June 2013
EMA/464286/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

EVARREST

Common name: Human Fibrinogen / Human Thrombin

Procedure No. EMEA/H/C/002515

Note

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

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List of abbreviations

AE	Adverse event
AR	Assessment report
aPPT	Activated Partial Thromboplastin Time
BMI	Body mass index
CAS	Chemical Abstracts Service
CBER	Center for Biologics Evaluation and Research
CDRH	Center for Devices and Radiological Health
CBC	Complete blood count
CEC	Clinical Events Committee
CFU	Colony Forming Units
CIM	Controlled immersion method
CSR	Clinical Study Report
cGMP	Current Good Manufacturing Practice
CT	Computed tomography
CV	Coefficient of variation
DEAE	Diethyl amino ethyl
DF	Diafiltration
DVT	Deep vein thrombosis
HFE 7000	Methyl perfluoropropyl ether
HPLC	High pressure liquid chromatography
ICH	International Conference of Harmonization
IgG	Immonglobulin G
In	Inch
IPA	Iso propyl alcohol
IPC	In-Process control
IU	International Units
LoQ	List of questions
MAA	Marketing authorisation application
MLE	Maximum likelihood estimation
N/A	Not applicable
NMT	Not more than
OOS	Out-of-specification
ORC	Oxidized regenerated cellulose
PIP	Paediatric Investigation Plan
PE	Pulmonary embolism
PG910	Polyglactin 910
ppm	Parts per million
Ph Eur	European Pharmacopoeia
QA	Quality Attribute
RSD	Relative standard deviation
SA	Scientific Advice
SAE	Serious adverse event
SD	Standard deviation

S/D	Solvent detergent
SDS-PAGE	Sodium dodecyl sulphate polyacrylamide gel electrophoresis
SEM	Scanning electronic microscopy
SoC	Standard of care
SOC	System Organ Class
TA	Tranexamic acid
TAH	Topical absorbable haemostat
TBS	Target bleeding site
TnBP	Tri-n-butyl-phosphate
TOC	Total Organic Carbon
TTH	Time to haemostasis
TVC	Total Viable Count
U	Unit
UF	Ultra Filtration
USP	United States Pharmacopoeia
VTE	Venous thromboembolism
WFI	Water for Injection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Omrix Biopharmaceuticals NV submitted on 28 February 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for EVARREST, 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 17 March 2011. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant technical innovation.

The applicant applied for the following indication:

EVARREST is indicated for supportive treatment in surgery, for improvement of haemostasis, where standard surgical techniques are ineffective or impractical.

EVARREST has also been shown to be effective as an adjunct to haemostasis in challenging and/or severe bleeding.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

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 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0025/2012 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

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 22-10-2009. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

EVARREST has been given a Marketing Authorisation in US on 05-2012.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Piotr Fiedor

- The application was received by the EMA on 28 February 2012.
- The procedure started on 21 March 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 June 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 June 2012.
- During the meeting on 16-19 July 2012, 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 July 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 10 January 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 March 2013.
- During the CHMP meeting on 18-21 March 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 29 April 2013.
- PRAC Rapporteur RMP Assessment Report, dated 3 May 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 23 May 2013.
- During the CHMP meeting on 27-30 May 2013, outstanding issues were addressed by the applicant during an oral explanation before the CHMP and the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 5 June 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 13 June 2013.
- During the meeting on 24-27 June 2013, 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 EVARREST.

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. 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.

The Applicant, OMRIX Biopharmaceuticals NV initially sought marketing authorisation for EVARREST Sealant Matrix via the centralised procedure for the proposed indication *'supportive treatment in surgery, for improvement of haemostasis where standard surgical techniques are ineffective or impractical. EVARREST has also been shown to be effective as an adjunct to haemostasis in challenging and/or severe bleeding*'.

EVARREST is a sterile bio-absorbable combination product made from a composite matrix coated with fibrinogen and thrombin. It is presented as a sealant matrix, which combines two haemostatically active components: a flexible matrix consisting of polyglactin 910 (PG910) filaments needle punched into a backing fabric of oxidized regenerated cellulose (ORC), and a coating of two biological components, human fibrinogen and human thrombin. Polyglactin is contained in surgical products like suture or mesh material and oxidized regenerated cellulose is widely used during surgery as a topical absorbable haemostat. The biological components are manufactured from normal human plasma and are identical to those used in the manufacture of the approved product Evicel as "solutions for sealant" by the same MAH. Upon contact with blood or fluid, the biological components hydrate and react by generation of fibrin. The matrix holds the fibrin clot at the site of bleeding and additionally offers a texture for blood components in order to support local haemostasis.

2.2. Quality aspects

2.2.1. Introduction

The drug substances (Human Fibrinogen and Human Thrombin) are identical to those used in the currently approved product, EVICEL Solutions for Sealant (licence numbers EU/1/08/473/001, EU/1/08/473/002 and EU/1/08/473/003) manufactured by OMRIX Biopharmaceuticals NV.

EVARREST Fibrin Pad is a sterile bio-absorbable haemostatic combination product (ATC code: B02BC30) consisting of a flexible matrix coated with two biological components (Human Fibrinogen and Human Thrombin).

The term "Sealant Matrix" is used to describe the pharmaceutical form of EVARREST. The strengths of the active substances on the Fibrin Pad are 8.1 mg/cm^2 Human Fibrinogen and 40 IU/cm^2 Human Thrombin. Each EVARREST unit is packaged in a Single Dose Container consisting of a polyester tray and lid assembly enclosed in a foil pouch. Package size is one 10.2 cm x 10.2 cm Fibrin Pad.

The mechanism of action follows the principles of normal physiological fibrin clot formation. Upon contact with a bleeding wound surface, the biological components (Human Fibrinogen and Human Thrombin) on the composite matrix hydrate and the subsequent fibrinogen – thrombin reactions initiate the last step of blood clot formation.

The manufacture of Fibrin Pad comprises three distinct production processes: 1) manufacture of the composite matrix, 2) manufacture of the active biological ingredients (Human Fibrinogen and Human Thrombin drug substances) and 3) manufacture of the finished combination product.

2.2.2. Active Substance

Human Fibrinogen

Human Fibrinogen drug substance is a concentrate of cryoprecipitated plasma proteins, containing mainly fibrinogen, but also fibronectin, albumin, immune globulins, and small amounts of other plasma proteins (e.g. Factor VIII, Factor XIII, von Willebrand Factor).

Human Fibrinogen is derived from human source plasma collected from donors in the USA as described in the OMRIX PMF EMEA/H/PMF/000013/07.

Manufacture

The manufacturing process of the fibrinogen component is comprehensively described.

Starting material for the manufacture of Fibrinogen is cryoprecipitate. Prothrombin, factors VII, IX, X, and prekallikrein are removed by aluminum hydroxide adsorption to prevent activation of fibrinogen. The first virus-inactivation step is solvent detergent (S/D) treatment.

Selective removal of the S/D reagents is performed by extraction and reverse phase chromatography. Pasteurisation provides a second virus inactivation step for both lipid-enveloped and non-lipid-coated viruses. Sucrose and glycine are added to the fibrinogen solution as stabilisers. The protein solution is then loaded on a chromatographic column for plasminogen adsorption. Glycine and arginine hydrochloride are added for stabilisation. Human Fibrinogen drug substance is stored in bulk containers prior to further processing. The applicant has established in-process controls and defined acceptance criteria at critical steps of the manufacturing process to assure that the process is controlled. A rationale is given for all in-process controls supported by experimental data from cryoprecipitate and human fibrinogen batches. The in-process controls performed during manufacture of human fibrinogen bulk are appropriate to ensure the quality and consistency of the drug substance.

The batch size for the production of fibrinogen drug substance is adequately defined. The only step where pooling of intermediates may take place is at the cryoprecipitation level.

All ingredients, reagents and auxiliary material purchased are retested upon receipt by the manufacturer according to Ph. Eur. In the case where there is no pharmacopoeial specification, the suppliers' Certificates of Analysis are provided.

Cryoprecipitate used as intermediate for the production of fibrinogen is produced from human plasma. Collection, testing, storage and transport of the plasma is documented and evaluated within the OMRIX PMF certification procedure (EMEA/H/PMF/000013/07). Real time stability data provided confirm the claimed hold time of the cryoprecipitate intermediate.

Manufacturing steps critical for safety and quality of fibrinogen drug substance were identified and adequately validated based on data from three commercial scale batches. The manufacturing process is sufficiently controlled to ensure batch to batch consistency.

Product related impurities as well as process related impurities are identified and adequate upper limitations are set for the bulk to ensure quality and safety of the drug substance.

Specification

Appropriate drug substance specifications are set for Human Fibrinogen and sufficiently justified.

Analytical procedures selected to determine the above parameters are suitable for their intended use and have been validated according to ICH guidelines.

For batch release, the content of Human Fibrinogen active substance is measured by a method based on Ph Eur monograph Fibrin Sealant Kit (01/2008:0903) which involves clotting in the presence of thrombin, removal of unclottable proteins followed by dissolution of the clot and quantification of the clotted proteins. The specification set for clottable protein complies with Ph. Eur requirement of ≥ 40 g/L of clottable protein, and is within a range of the stated content.

FXIII is responsible for cross-linking and stabilisation of the fibrin clot. Specification for FXIII activity is justified by statistical analysis and a regular evaluation against alert limits.

In general, the specifications set for release testing of Human Fibrinogen drug substance are acceptable. However, the specification defined for plasminogen should be tightened as stability studies of Human fibrinogen spiked with different amounts of plasminogen showed a decrease in clottable fibrinogen in the presence of higher concentrations of plasminogen. The Applicant will revise the assay for determination of plasminogen with the revised specification at post authorisation. The applicant will introduce endotoxin testing as a Human Fibrinogen drug substance release test after collection and analysis of adequate data at post authorisation.

Stability

Human Fibrinogen drug substance is stored in bulk containers prior to further processing.

Three batches of human fibrinogen drug substance have been analysed for stability. Stability studies were performed according to requirements of the current guidelines. Appropriate chemical and microbial properties were monitored.

Human Thrombin

Human Thrombin drug substance contains purified human α-thrombin (800 to 1200 IU/mL) with small amounts of enzymatically inactive β- and γ-thrombin. Human albumin and mannitol are added to the solution as stabilisers, and calcium chloride required for cross-linking and stabilisation of the fibrin clot.

Human Thrombin is derived from human source plasma collected from donors in the USA as described in the OMRIX PMF EMEA/H/PMF/000013/07.

Manufacture

Starting material for manufacture of Human Thrombin is cryopoor plasma. Prothrombin is first captured from cryopoor plasma on an anion exchange chromatography column resin. In this step, prothrombin is activated in the presence of Ca^{2+} to generate α-thrombin, thereby releasing it from the resin. Thrombin generated is further purified in the manufacturing process on a cation exchange chromatography column.

The preparation includes two distinct virus inactivation steps: S/D treatment followed by nanofiltration. S/D treatment is preceded by a filtration. Subsequent validated purification procedures reduce the concentration of S/D reagents to levels specified in release testing. S/D reagents are eliminated using cation exchange chromatography.

Critical steps have been identified in the human thrombin drug substance production process and adequate in-process controls established. A rationale is given for all in-process controls supported by experimental data from plasma batches and human thrombin batches. The in-process controls performed are appropriate to ensure the quality and consistency of the drug substance.

The manufacturing process has been validated for three production scales.

The manufacturing process of Human Thrombin is a continuous process: there are no intermediates and/or holding points within the process.

Raw materials used during manufacture of Human Thrombin drug substance comply with pharmacopoeial specifications and are tested to that specification by the supplier. On receipt, the tests for characteristics, identification, and assay are applied as a minimum. Due to the absence of compendial specifications for chromatographic media internal monographs have been established.

Albumin

Human Thrombin component contains Human Albumin for stabilisation. The albumin used is Human Albumin 20% and 25%.

In accordance with EMA/CHMP/BWP/706271/2012 Guideline on Plasma-Derived Medicinal Products, information on Human Albumin 20% and 25%, to be used as excipient in the manufacture of Human Thrombin drug substance, was provided regarding the names, country (-ies) where approved, manufacturing flow charts, the finished product specifications, summary of stability data including the approved shelf life, virus risk assessment, and the qualitative and quantitative compositions.

The albumin used is within its shelf life at the time of addition to thrombin as a stabiliser and is batch-released by a European OMCL. When a plasma-derived product is used as an excipient, synchronisation of expiry dates with the finished product is recommended (EMA/CHMP/BWP/706271/2010) and deviations should be justified. Albumin used as stabiliser in the manufacture of Human Thrombin drug substance has national marketing authorization in some EU member states, thus the MAA's argumentation that in-process controls, batch release specifications, and the stability program ensure compliance of the pharmaceutical characteristics with current requirements, is acceptable. Furthermore, the Applicant's justification, that the PMF, which is annually renewed and covering the starting material human plasma for fractionation, used for the manufacture of the excipient albumin, ensures compliance with the current recommendations for donor selection, donation screening and plasma pool testing and that state-of-the-art testing methods are used for these purposes, is regarded appropriate. Taken together, the absence of synchronisation of the expiry dates for EVARREST Fibrin Pad and the excipient human albumin has been adequately justified.

Regarding the excipient albumin, it has been confirmed that there is a system for traceability in place from each plasma donation to the final drug product EVARREST and vice versa. It has also been confirmed that a contract exists between the manufacturer of the human albumin and the manufacturer of EVARREST in which maintenance of traceability records for at least 30 years after the time of donation is specified.

Process validation

The consistency and robustness of the manufacturing process used for production of Human Thrombin was validated by the manufacture of three consecutive batches at 1x scale. Critical manufacturing steps were identified and adequately validated (anion exchange chromatography; S/D treatment; cation exchange chromatography). All results were within the specified limits demonstrating the batch to batch consistency of drug substance production. Comparative reports of process validation for the different scale productions of thrombin and comparability to the 1x scale have been provided.

The applicant has identified and sufficiently discussed product related as well as process related impurities in Human Thrombin Drug Substance and provided (where applicable) analysis of their quantitative presence in the bulk. Appropriate limits are set.

Specification

Adequate specifications are set for human Thrombin drug substance and sufficiently justified.

Analytical procedures selected to determine the above parameters are suitable for their intended use and have been validated according to ICH guidelines. The Applicant will revise the specification set for Human Thrombin drug substance by introducing endotoxin release testing after analysis of collected data at post-authorisation.

Human Thrombin drug substance is filled in single use, disposable sterile plastic bags . A detailed description has been produced. Based on extraction data the bags are considered appropriate for the intended use.

Stability

Real-time stability studies on commercial batches were performed confirming the claimed storage conditions for Human Thrombin drug substance.

Stability studies have been evaluated according to the requirements of ICH Guideline Q1E Evaluation of Stability Data. Appropriate biological and chemical as well as microbial properties of the drug substance susceptible to change during the storage were monitored. An adequate test is performed to detect degradation products in the drug substance over time.

2.2.3. Finished Medicinal Product

EVARREST sealant matrix is a sterile bio-absorbable haemostatic medicinal product made from a flexible matrix component coated with Human Fibrinogen and Human Thrombin active substances.

The composite matrix is regarded to be a novel excipient in the production process of EVARREST and forms an integral part of the final drug product. The Matrix is manufactured by a contract manufacturer . A full quality dossier regarding the matrix has been provided.

The matrix is composed of a knitted, oxidised, regenerated cellulose (ORC) backing layer under a layer of synthetic polyglactin 910 (PG910) nonwoven fibres. The components are known bioabsorbable materials found in currently marketed medical devices. During the Matrix manufacturing process, the PG910 fibres are carded into a batt and needle-punched onto the ORC backing. The composite matrix is scoured, dried, cut to a defined size, packaged in individual plastic trays and sterilised by gamma irradiation. The size of the matrix is 10.2 cm x 10.2 cm with a thickness of about 2 mm. The manufacturing process has been described sufficiently.

Critical steps have been defined and adequate in-process controls established. Raw materials are tested upon receipt. The manufacturing process has been validated by producing three consecutive validation batches. Batch analyses data of a sufficient number of production scale batches show batch-to-batch consistency. Release testing of the matrix includes adequate parameters with limits based on historical data to assure quality and consistency of the manufacturing process. Analytical methods used during batch release testing have been validated according to current guidelines.

An initial proposed shelf life of the matrix was confirmed by real-time stability data. Due to cases of discoloration identified, the Applicant reduced the shelf life for the matrix from gamma irradiation of matrix units up to the introduction into the manufacturing process of the Fibrin Pad internally. Furthermore, the Applicant will incorporate a suitable test method for the assessment and adequate acceptance criteria of discolouration of matrix material to allow identification of adverse exposures at post authorisation. The Applicant states that the matrix used for manufacture of Fibrin Pad is within its shelf life.

Pharmaceutical Development

Formulation development was aimed at optimizing physicochemical properties of carrier material in order to make it capable of controlling challenging bleeding while containing moderate concentrations of biological drug substances, at optimizing the target input dose of fibrinogen and at establishing the dose for commercial product.

During the procedure, the Applicant has adequately addressed the differences between the target input doses of the drug substances used for application of the active ingredients onto the matrix and

the values determined during batch release of the finished drug product. A linear relationship between the target input dose and the active substances on the Fibrin Pad had been demonstrated in dose-ranging studies. Furthermore, a comprehensive explanation supported by experimental data has been provided for the observation that the amount of fibrinogen assayed on the fibrin pad was found higher than the amount of fibrinogen used in manufacture for application onto the matrix: The "Fibrin Pad Clottable Proteins" assay, used to determine fibrinogen content during drug product batch release, overestimates fibrinogen content because additional plasma proteins are captured within the clot formed on the matrix which cannot be fully removed by washing due to the physical barrier of the matrix.

The change in the input fibrinogen dose during development does not affect the final product specification for this active ingredient. Although the change is within the specification, the mean of the active substance of this medicinal product modifies. Meanwhile, the first Pivotal Clinical studies performed with Fibrin Pad batches manufactured with lower fibrinogen dose have been reproduced with Fibrin Pad batches produced with the higher fibrinogen dose.

Process Validation

Process validation for manufacture of Fibrin Pad was performed on consecutive production-scale batches according to process parameters established during manufacturing process development. Robustness studies provided the basis of operating ranges for process validation. Fibrin Pad manufacturing process was found to consistently yield drug product meeting its predetermined specifications and quality attributes.

The applicant has adequately demonstrated inter and intra-pad dose uniformity. Data for process validation of one validation batch indicated a relatively large inter and intra-pad variability with regard to the distribution of thrombin activity. This was attributed to a high variability of the test method. In October 2010, an improved thrombin activity assay was implemented and results for thrombin activity of recent experiments confirmed it.

A linear correlation between the thrombin input target dose and the thrombin activity measured on the Fibrin Pad demonstrated a reproducible manufacturing process of the Fibrin Pad with consistent thrombin activities. Furthermore, a linear relationship between the clottable fibrinogen target input dose and clottable proteins measured on the Fibrin Pad was demonstrated in the fibrinogen dose-ranging study.

Product specification

Adequate release and shelf life specifications have been set to ensure the product quality and consistency.

During the procedure the specifications for fibrinogen and total protein defined for batch release of the drug product were revised to reflect the data generated of Fibrin Pad production batches manufactured so far. The dossier has been revised to indicate 8.1 mg/cm^2 fibrinogen, measured as clottable proteins, as nominal potency. Specification for thrombin activity at batch release, proposed in the initial submission, has been tightened based on data of Fibrin Pad batches measured using the proposed improved assay for determination of thrombin activity. The corresponding stability specifications have been revised to be identical with the batch release specifications.

Fibrin Pad with the active ingredients Human Fibrinogen and Human Thrombin applied onto a matrix is potentially prone to abrasion. Friability is a measure to assess the amount of biological powder retained to the pad. Such retention is adequately assessed during drug product release and stability testing through the potency assays of active ingredients. Therefore, the omission of "Friability testing" at drug product release testing is acceptable.

Residual organic solvent is controlled as an impurity in the final product. The limit for the residual solvent in the Fibrin Pad drug product is defined. The residual solvent is not contained in the list of classified residual solvents presented in Ph Eur monograph (01/2008:50400). Data from literature indicate that the residual solvent is non-irritating and non-mutagenic. The no observed effect level (NOEL) was determined in an inhalation study in rats. Calculated maximal clinical exposure to the residual solvent due to application of two 10.2 cm x 10.2 cm units of sealant matrix is considered not to present a risk to patient health. The use of this organic solvent is acceptable.

Water content is a crucial parameter for the quality of the Fibrin Pad as elevated levels of humidity were demonstrated to lead to partial activation of the biological components on the pad. Specification for water content is set . To assure controlled water content as well as the sterility of the irradiated Fibrin Pad, visual inspection and a physical test on the integrity of the foil pouch are part of the release testing.

Testing site for EU release is performed at a manufacturing site located within the EU. The applicant will submit satisfactory assay transfer reports regarding the testing site at EU release to EMA prior to its release into the EU market. EVARREST sealant matrix will be batch-released by a European OMCL. Quality test parameters “fibrinogen” and “thrombin” have been selected for testing by OMCLs during post-authorisation surveillance.

Container closure

The primary packaging system consists of a polyester tray and lid assembly sealed in a foil pouch. The same tray/lid assembly is used for storage and shipment of the matrix component to the Fibrin Pad manufacturing facility and throughout the Fibrin Pad manufacturing process. Selection of material for tray and lid was based on the ability to withstand both gamma and e-beam irradiation, appropriateness of use during the “CIM” process and suitability for use with medical products. Evaluation of the primary packaging materials for potential leachable substances has been performed.

The container closure system proposed is regarded suitable for the intended use.

Stability of the product

Real-time stability data has been provided for Fibrin Pad process validation batches and pivotal clinical batches. Both studies included long–term storage of the batches as well as storage at accelerated conditions.

Values for the stability indicating parameter “thrombin activity” showed partly a widely scattering pattern during stability studies of pivotal clinical batches and process validation batches. Recently, an optimised test was established and the specification changed accordingly.

A shelf life claim of 24 months for Fibrin Pad drug product at a storage temperature of up to 25°C is considered acceptable, since the Applicant commits to enter three Fibrin Pad commercial batches into a stability program. Testing will follow the protocol proposed for commercial batches including revised drug product specifications using the optimised test method for determination of thrombin activity.

Adventitious agents

Two plasma proteins (human fibrinogen and human thrombin) are used as drug substance. The overall viral safety strategy includes selection of qualified donors and testing of plasma donations. Plasma is collected in the USA. Single donations are screened by an adequate testing program for viral infections (Anti HIV, HBsAg, Anti-HCV). Furthermore, nucleic acid amplification tests are performed on minipools with regard to HIV, HBV, HCV, HAV, and parvovirus B19. Manufacturing pools are tested by NAT for HIV-RNA, HBV-DNA, and HCV-RNA. The donor selection and plasma donation testing strategy for viral markers is considered adequate.

Two dedicated steps for virus inactivation/removal have been introduced into the manufacture of fibrinogen: (1) solvent detergent (S/D) treatment and (2) liquid heat treatment. Enveloped viruses are efficiently inactivated at S/D treatment and at the liquid heat treatment step. The latter step also inactivates efficiently non-enveloped viruses such as Hepatitis A virus.

The virus reduction strategy for thrombin is based on an efficient inactivation step for enveloped viruses (S/D treatment) and a small pore nanofiltration step which has been demonstrated to remove enveloped viruses as well as small non-enveloped viruses such as parvoviruses.

Albumin prepared from human plasma is added at final stages to the drug substance. Plasma is sourced in USA from adequately-selected and tested donors. Plasma pools for albumin are tested according to the regulations. Due to the established and validated cold ethanol fractionation procedure and final pasteurisation step, the viral risk from albumin has been adequately minimised.

TSE/CJD safety

No animal TSE risk materials have been identified for production of fibrinogen component, thrombin component, and the matrix component.

Human fibrinogen, human thrombin and human albumin used as excipient are manufactured from human source plasma in USA. Donor exclusion measures for (v)CJD risk are place and in line with current EMA requirements.

A system is in place which allows traceability of each plasma donation supplied to OMRIX. If a donor develops (or is strongly suspected to have developed) vCJD, OMRIX must be informed of every donation from this individual supplied to OMRIX. In this event, any batches of EVARREST which included suspect donations would be withdrawn and the appropriate Control Authorities notified.

Two spiking studies to evaluate the capacity of the manufacturing process to remove scrapie agents have been completed on the Human Fibrinogen. Results indicated that the manufacturing process has the potential to remove ≥2.7 log10 prion protein by the absorption step and the extraction and filtration steps. Regarding human thrombin, evaluation of the SD-filtration and chromatography steps demonstrated a prion protein reduction factor of >4 log. Furthermore, additional significant prion reduction of 3 log could be assumed from the nanofiltration step in the human thrombin manufacture. The entire manufacturing process of Human albumin used as excipient was investigated with regards to its capacity to remove TSE agents demonstrating an overall reduction factor >7log.

In summary, donor selection and prion reduction capacity demonstrated in the manufacture of human fibrinogen, human thrombin and human albumin ensure an adequate TSE safety of EVARREST.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The active ingredients of EVARREST Sealant matrix (Human Fibrinogen and Human Thrombin) are two known active substances, being the drug substances of the centrally approved fibrin sealant EVICEL manufactured by OMRIX.

The plasma used in the manufacture of the Human Fibrinogen, Human Thrombin and Human Albumin used as excipient of human thrombin are covered by Plasma Master files certified by EMA and are in compliance with current quality and safety requirements in the EU.

In general, the production process of the Fibrin Pad is adequately described. Critical manufacturing steps were identified and in-process controls were established to ensure the consistency of the production process. Release and shelf life specifications as well as the corresponding analytical procedures are considered suitable to ensure product quality. Current specifications have been updated based on data generated at production scale.

Safety with regard to transmissible agents, such as human TSE and enveloped and non-enveloped viruses has been demonstrated in compliance with the relevant CHMP guidelines.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the submitted data, the marketing authorisation application for EVARREST is recommended for approval based on quality grounds.

Overall, information on manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important quality characteristics.

A list of recommended measures will ensure an adequate maintenance of the quality of the product.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. Endotoxin testing with an adequate specification should be introduced into release testing for Human Fibrinogen drug substance.
2. Endotoxin testing with an adequate specification should be introduced into release testing for Human Thrombin drug substance.
3. Three Fibrin Pad batches should be entered into a stability program consisting of both long-term stability conditions and accelerated conditions. Testing should follow the protocol proposed for commercial batches including revised drug product specifications.
4. All assay transfer reports regarding the EU release testing site should be submitted to EMA prior to its release into the market.
5. A revision of the assay for determination of plasminogen with the revised specification should be submitted at post authorisation.
6. The test method and adequate acceptance criteria for the assessment of discolouration of the matrix material should be incorporated in the application dossier.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical safety and efficacy of Fibrin Pad was studied in a series of traditional and customized non-clinical models. In addition, cross reference is made to the non-clinical studies submitted in support of the non-clinical safety of EVICEL.

GLP aspects

Studies on primary pharmacodynamics were GLP compliant, except studies 08-0349 (pilot study to investigate the 48 hours observation period), 09-0155 (pilot study to evaluate Fibrin Pad with lower Fibrinogen content) and CPC-2007-0177 (the in-vitro hydraulic burst leak test). PK studies investigating the whole Fibrin Pad were not GLP compliant (08-0122, 08-0146/08-0220 and 09-007). The PK study testing only the matrix is GLP compliant (05-0636). Studies on toxicology were GLP compliant except studies on local tolerance (08-0264, 08-0122, 08-0146/08-0220 and 09-007) and the two studies on antimicrobial activity (09-0230 and 10-0045).

2.3.2. Pharmacology

The submitted studies aimed to demonstrate the efficacy of Fibrin Pad to control and stop bleeding in different surgical situations. In-vitro investigations included an hydraulic burst leak test. Studies on primary pharmacodynamics are listed in table 1.

Table 1: Studies on primary pharmacodynamics

Study No.	Study Title
Study 06-0658	An 8-Week Evaluation of a Fibrin Pad for Partial Nephrectomy in the Farm Pig
Study 08-0349	Pilot Evaluation of Fibrin Pad in the Porcine Partial Nephrectomy Model (48 Hours)
Study 09-0074	Comparability Evaluation of a Fibrin Pad Manufactured with Embossed Matrix in the Porcine Partial Nephrectomy Model (48 Hours)
Study 09-0188	An Evaluation of a Low Fibrinogen (4.0 Target Dose) Fibrin Pad in the Porcine Partial Nephrectomy Model
Study 09-0155	Pilot Evaluation of Low Fibrinogen (4.0 and 5.0 Target Dose) Fibrin Pad in the Porcine Partial Nephrectomy Model (3 Hours)
Study 10-0143	Two-Day Evaluation of Fibrin Pad Made Using a High BAC Input Dose in the Porcine Partial Nephrectomy Model (48 Hours)
Study 05-0662	Evaluation of the Ethicon Hemostatic Dressing on Blood Loss in a Model of Severe Large Venous Hemorrhage Injury in Swine
Study 06-0001	Evaluation of the Ethicon Hemostatic Dressing on Blood Loss in a Model of Severe Large Venous Injury and Hemorrhage in Coagulopathic Swine
Study 69718	Evaluation of a New Hemostatic Matrix after Partial Liver Lobectomy and Partial Splenectomy in the Rabbit
Study 09-0274	Two-Day Evaluation of the Test Device when Applied to a Partial Nephrectomy in the Coagulopathic Swine Model
Biomechanical strength	Ex Vivo Biomechanical Strength, Completion Report: Validation of Hydraulic Burst Leak Test, Version 1
Biomechanical strength	In Vivo Biomechanical Strength Evaluation of the Ethicon Hemostatic Dressing on Blood Loss in a Model of Severe Large Venous Injury and Hemorrhage in Coagulopathic Swine

The swine partial nephrectomy study (Study 06-0658) is considered the pivotal non-clinical efficacy trial of the Fibrin Pad in a recovery model relevant to the proposed indication. Severe bleeding from a partial nephrectomy wound in the absence of renal artery clamping can be considered a worst-case scenario, due to high pressure and high volume of bleeding, for testing a topically applied hemostatic agent for primary control of soft tissue hemorrhage.

In this study of severe bleeding and recovery, Fibrin Pad was as effective as the conventional therapy (i.e. including clamping of the renal artery during the procedure) at establishing and maintaining haemostasis in a swine partial nephrectomy model. Intraoperative haemostasis was achieved in all animals in both treatment groups and no animals in either group developed evidence of postoperative bleeding at the treated sites. In addition to this pivotal study, Fibrin Pad was applied in several other studies: study 09-0074 (n=24, 48-hour survival period), study 09-0188 (n=12, 48-hour survival period), study 08-0349 (n=12, 48-hour survival period), study 09-0155 (n=12, 3-hour survival period), and study 10-0143 (n=24). In all studies Fibrin Pad was considered effective in achieving haemostasis under the chosen bleeding conditions. However, within study 08-0349 re-application were necessary in 4 out of 12 animals.

Bridging study 09-0074 (GLP Study 09-0074) was conducted in the swine partial nephrectomy model to demonstrate comparability between older prototypes and the version of the Fibrin Pad product intended for marketing (batch M06F164). This study included additional evaluations for thrombogenicity (including assessment of biomarkers of venous thromboembolism) and safety pharmacology. Extending from the pivotal work demonstrated in Study 06-0658, the safety and efficacy of the final product was confirmed in all Fibrin Pad treated animals (12/group). Pathologies (i.e., venous thromboembolism) were observed in the sham operation group (3 of 12 animals), and no pathologies were attributed to Fibrin Pad. All animals survived to the 48-hour scheduled necropsy at which time no evidence of additional renal haemorrhage was evident. All of these animals met the study success criteria and no pathologies associated with Fibrin Pad application were identified upon necropsy. Unlike previous studies, no repeat applications of the test article were required using Fibrin Pad manufactured using the current process.

Furthermore, the pivotal model was tested in an exaggerated condition of bleeding involving hemodilutional and hypothermic coagulopathy (Study 09-0274). Haemostasis and survival to the scheduled necropsy (48 hours) was achieved in 12 of 12 animals treated with Fibrin Pad and 2 of 12 animals in the TachoSil (human fibrinogen / human thrombin) -treated group. Hematology and thromboelastography evaluations confirmed the coagulopathic condition and the low survival rate in the TachoSil-treated group attested to the severity of the model.

An acute swine model with (Study 06-0001) and without coagulopathy (Study 05-0662) involving extensive hepatic parenchymal injury and severe venous hemorrhage provides supporting data on the efficacy of Fibrin Pad in severe bleeding in animal models was achieved in the majority of the animals treated with Fibrin Pad and Fibrin Pad was shown to be substantially superior to the control groups. In addition, biomechanical strength of the product was demonstrated *in vivo* by measuring adherence of the product after application to liver wounds (Study 06-0001). Fibrin Pad demonstrated a statistically significant increase in mean adhesive strength on both the diaphragmatic and visceral aspects of the liver in swine when compared to control (matrix with albumin coating). These findings were further supported by *ex vivo* testing using the hydraulic burst leak testing (Study CPC-2007-0177).

An exploratory safety study was conducted using rabbits with partial hepatic lobectomy and partial splenectomy (Study 69718) where hemostatic efficacy was evaluated at surgery as a secondary endpoint. Although the study was not considered sufficiently developed to contribute to the safety evaluation, Fibrin Pad demonstrated better hemostatic efficacy than the control article (SURGICEL). The intraoperative hemostatic efficacy endpoints were not confounded by the numerous protocol deviations and/or complications that did impact the safety (recovery) portion of the study.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies related to the intended use of the product were submitted (see discussion on non-clinical aspects).

Safety pharmacology programme

Specific non-clinical conventional safety pharmacology studies of the Human Fibrinogen and Human Thrombin in Fibrin Pad were not submitted. However, selected conventional safety pharmacology endpoints (e.g., cardiovascular and respiratory function) were monitored after Fibrin Pad application within the following pharmacodynamic studies:

Comparability Evaluation of a Fibrin Pad Manufactured with Embossed Matrix in the Porcine Partial Nephrectomy Model (48 Hours), Study 09-0074

Secondary evaluation in this study included safety pharmacology assessment of acute systemic cardiovascular effects completed intraoperatively. Animals were monitored for cardiovascular and respiratory function during the surgical procedure. Thirty-six female farm pigs were subjected to a partial nephrectomy procedure and received treatment with Fibrin Pad batch N06F274M or the clinical comparator, Fibrin Pad batch M06F164. Safety pharmacology endpoints were evaluated using ECG data. ECG tracings collected from a subset of four animals from each treatment arm (12 animals in total) were made prior to surgery and post-surgery at 15 minutes and 1 hour for the test and comparator groups, and 15 minutes and 1 hour after completion of the total nephrectomy in the standard of care sham surgical procedure group. ECG values were evaluated by an independent expert and revealed no treatment-related cardiovascular safety pharmacology effects when observed for cardiac arrhythmias, morphology, and conduction disturbances, heart rate, RR, PR, and QRS and QT durations. All findings were considered insignificant and unrelated to the test article application.

Two-Day Evaluation of Fibrin Pad Made Using A High BAC Input Dose in the Porcine Partial Nephrectomy Model (48 Hours), Study 10-0143

The main objective of this study was outlined in the Primary Pharmacodynamics section and included a secondary safety pharmacology assessment of acute systemic cardiovascular effects completed intraoperatively. Animals were monitored for cardiovascular and respiratory function during the surgical procedure. All animals in all groups received an electrocardiographic examination immediately prior to surgery, and 15 minutes and 1 hour following test article application. The results were interpreted by a consultant veterinary cardiologist. No notable variations in electrocardiograph readings were noted at any time point.

Pharmacodynamic drug interactions

No non-clinical pharmacodynamic studies on drug interactions have been submitted (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

Studies focussing on the haemostatic properties of Fibrin Pad, on the basis of the physical effect of a matrix pad and active clotting proteins, fibrinogen and thrombin, included a non-traditional ADME absorption study (see table 2 below).

Table 2: Studies focussing on the haemostatic properties of Fibrin Pad

Study no	Test article	Administration	Species	Findings
08-0122	Fibrin Pad, Matrix, Evicel	Gluteal muscle implantation	Athymic Rat	Complete absorption after 56 days
08-0146/ 08-0220	Fibrin Pad, Matrix, Evicel	Intrahepatic implantation	Athymic Rat	Complete absorption after 56 days
09-0077	Fibrin Pad, Matrix	Intrahepatic implantation	Athymic Rat and Sprague-Dawley Rat	Early immune response in immune-competent rats
05-0663	Matrix, Vicryl mesh,	Subcutaneous implantation	Long Evans Rat	Essentially absorbed After 56 days p.i.
OFI-T004	Quixil	Intravenous, Topical to partial liver resection	NZW Rabbits	Thrombin slowly released from the clot, Peak 6-10 h,
900-005	Quixil,	Intravenous,	NZW Rabbits	

	Fibrinogen, Thrombin, Tranexamic acid	Topical to partial liver resection		degradation products beyond 20 hours.

The mass absorption of Fibrin Pad was characterized in local tolerance/tissue reaction studies conducted in athymic rats (non-GLP Study 08-0122, 08-0146/08-0220, and 09-0077). The athymic rat was chosen to rule out the effect on absorption due to the early immune response from a product containing human-derived blood products in a non-clinical animal model.

Two studies conducted in athymic nude rats (non-GLP Study 08-0122, gluteal muscle implantation, and 08-0146/08-0220, intrahepatic implantation) evaluated the tissue response to Fibrin Pad and its two major components (matrix alone and biological components) at four timepoints (3 days, 7 days, 14 days, and 56 days post-implantation) and additionally, in study 08-0122, compared to a sham defect. In both studies, it was found that Fibrin Pad (containing biologics) and matrix (without the biological components) were completely absorbed by 56 days post-implantation.

In study 09-0077 Fibrin Pad and matrix were implanted intrahepatically to athymic and to normal rats. As expected in normal rats there was an early immune response after application of Fibrin Pad but not after application of the matrix.

Furthermore, the absorption of matrix alone was investigated after subcutaneous application in Long Evans rats. The ORC material was absorbed 7 days post-implantation and the PG910 material was essentially absorbed 56 days post-implantation.

Studies have been conducted in rabbits to evaluate the absorption and elimination of thrombin when applied to the cut surface of the liver resulting from partial hepatectomy. Using ^{125}I-thrombin it was shown that a slow absorption of biologically inactive peptides resulting from the breakdown of thrombin occurred, reaching a C_{max} in the plasma after 6-8 hours. At the C_{max}, the plasma concentration represented only 1 to 2% of the applied dose.

The fibrin, resulting from the Fibrin Pad application, is removed by fibrinolysis and phagocytosis. No studies on distribution, metabolism, excretion and drug interactions were submitted.

2.3.4. Toxicology

Single dose toxicity

One pivotal single dose toxicity study has been performed in rats testing the subchronic toxicity of Fibrin Pad as a whole as well as of matrix alone.

In this study (PSE 05-0474) four groups of rats (10–12 rats/sex/group) were surgically implanted, subcutaneously, with EVARREST, Matrix and EVICEL, EVICEL alone, or Matrix alone and toxicity of Fibrin Pad and the Matrix was evaluated over a 90-day observation period.

EVARREST was administered at an exposure approximately 10 times greater (based on mass/body weight) than a typical surgical exposure (one 10.2 x 10.2 cm sponge) and 2.5 times greater than a worst-case surgical exposure (four 10.2 x 10.2 cm sponges). Implantation of EVARREST, Matrix and EVICEL, EVICEL alone, or Matrix alone had no effect on clinical observations, body weight gain, food consumption, hematology, coagulation parameters, clinical chemistry, urinalysis, necropsy findings, or organ weights. ELISA and Western blot analyses indicated there were no relevant differences in antigenicity of the biological components contained in EVARREST when compared to EVICEL. In conclusion, no adverse effects were found in this study besides typical foreign body response. Furthermore, saline (IV) and sesame oil (IP) extracts of the Matrix were evaluated and no evidence for systemic toxicity was found.

Repeat dose toxicity

No repeat-dose toxicity studies have been performed. (See discussion on non-clinical aspects.)

Genotoxicity

No studies on genotoxicity were performed with the whole Fibrin Pad.

The sealant matrix has been tested with a battery of genotoxicity studies (data not shown). In these studies no signs for genotoxicity were found.

Carcinogenicity

Carcinogenicity studies have not been submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

Reproductive and developmental toxicity have not been submitted (see discussion on non-clinical aspects).

Toxicokinetic data

Not applicable (see discussion on non-clinical aspects).

Local Tolerance

Local tolerance of the product has been studied in several studies. Since Fibrin Pad contains xenogeneic proteins the immune response in typical animal models interfered with wound healing, ingrowth and absorption. In order to circumvent such immune reactions, further studies were performed using immunodeficient animals, here athymic rats. In these studies wound healing was considered to be "normal" and Fibrin Pad as well as the matrix was considered to be well tolerated. Traditional local tolerance studies evaluating the matrix included an in vitro assay of cytotoxicity and an intracutaneous reactivity study in rabbits. The local tolerance to the Matrix was investigated in the 119-day rat subcutaneous tissue reactivity and absorption study described above. The Matrix was shown to induce a minimal-to moderate tissue response. The ORC component was absorbed by 7 days post-implantation, and the PG910 component was completely absorbed by 56 days post-implantation. The tissue response was considered acceptable for implantation as compared to a commercially available product.

Other toxicity studies

Impurities
Safety assessments were conducted for the following impurities: residual solvents methyl perfluoropropyl ether (HFE 7000) and isopropanol, potential leachables from packaging materials including the primary packaging for Fibrin Pad, and other chemical residues identified during the development of Fibrin Pad. It was determined that all residues and leachable substances were below toxicologically significant levels.

Pyrogenicity
A biocompatibility study was conducted to determine the potential of the matrix for material -mediated pyrogenicity in male New Zealand White rabbits. An extract of the matrix (irradiated and e-beamed) was prepared at a ratio of 6 cm^2 of surface area/mL using sterile, nonpyrogenic 0.9% sodium chloride solution with manual agitation at 37°C for 72 hours. No single animal had an increase in temperature above baseline of more than 0.4°C, thus under the conditions of this study, the test article extract was within acceptable USP limits, and was considered to be nonpyrogenic.

Haemocompatibility
Two haemocompatibility studies were submitted: An in vitro haemolysis Study of Hercules Fibrin fleece using saline Extract (study 05-0603) and another study using the Direct Contact Method (Study 05-0682). No findings that could raise concerns were noted (data not shown).

Anti-microbial activity
Study 09-0230 assessed the antimicrobial activity of Fibrin Pad compared to the matrix and TachoSil (Nycomed Austria GmbH), a commercially available haemostatic product, in an infection potentiation model in rats. No evidence of infection was observed at necropsy at any timepoint, which correlated with the low numbers of bacteria recovered from the implant sites. None of the implants would be considered to potentiate infection. Study 10-0045 assessed the ability of *Staphylococcus aureus* to colonize Fibrin Pad compared to another implant. The number of recovered bacteria was less than the initial inoculum (almost 10^8 CFU/mL), therefore, none of the implants would be considered to potentiate infection. The number of recovered *Staphylococcus aureus* from Fibrin Pad was almost 5 logs less than the initial inoculum and no evidence of infection was observed - correlated with the relatively low numbers of bacteria recovered from the implant sites.

2.3.5. Ecotoxicity / environmental risk assessment

An environmental risk assessment has not been submitted (see discussion on non-clinical aspects).

2.3.6. Discussion on non-clinical aspects

Primary pharmacodynamics studies aimed to demonstrate the efficacy of Fibrin Pad to control and stop bleeding in different surgical situations. Most of the studies have been performed in the "pivotal" non-clinical model, i.e. a partial nephrectomy model in swine. Furthermore, a hepatic injury model in swine and a partial liver and splenectomy model in rabbit were used. In terms of in-vitro investigations, a hydraulic burst leak test was submitted.

Initial studies testing Fibrin Pad with low or higher fibrinogen content were inconclusive in terms of possible dose-dependency of fibrinogen content. Consequently the assay techniques used to measure clottable protein were refined to enhance sensitivity, resulting in more accurate values being obtained in later studies. The pivotal comparability study (09-0074) demonstrated the hemostatic efficacy of the final product. Furthermore, all nonclinical data support the suggested range of fibrinogen concentrations as efficacious in achieving haemostasis.

The pivotal pharmacodynamic study 06-0658 (An 8-Week Evaluation of a Fibrin Pad for Partial Nephrectomy in the Farm Pig) revealed evidence that haemostasis was achieved after Fibrin Pad application without arterial clamping.

In most of the studies a single application of Fibrin Pad was sufficient to control the bleeding in terms of time to haemostasis and total blood loss. However, within study 08-0349 re-application were necessary in 4 out of 12 animals, attributed to product failure.

Secondary pharmacodynamics studies were submitted in which the efficacy of Fibrin Pad was assessed in animal models of large vessel defect repair, haemostatic and adhesive efficacy and adhesion potential, however these studies do not reflect the intended use and were not assessed in the context of pharmacodynamics. Of note, in these studies of large vessel defect models (not the intended use of the product) application of Fibrin Pad caused pseudoaneurysm in aortotomy models and an increase in pulmonary emboli in venotomy models. Use of Fibrin Pad in large vessel defects is contraindicated within the SmPC (see also discussion on Clinical efficacy).

Specific non-clinical conventional safety pharmacology studies of the Human Fibrinogen and Human Thrombin in Fibrin Pad were not conducted, but, selected conventional safety pharmacology

endpoints (e.g. cardiovascular and respiratory function) were monitored after Fibrin Pad application within the pharmacodynamic studies 09-0074 and 10-0143 and no safety signals were observed.

The presented studies on non-clinical pharmacodynamics reveal evidence that Fibrin Pad will exert hemostatic effects as desired, however, the interpretation of results of such studies and the possible extrapolation to clinical situation in patients is limited.

Within absorption/local tolerance study no. 08-0146/08-0220 (intrahepatic implantation in athymic rat) after 56 days, complete absorption of the matrix was observed in animals eligible for the evaluation. Local tolerance to the matrix was investigated in the 119-day rat subcutaneous tissue reactivity and absorption study. The matrix was shown to induce a minimal to moderate tissue response which was considered acceptable for implantation as compared to a commercially available product. The ORC component was absorbed by 7 days post-implantation, and the PG910 component was completely/essentially absorbed by 56 days post-implantation.

In terms of pharmacokinetics (and toxicokinetics) no conventional non-clinical studies have been performed. In view of the special type of product i.e. topically applied sealant matrix, this is considered acceptable. The absorption of Fibrin Pad and the matrix was characterized in pivotal local tolerance/tissue reaction studies conducted in athymic rats in order to circumvent immune responses to the xenogenic proteins. In these studies wound healing process was classified as "normal" and the ORC and PG910 material was considered to be absorbed at day 56. The fibrin, resulting from the Fibrin Pad application, is removed by fibrinolysis and phagocytosis (Lane et al. 2005, Tanaka et al. 2009, and Wheat et al. 2009) therefore, tissue distribution studies on the biological components of Fibrin Pad are not necessary or required. The Human Fibrinogen and Human Thrombin of Fibrin Pad are human proteins that are expected to degrade into amino acids, and be recycled or excreted by normal innate processes, therefore no studies on metabolism and excretion are required. This is in accordance with ICH S6 guidelines. Drug interactions between drug therapies for comorbidities and haemostatic Matrix are not anticipated, the omission of such studies is justified.

Toxicity of the product was assessed for the matrix component alone, the biologic components alone, and the combined product, including all processing and sterilization steps. There have been no significant pathologies attributed to Fibrin Pad or any of its constituents.

No studies for reproductive and developmental toxicity have been submitted. Adverse effects on fertility, postnatal development and reproduction as well as teratogenic effects are not expected in humans, as active ingredients are derived from human plasma. Non-clinical studies with repeated dose applications (chronic toxicity and carcinogenicity) cannot be performed in conventional animal models due to the development of antibodies following the application of heterologous human proteins (see SmPC section 5.3). Moreover no studies on the genotoxic potential of human fibrinogen / human thrombin are not considered necessary as these are physiological human plasma proteins and potential genotoxicity is not expected. This is in line with ICH S6 (R1) guideline for preclinical safety evaluation of biotechnology-derived pharmaceuticals. Genotoxicity studies with the matrix have not revealed any findings.

The applicant submitted studies on impurities, no safety concerns arise from the presented data. No findings were noted from pyrogenicity and haemocompatibility studies. Two studies were conducted to determine the antimicrobial activity of Fibrin Pad. Based on the results, there were no findings that could raise concern on the potential for the development of infections.

The applicant has not performed an Environmental Risk Assessment (ERA) in accordance with the “Guideline on the Environmental Risk Assessment of the medicinal products for human use” (EMEA/CHMP/SWP/4447/00) – as Evarrest active components are naturally derived substances unlikely to result in significant risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The submitted studies on non-clinical aspects are considered adequate. Non-clinical data presented are considered sufficient to support the marketing authorisation application of Fibrin Pad for the intended use. The haemostatic efficacy of EVARREST was demonstrated in a number of animal models assessing time to and post-treatment blood loss, among other endpoints.

Non-clinical data on the matrix component reveal no special hazard for humans based on studies of cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, material-mediated pyrogenicity, subchronic toxicity, genotoxicity, implantation, and hemocompatibility.

A 90-day study in rats to evaluate subchronic systemic toxicity and immunogenicity of EVARREST after subcutaneous implantation of the maximum acceptable dosage of EVARREST found no signs of toxic effects and no evidence of increased immunogenicity relative to fibrin sealant products. Relevant information has been adequately reflected in the SmPC section 5.3.

Data on absorption and elimination of thrombin and the matrix are adequately described in section 5.2 of the SmPC. Fibrin sealants/haemostatics are metabolised in the same way as endogenous fibrin, by fibrinolysis and phagocytosis, therefore no additional studies were needed. Intravascular pharmacokinetic studies were not performed in man as EVARREST is intended for epilesional use only. Application of Fibrin Pad caused pseudoaneurysm in aortotomy models and an increase in pulmonary emboli in venotomy models, however use in large vessel is not part of the indication and a relevant contraindication in intravascular administration has been added in the SmPC section 4.3 and is also stated in SmPC section 5.2.

2.4. Clinical aspects

2.4.1. Introduction

A marketing authorization is sought for this new haemostatic product for the indications 'Supportive treatment in surgery, for improvement of haemostasis where standard surgical techniques are ineffective and impractical. EVARREST has also been shown to be effective as an adjunct to haemostasis in challenging and/or severe bleeding.'

Three pivotal clinical studies were performed to support this application. These were all prospective, randomized, controlled superiority studies. Two small further studies are considered as supportive for efficacy and contribute to safety evaluation.

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 3: Tabular listing of clinical studies

Study ID	No. of study centres / locations	Design	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Target bleeding site	Primary
400-07-002	11/USA	Prospective, randomized, controlled superiority evaluation Control: Surgicel	To evaluate safety and haemostatic effectiveness of Fibrin Pad as an adjunct to control soft tissue bleeding during abdominal, pelvic, retro-peritoneal, and (non-cardiac) thorac. surgery	Randomized:90 (Fibrin Pad: 60 Control: 30) FP Non-randomized:51	Subject treated intraoperatively only. Safety follow-up through 30-day visit (+14-day window)	89 M / 52 F 62.0 y (26-89)	The first actively bleeding site identified in the soft tissue with challenging **mild to moderate bleeding**, where conventional methods of control (i.e., suture, ligature, cautery) are ineffective or impractical, and an adjunctive product is required to achieve haemostasis.	Proportion of subjects achieving hemostatic success at 4 minutes after randomization with no re-bleeding requiring treatment during a subsequent 6-minute observation period.
400-08-002	15/UK, Germany, Australia, New Zealand	Prospective, randomized, controlled superiority evaluation Control: Standard of care	To evaluate safety and hemostatic effectiveness of Fibrin Pad in controlling challenging, severe soft tissue bleeding during abdominal, pelvic, retro-peritoneal, and non-cardiac thoracic surgery	Randomized:91 (Fibrin Pad: 59 Control: 32)	Subject treated intraoperatively only. Safety follow-up through 60-day visit (±10-day window)	57 M / 34 F 65 y (33-83)	The first actively bleeding site identified in the soft tissue with persistent, challenging **severe bleeding**, where conventional methods of control (i.e., suture, ligature, cautery) are ineffective or impractical, and where an alternative method was required in order to achieve haemostasis.	Proportion of subjects achieving haemostatic success at 4 minutes after randomization with no re-bleeding requiring treatment at the TBS at any time prior to wound closure.
400-10-001	10/UK, Germany,	Prospective, randomized,	To evaluate safety and	Randomized:84 (Fibrin Pad: 39	Subject treated intraoperatively	61 M / 43 F	The first actively bleeding site identified in the **hepatic**	Proportion of subjects achieving

	Netherlands, Australia, New Zealand	controlled superiority evaluation Control: Standard of care	haemostatic effectiveness of Fibrin Pad in controlling parenchymal bleeding during hepatic surgery	Control: 45) FP Non-randomized:20	only. Safety follow-up through 60 days (+14 days)	65 y (31-82)	**parenchyma** after parenchymal transection had been completed, that:(a)did not respond to 30 sec of manual compression following which (b)had persistent bleeding requiring the surgeon's immediate attention; and (c)where conventional methods of control (i.e., suture, ligature, cautery) were deemed ineffective, impractical or inappropriate and an alternative method was required to achieve haemostasis.	hemostatic success at 4 minutes after randomization with no re-bleeding requiring treatment at the TBS at any time prior to the initiation of wound closure.
FL-PN-001-IS	1/Israel	Prospective, open-label, Phase I study	To evaluate safety of Fibrin Fleece in open partial nephrectomy	10	Single administration	8 M / 2 F 61.5 y (49-78)	Elective open partial nephrectomy with a bleeding site (mild to moderate bleeding) identified, after conventional surgical techniques had been exhausted	Efficacy was not evaluated.
FL-PN-002-IS	2/Israel	Prospective, randomized, single blind, two-cohort Phase II study Control: Standard of care	To evaluate safety and haemostatic efficacy of Fibrin Fleece in open partial nephrectomy	Randomized:7 (Fibrin Fleece:4 Control: 3) (terminated prematurely)	Single administration	5 M / 2 F 57 y (45-74)	Elective open partial nephrectomy due to a renal tumor smaller than 4 cm.	Achievement of haemostasis within 10 minutes and no further bleeding requiring treatment during a 6-minute observation period.

2.4.2. Pharmacokinetics

No clinical pharmacokinetic studies were submitted (see discussion on clinical pharmacology).

2.4.3. Pharmacodynamics

Mechanism of action

No relevant studies have been submitted (See discussion on clinical pharmacology).

Primary and Secondary pharmacology

No relevant studies have been submitted.

2.4.4. Discussion on clinical pharmacology

EVARREST is for epilesional use and must not be used intravascularly, therefore pharmacokinetic investigations are not applicable. The biological components human fibrinogen and human thrombin react at the site of administration by formation of fibrin. The matrix is bio-absorbed and does not appear systemically. No formal interaction studies have been performed.

The absence of clinical pharmacology studies is considered justified.

Similar to comparable products, the product may be denatured after exposure to solutions containing alcohol, iodine, or heavy metals (e.g. antiseptic solutions). Such substances should be removed to the greatest possible extent before applying the product (see SmPC section 4.5).

2.4.5. Conclusions on clinical pharmacology

Due to the nature, the intended use of the product and contraindications in intravascular administration, clinical pharmacology studies are not applicable.

2.5. Clinical efficacy

2.5.1. Dose response studies

No dose response studies have been submitted (See discussion on clinical efficacy).

2.5.2. Main studies

Three pivotal studies in adult subjects undergoing non-emergent, open surgical procedures have been submitted to support the claimed indication; study 400-07-002: versus Surgicel in mild to moderate soft tissue bleeding during abdominal, pelvic, retroperitoneal, or (non-cardiac) thoracic surgery; 400-08-002: versus Standard of Care in controlling challenging, severe soft tissue bleeding during abdominal, pelvic, retroperitoneal, or (non-cardiac) thoracic surgery; 400-10-001: versus Standard of Care in controlling parenchymal bleeding during elective liver surgery (see also table 9)

A classification of bleeding intensity was developed and used in the trials (see table 4).

Table 4: Classification of bleeding intensity

Mild Bleeding	A TBS with a small area of capillary, arteriole or venule oozing.
Moderate Bleeding	A TBS with a larger area of capillary, arteriole, or venule oozing that presents a significant challenge because of the larger area involved, increasing the volume of blood loss, *or* A TBS with bleeding that is more pronounced than oozing, that could also come from a small artery or vein, but is not massive, pulsatile, and flowing.
Severe Bleeding	Bleeding (arterial, venous, or mixed) that is rapidly flowing, pulsatile or spurting that in the surgeon's judgment requires rapid control to prevent hemodynamic consequences (e.g. hypovolemia, tachycardia, or hypotension) and could involve major volume loss which if not treated rapidly could be life threatening. Fibrin Pad should not be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial bleeding.

Test treatment used in the trials

Units of Fibrin Pad (FP) used in the clinical trials were 10.2 cm x 10.2 cm (4 x 4 inches) in size and should adequately cover the TBS with an overlap extending 1-2 cm beyond the margins of the wound (or as necessary to achieve haemostasis). Application of treatment and assessment of haemostasis in all pivotal trials was as follows:

After randomization, the treatment article (Fibrin Pad or control) was to be applied with manual compression and maintained until 4 minutes post randomization. A surgical sponge (laparotomy pad or surgical gauze) could be used to assist in providing adequate pressure to stem all bleeding over the entire treated surface area. Haemostasis was then to be assessed by carefully releasing manual compression and removing the surgical sponge (if used) without disturbing the hemostatic product. If haemostasis was achieved at 4 minutes, a subsequent 6-minute observation period was to follow.

If in Fibrin Pad (FP)-treated subjects haemostasis was not achieved during the 4-minute treatment period, the surgeon was permitted to apply additional units of Fibrin Pad if clinically appropriate. If bleeding was due to insufficient coverage of the TBS, the additional units were to be applied so that they overlapped the previously applied product. If bleeding was due to incomplete adherence to the soft tissue, the previous unit was to be removed and replaced with a new unit. After re-treatment, manual compression was to be applied for 2-3 minutes; haemostasis was to be assessed, followed by another 6-minute observation period after haemostasis was achieved. FP was not to be removed from the TBS surface following the achievement of haemostasis.

Together with application on additional bleeding sites, no more than four units (10.2 x 10.2 cm) of FP were to be left implanted.

Standard of Care (SoC) as control treatment was a composite of techniques/methods typically used to control severe bleeding after conventional methods (e.g. suture, ligature, cautery) were found to be ineffective or impractical. SoC was initiated with 4 minutes of continuous manual compression with or without gauze or sponge and with or without a topical absorbable haemostat (TAH).

Definitions used in the trials.

The Target Bleeding Site (TBS) was defined as the first actively bleeding site identified (see specific definition for each trial) where conventional methods of control (i.e., suture, ligature, cautery) were deemed ineffective or impractical, or inappropriate and where an adjunctive product or an alternative method was required to achieve hemostasis. The TBS had to be a site where occlusion of the injured tissue surface blood vessels was required to achieve hemostasis. This excluded large defects in large arteries or veins where the injured vascular wall required repair with maintenance of vessel patency and with persistent exposure of the Fibrin Pad to blood flow and pressure during healing and resorption of the product. The TBS was required to be of a size that could be adequately covered with a single unit of FP, with an overlap extending 1-2 cm beyond the margins of the wound (or as necessary to achieve haemostasis).

If required, Fibrin Pad (FP) could be cut with sterile scissors to fit the size of the bleeding site.

If breakthrough bleeding occurred at the TBS during the initial 4-minute period, the surgeon could apply additional units of FP if clinically appropriate. If breakthrough bleeding requiring treatment other than FP occurred during the 4-minute treatment period, or during the subsequent observation period at any time prior to wound closure, the surgeon was to revert to SoC and the subject was to be considered a treatment failure for the primary efficacy parameter.

Haemostatic success was defined as no detectable bleeding from the TBS at the specified time-points following randomization and the additional 6 minutes observation period after haemostasis was achieved.

Ease of Use (for the first three subjects at each clinical study site only), intensive care unit (ICU) time (in days) and overall Length of Stay in days (admission to discharge) information, operative time, estimated blood loss including transfusion information, cell salvage use, number of FP or SURGICEL units used and ventilator time (if applicable) and use of other haemostatic measures was to be collected. Adverse events from start of randomization were to be documented. Within 24-hours prior to hospital discharge, blood samples for complete blood count (CBC) with Differential and Coagulation parameters (PT, APTT, INR, Platelet count, Fibrinogen, and D-Dimer), physical examination, changes in concomitant medications, adverse events, including any complications potentially related to bleeding and/or thrombotic events, and/or any interim transfusion exposure or AEs potentially related to transfusion exposure, were to be documented. Same documentations applied for the one-Month Follow-Up Visit (+ 14 days) with additional antibody assessments.

Three analysis sets were defined in the trials:

- Intent-to-treat set (ITT or full analysis set) consisting of all randomized subjects. Subjects who did not complete the procedure after randomization were to be considered as failures and included in the ITT analysis.
- Evaluable set (or per protocol; PP) consisting of all ITT subjects who had no major protocol deviations.
- Safety set consisting of all subjects who received treatment.

The primary endpoint analysis was based on the ITT analysis set. The PP population was used in a supportive analysis of the primary effectiveness variable only. The incidences of subjects with AEs that were potentially related to bleeding at TBS or to thrombotic events were summarized

descriptively for the ITT and Safety analysis set, because these secondary endpoints are also safety endpoints. All other secondary endpoints were analyzed using the ITT and Per-Protocol set.

Study 400-07-002

This is a prospective, randomized, controlled study for the evaluation of superiority of Fibrin Patch (Fibrin Pad) as an adjunct to control soft tissue bleeding during abdominal, retroperitoneal, pelvic, and thoracic surgery.

Methods

Study participants

Inclusion criteria

Subjects should be aged 18 years or over, requiring non-emergent, open, abdominal, retroperitoneal, pelvic or thoracic (non-cardiac) surgical procedures and provide informed consent. The presence of an appropriate soft tissue TBS should be identified intra-operatively by the surgeon.

The TBS in study 400-07-002 was defined as the first actively bleeding site identified in the soft tissue with mild or moderate bleeding.

Exclusion criteria

Subjects were excluded from the study if any of the following conditions applied:

- Intra-operative findings were identified by the surgeon that could preclude study conduct
- TBS was within an actively infected field
- Bleeding site was in, around, or in proximity to foramina in bone, or areas of bony confine
- Known intolerance to blood products or to one of the components of the study product
- Subject was unwilling to receive blood products
- Subject had an immunodeficiency condition (including known HIV)
- Subject was known current alcohol and / or drug abuser
- Subject had participated in another investigational drug or device research study within 30 days of enrolment
- Subject was pregnant or nursing.

Treatments

Fibrin Patch was supplied for the study in units of 4 x 4 inches (10.2 x 10.2 cm) in size.

The treatment used in the control group was Surgicel, absorbable haemostat, a sterile absorbable knitted fabric prepared from oxidized regenerated cellulose (ORC) manufactured by Johnson & Johnson Wound Management, a Division of Ethicon Inc.,was used as comparator.

Objectives

The primary objective of this study was to evaluate the safety and hemostatic effectiveness of FP as an adjunct to control mild and moderate soft tissue bleeding during abdominal, pelvic, retroperitoneal, and (non-cardiac) thoracic surgery.

Outcomes/endpoints

Primary endpoint was the proportion of success in achieving haemostasis at the target bleeding site (TBS) within 4 minutes after randomization with no re-bleeding requiring treatment during a subsequent 6-minute observation period. Haemostasis was defined as no detectable bleeding at the TBS.
Secondary endpoints were:

- Proportion of subjects achieving hemostatic success at 10 minutes following randomization (Success at 10 minutes was defined as the achievement of haemostasis within 10 minutes and no further bleeding requiring treatment during the final 6-minute observation period);
- Incidence of treatment failures (if haemostasis was not achieved within 4 minutes or if bleeding requiring additional intervention during the 6 minute observation period occurred);
- Incidence of AEs that were potentially related to bleeding at the TBS;
- Incidence of AEs that were potentially related to thrombotic events;
- Incidence of AEs potentially related to transfusion exposure (transfusion related lung injury, multi-organ system failure, transfusion reactions, infectious complications potentially related to transfusion);
- Incidence of re-treatment at the TBS;
- Incidence of AEs.
  Safety variables included AEs, complete blood count (CBC), and coagulation status (INR, PT, APTT, platelet count, fibrinogen, and D-dimer).

Sample size

Due to the sequential study design no fixed sample size was calculated. Instead for each trial the maximum sample size for a triangular design with continuous monitoring was contrasted with the sample size for a fixed design. Subjects were calculated in case of a continuously monitored triangular test and a 2:1 allocation ratio. The corresponding numbers of subjects in a fixed sample design were about 178.

Randomisation

Subjects were randomized applying a 2:1 (active: control) ratio with a computer generated method once intra-operative eligibility was confirmed and stratified for bleeding severity (mild / moderate). In the event that a potential subject failed intra-operative criteria, and was not randomized to the study, the unused randomization envelope was to be returned to the series, and used for the next subject. If superiority in efficacy was demonstrated for FP before 100 total subjects had been enrolled in the FP arm, enrollment of subjects into the FP arm was to continue in a non-randomized fashion to ensure that a minimum of 100 subjects were enrolled in the FP arm.

If additional soft tissue bleeding sites requiring a topical hemostatic product were identified after the treatment of the initial TBS, these were also to be treated according to the subject's randomization assignment, if clinically appropriate. If other hemostatic products were needed, the surgeon was to revert to standard of care (excluding fibrin sealants or topical thrombin).

Blinding (masking)

The study was not blinded.

Statistical methods

In each pivotal trial a sequential triangular test was used to analyse the primary endpoint based on the ITT population of all randomized subjects. For this analysis subjects with missing endpoint information were considered as treatment failures. Analyses were planned for the first 90 subjects with further analyses at completion of every 30 subjects if required. At each interim analysis the value of the appropriate test statistics were calculated and compared with the appropriate stopping boundary (adjusted for discrete monitoring). In case the upper boundary was crossed, the study was stopped as superiority of FP over the control treatment was concluded.

As part of sensitivity analyses the primary analysis was repeated considering missing data as successes, and as worst-case, with missing data for the FP group considered as failures and missing data for the control group considered as successes. The following secondary endpoints were analysed: By means of logistic regression: Proportion of subjects achieving hemostatic success at 10 minutes following randomization; Incidence of treatment failures and Incidence of re-treatment at TBS. All categorical data were summarized by frequencies along with associated percentages for each group. Continuous variables were summarized by number of subjects, mean, standard deviation, minimum, and maximum for each group.

Results

Participant flow

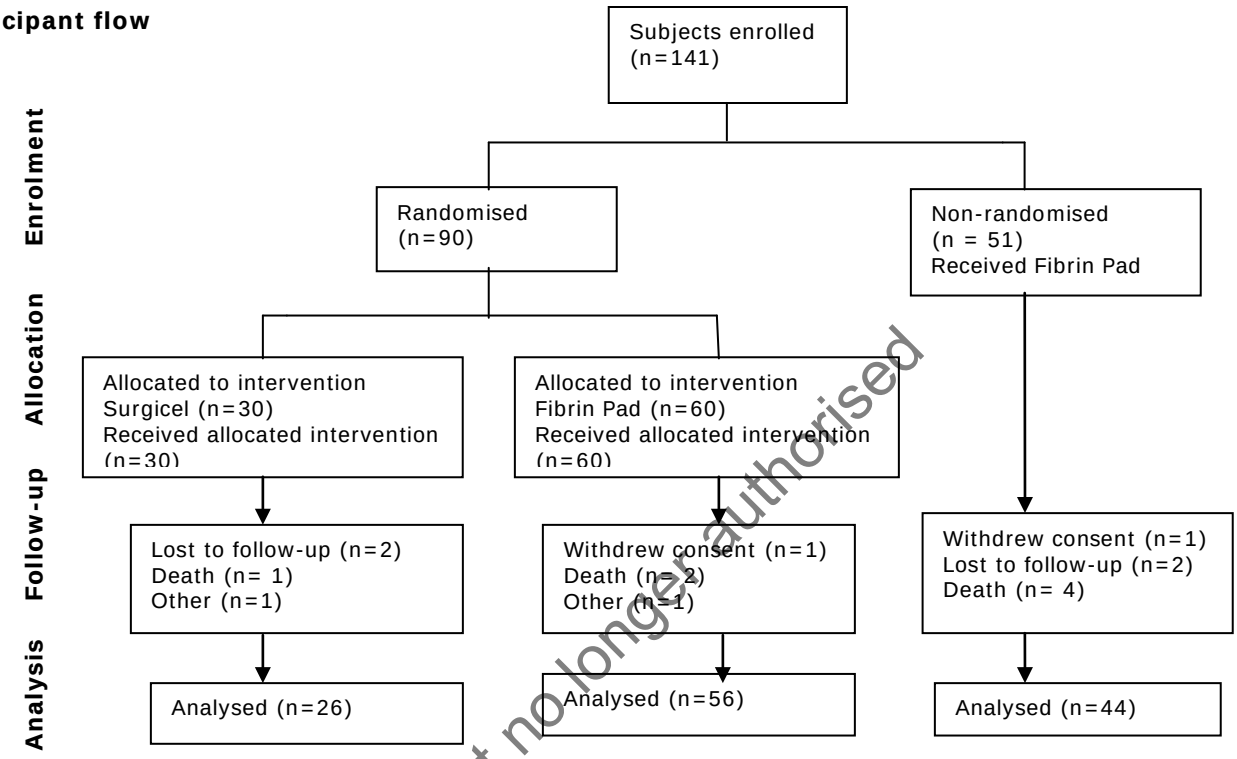


Table 5: Major Protocol Deviations (Study 400-07-002)

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

*described in detail in CSR 400-07-002 Section 11.4.1.2.3

Recruitment

First subject was enrolled on 26 March 2008; last subject completed on 24 April 2009.

Conduct of the study

The protocol was amended in February 2008 before inclusion of the first study participant and administrative changes were included in June 2008. The study was conducted at 11 institutions in the USA. Sponsor audits were performed at sites 21 and 22.

A Data Safety Monitoring Board (DSMB) was established and had responsibility for the review of data and identification of any potential safety issues throughout the duration of the study. In addition, a Clinical Events Committee (CEC) was appointed to adjudicate Adverse Events (AEs), or Serious Adverse Events (SAEs) that were potentially related to TBS bleeding, thrombotic events and transfusion exposure.

Results

- **Baseline data**

Table 6: Subject Demography (Study 400-07-002, Safety Set)

Category	Statistic	FP Randomized N = 60	SURGICEL (N = 30)	FP All (N = 111)	Total N = 141
Age (years)	Mean (SD)	59.9 (11.8)	58.5 (14.4)	61.5 (11.4)	60.9 (12.1)
Age (grouped)	18 - <50 years	11 (18.3%)	9 (30.0%)	16 (14.4%)	25 (17.7%)
	50 - <65 years	28 (46.7%)	12 (40.0%)	47 (42.3%)	59 (41.8%)
	65 - <75 years	12 (20.0%)	5 (16.7%)	32 (28.8%)	37 (26.2%)
	≥75 years	9 (15.0%)	4 (13.3%)	16 (14.4%)	20 (14.2%)
Gender	Male	39 (65.0%)	20 (66.7%)	69 (62.2%)	89 (63.1%)
	Female	21 (35.0%)	10 (33.3%)	42 (37.8%)	52 (36.9%)
Race	White	50 (83.3%)	23 (76.7%)	90 (81.1%)	113 (80.1%)
	Black/African American	10 (16.7%)	5 (16.7%)	21 (18.9%)	26 (18.4%)
	Asian	0 (0.0%)	1 (3.3%)	0 (0.0%)	1 (0.7%)
	Hispanic /Latino	0 (0.0%)	1 (3.3%)	0 (0.0%)	1 (0.7%)
BMI (kg/m^2)	Mean (SD)	29.3 (6.7)	28.5 (6.5)	28.7 (6.9)	28.7 (6.8)
	Median (range)	28.5 18.0 – 50.0	28.0 (20.0 - 49.0)	27.0 17.0 – 53.0	27.0 17.0 – 53.0
	95% CI of mean	27.5; 31.0	26.1; 30.9	27.4; 30.0	27.5; 29.8
BMI (grouped)	Underweight	1 (1.7%)	0 (0.0%)	3 (2.7%)	3 (2.1%)
	Normal	13 (21.7%)	9 (30.0%)	24 (21.6%)	33 (23.4%)
	Overweight	22 (36.7%)	10 (33.3%)	44 (39.6%)	54 (38.3%)
	Obese	19 (31.7%)	10 (33.3%)	32 (28.8%)	42 (29.8%)
	Morbidly obese	5 (8.3%)	1 (3.3%)	8 (7.2%)	9 (6.4%)
History of smoking	Yes	40 (66.7%)	19 (63.3%)	74 (66.7%)	93 (66.0%)
	No	20 (33.3%)	11 (36.7%)	37 (33.3%)	48 (34.0%)

Source: Tables 14.1.2.1 and 14.1.2.1a

The study included a wide range of major surgical procedures; mean duration of surgery was 235.7 ± 133.7 minutes. Pulmonary resection and radical pancreatic duodenectomy were the most common procedures (26.2% and 12.8% of all subjects respectively). No other type of procedure represented more than 5% of cases overall. In the FP Randomized group, radical nephrectomy represented 10% of cases and abdominoperineal resection 6.7% of cases, but neither was reported in the SURGICEL group. Procedures were classified as 'other' more frequently in the SURGICEL than the FP Randomized group (30% versus 21.7% of subjects). Procedures classified as 'other' included operations where multiple surgical procedures were performed.

Table 7: Primary Operative Procedure (Study 400-07-002, Safety Set)

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

* Details of procedures categorized as 'other' are given in Listing 16.2.5.1

Source: Section 14, Tables 14.1.3.1 and 14.1.3.1a

Table 8: Anatomical Location of TBS (Study 400-07-002, Safety Set)

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

Source: Section 14, Tables 14.1.3.2 and 14.1.3.2a

Table 9: Tissue Type at TBS (Study 400-07-002, Safety Set)

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

Source: Section 14, Tables 14.1.3.2 and 14.1.3.2a

The type of bleeding at the TBS was mild for 31/60 subjects (51.7%) and moderate for 29/60 subjects (48.3%) in the FP Randomized group and mild for 15/30 subjects (50%) and moderate for 15/30 subjects (50%) in the SURGICEL group (CSR, Table 14.1.3.2). In the FP All group the bleeding was mild in 59/111 cases (53.2%) and moderate in the remaining 52/111 cases (46.8%).

The primary method of haemostasis at the TBS prior to randomization was cautery in 48.2% of cases (68/141), suture in 1.4% of cases (2/141) and 'other' in 9.9% of cases (14/141). No haemostatic methods were used at the TBS prior to study treatment in 40.4% of cases (57/141) as they were deemed to be impractical by the surgeon.

Numbers analysed

Three analysis sets were defined:

Intent-to-treat set (ITT or full analysis set) consisting of all randomized subjects. Subjects who did not complete the procedure after randomization were included in the ITT analysis as failures.

Evaluable set (or per protocol; PP) consisting of all ITT subjects with no major protocol deviations.

Safety set consisting of all subjects who received treatment.

The primary endpoint analysis was based on the ITT analysis set. Stratification factors were utilized in the overall analysis. Sub-group analysis (by each stratification factor level) was also performed.

Table 10: Analysis Sets (Study 400-07-002)

	FP Randomized	SURGICEL	FP All	Total
Intent to Treat (ITT)	60	30	60	90
Per Protocol (PP)	57	30	57	87
Safety Set	60	30	111	141

Source: Tables 14.1.1.3 and 14.1.1.3a

Outcomes and estimation

Primary efficacy endpoint

Achievement of haemostasis at 4 minutes, after release of manual compression, is described in table 17. No re-bleeding requiring treatment during a subsequent 6-minute observation period was observed in 59/60 subjects (98.3%) in the FP group and 16/30 (53.3%) in the SURGICEL group.

Table 11: Primary Endpoint Results (Study 400-07-002, ITT Set)

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

Source: Tables 14.2.1.1, 14.2.1.1.1, 14.2.1.1.2

The supportive analysis in the PP set showed very similar results.

Secondary efficacy endpoints

Results of haemostatic success at 10 minutes with no further bleeding are presented in table 12.

Table 12: Hemostatic Success at 10 minutes (Study 400-07-002, ITT Set)

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

Source: Tables 14.2.1.1, 14.2.1.1.1, and 14.2.1.1.2

Incidence of Retreatment during Efficacy Assessment

No breakthrough bleeding occurred in either group during the initial manual compression period. One subject in the FP Randomized group was classed as a treatment failure. In this subject the FP was applied to intercostal muscle during a chest wall resection. At 4 minutes, bleeding from around the edges of the FP was noted. The FP was removed and further dissection identified the bleeding to be coming from a defect in the wall of the internal thoracic artery, deep to the muscle onto which the FP had originally been applied. The protocol dictated that the treatment article was to be placed directly onto the source of the bleeding. In this instance the internal thoracic artery was the bleeding source and the FP had not been placed on it. A suture was then used to achieve haemostasis. This subject was identified as having a major protocol deviation, in that an inappropriate TBS was treated.

Of the 14 treatment failures in the Surgicel group, 12 had not achieved haemostasis at 4 minutes and therefore required re-treatment. Of the 18 subjects that had achieved haemostasis at 4 minutes, rebleeding requiring re-treatment occurred during the 6-minute observation period in 2 cases.

Haemostatic Efficacy in the Safety Analysis Set

Table 13: Summary of Haemostasis (Study 400-07-002, Safety Set)

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

Source: Table 14.2.2.1a

Blood Loss and Transfusion Requirement

Overall during the course of the study, transfusions were required by 38.7% (43/111) of subjects treated with FP versus 53.3% (16/30) of subjects in the SURGICEL group (p=0.15).

Interim analyses

The first interim analysis, after the first 90 randomized subjects, revealed that Fibrin Pad treatment was declared superior to Surgicel with a significance level <0.05. The recruitment to the randomized portion of the trial was terminated and additional non-randomized subjects were enrolled for Fibrin Pad treatment in order to gain sufficient data for safety analysis.

Ancillary analyses

Blood samples for antibody response to human thrombin and fibrinogen were collected on the day of surgery (T0), and 4 and 8 weeks later (T4 and T8 respectively). The levels of specific antibodies to human thrombin and fibrinogen were analysed by Enzyme-Linked Immunosorbent Assays (ELISA). Samples of 99 patients treated with Fibrin Pad and of 22 patients treated with Surgicel were analysed. Two out of 99 (2%) of the FP treated patients have shown a slight and mainly transient increase in antibody response to human thrombin. No changes in coagulation parameters such as prothrombin time (PT), activated partial thromboplastin time (aPTT) or international normalized ratio (INR) occurred.

Study 400-08-002

A Phase III Randomized, Controlled, Superiority Study Evaluating the Fibrin Pad versus Standard of Care Treatment in Controlling Severe Soft Tissue Bleeding During Abdominal, Retroperitoneal, Pelvic, and Thoracic Surgery

Methods

Study participants

Inclusion criteria

Eligible subjects should be aged 18 years or over, requiring non-emergent, open, abdominal,

retroperitoneal, pelvic or thoracic (non-cardiac) surgical procedures, have an appropriate soft tissue TBS with severe bleeding as identified intra-operatively by the surgeon and provide written informed consent.

Exclusion criteria

Subjects were excluded from the study if any of the following conditions applied:

- Intra-operative findings were identified by the surgeon that could preclude conduct of the study procedure
- The bleeding site was from large defects in arteries or veins where the injured vascular wall required repair with maintenance of vessel patency and which would result in persistent exposure of the FP to blood flow and pressure during healing and absorption of the product
- TBS was within an actively infected field
- Bleeding site was in, around, or in proximity to foramina in bone, or areas of bony confine
- Subject had known intolerance to blood products or to one of the components of the study product
- Subject was unwilling to receive blood products
- Subject had a known immunodeficiency disease (including known HIV)
- Subject was known, current alcohol and / or drug abuser
- Subject had participated in another investigational drug or device research study within 30 days of enrolment
- Subject was pregnant or nursing.

Treatments

FP was supplied for the study in units of 4 x 4 inches (10.2 x 10.2 cm) in size. The control group was to be treated with the surgeon's Standard of Care (SoC) methods. SoC is a composite of techniques/methods typically used by the surgeon to control severe bleeding after conventional methods (e.g. suture, ligature, cautery) are ineffective or impractical. For this study, SoC was to be initiated with continuous manual compression with or without gauze or sponge and with or without a topical absorbable hemostat (TAH).

Objectives

The primary objective of this study was to evaluate the safety and haemostatic efficacy of the FP versus Standard of Care (SoC) treatment in controlling challenging severe soft tissue bleeding during abdominal, pelvic, retroperitoneal, and (non-cardiac) thoracic surgery.

Outcomes/endpoints

Primary endpoint was the proportion of subjects achieving haemostasis at the TBS at 4-minutes following randomization and with no re-bleeding at the TBS any time prior to wound closure.

Secondary endpoints were:

- Proportion of subjects achieving hemostatic success at 10 minutes following randomization; (defined as achievement of haemostasis at 10 minutes and no further bleeding requiring re-treatment prior to wound closure).
- Absolute time to haemostasis (defined as the absolute time to achieve haemostasis at or after 4 minutes from randomization);
- Proportion of subjects requiring re-treatment at the TBS prior to wound closure;
- Incidence of treatment failures;

Safety variables included:

- Incidence of adverse events that are potentially related to bleeding at the TBS
- Incidence of adverse events that are potentially related to thrombotic events;
- Incidence of adverse events

Follow-Up Visits

Two follow-up visits were scheduled at one-month follow-up visit (+14 days) and (with amendment 2 of the protocol) a two-month follow-up visit (60 days ± 10 days post-procedure), for blood tests (CBC with Differential and Coagulation parameters: PT, APTT, INR, Platelet count, Fibrinogen, and D-Dimer) and to record changes in concomitant medications, adverse events, including any complications potentially related to bleeding and/or thrombotic events.

Sample size

Sample size calculation was as in study 400-07-002.

Randomisation

Randomization was as in study 400-07-002 applying a 2:1 (active: control) ratio.

Blinding (masking)

The study was not blinded

Statistical methods

A sequential triangular test was used to analyse the primary endpoint based on the ITT population of all randomized subjects. For this analysis subjects with missing endpoint information were considered as treatment failures. Analyses were planned for the first 90 subjects with further analyses at completion of every 30 subjects if required. At each interim analysis the value of the appropriate test statistics were calculated and compared with the appropriate stopping boundary (adjusted for discrete monitoring). In case the upper boundary was crossed, the study was stopped and the superiority of FP over the control treatment was concluded. Secondary endpoints analysed by means of logistic regression were: the proportion of subjects achieving hemostatic success at 10 minutes; absolute time to haemostasis; the proportion of subjects requiring re-treatment at the TBS prior to wound closure and incidence of treatment failure. In addition all categorical data were summarized by frequencies along with associated percentages for each group. Continuous variables

were summarized by number of subjects, mean, standard deviation, minimum, and maximum for each group.

Results

Participant flow

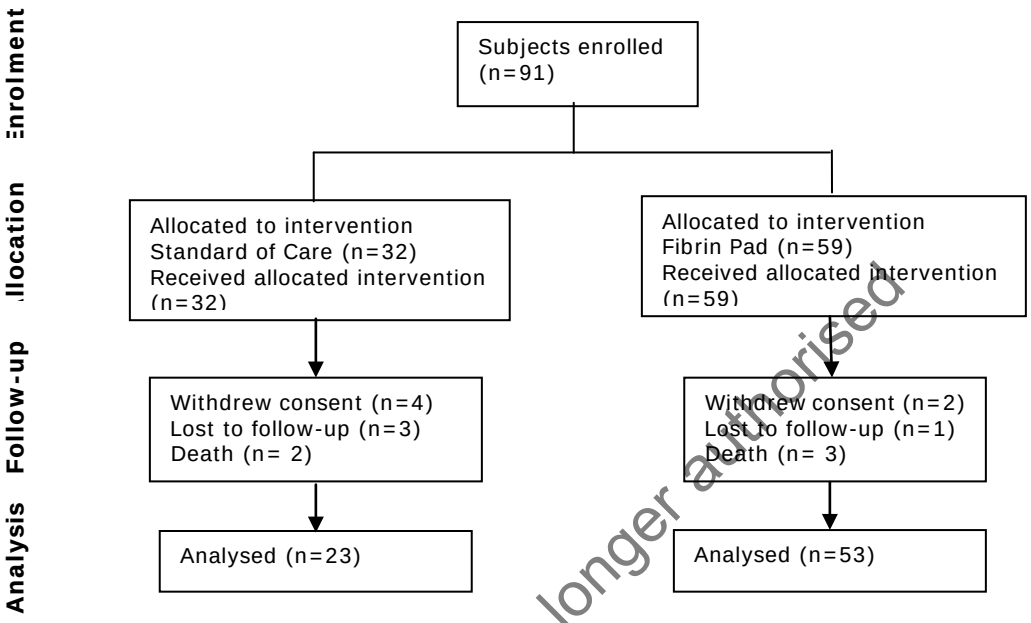


Table 14: Major Protocol Deviations (Study 400-08-002)

Subject #	Treatment	Deviation Category	Details
16001	Fibrin Pad	Study Procedure	TTH measured from time of application of FP rather than time of randomization.
16002	Fibrin Pad	Study Procedure	TTH measured from time of application of FP rather than time of randomization.
20010	Fibrin Pad	Study Procedure	Absolute TTH not recorded.
26001	Fibrin Pad	Study Procedure	TTH measured from time of application of FP rather than time of randomization
26002	Fibrin Pad	Study Procedure	TTH measured from time of application of FP rather than time of randomization.
26004	Fibrin Pad	Study Procedure	TTH measured from time of application of FP rather than time of randomization.
26005	Fibrin Pad	Study Procedure	TTH measured from time of application of FP rather than time of randomization.
16003	Standard of Care	Study Procedure	Absolute TTH not known as end time of rebleed not documented.
21003	Standard of Care	Study Procedure	SoC wrongly initiated with 2 min of diathermy prior to application of Surgicel.
26003	Standard of Care	Study Procedure	TTH measured from time of initiation of SoC procedures rather than time of randomization.
26006	Standard of Care	Study Procedure	TTH measured from time of initiation of SoC procedures rather than time of randomization.

Source: Appendix 16, Listing 16.2.2
CSR 400-08-002 Text Table 6

Recruitment

First subject was randomised on 31 August 2009; last subject completed on 3 March 2011.

Conduct of the study

The original protocol was amended prior to commencement of subject enrolment. A further amendment (2) later included the requirement for an additional follow-up visit at Day-60 ± 10 days. Subjects enrolled into the study before implementation of Amendment 2 were not required to attend a Day-60 follow-up visit.

The study was conducted at 15 institutions in Australia, Germany, New Zealand and United Kingdom. Sponsor audits were performed at sites 21, 15, and 22.

A Data Safety Monitoring Board (DSMB) was established and had responsibility for the review of data and identification of any potential safety issues throughout the duration of the study. In addition, a Clinical Events Committee (CEC) was appointed to adjudicate Adverse Events (AEs), or

Serious Adverse Events (SAEs) that were potentially related to TBS bleeding, thrombotic events and transfusion exposure.

Baseline data

Table 15: Subject Demography (Study 400-08-002, Safety Set)

Category	Statistic	Fibrin Pad N = 59	Standard of Care N = 32	Total N = 91
Age (years)	Median (Range)	65 (33 – 83)	67 (41 – 82)	65 (33 – 83)
Age (grouped)	18 - <50 years	9 (15.3%)	4 (12.5%)	13 (14.3%)
	50 - <65 years	20 (33.9%)	11 (34.4%)	31 (34.1%)
	65 - <75 years	19 (32.2%)	9 (28.1%)	28 (30.8%)
	≥75 years	11 (18.6%)	8 (25.0%)	19 (20.9%)
Gender	Male	40 (67.8%)	17 (53.1%)	57 (62.6%)
	Female	19 (32.2%)	15 (46.9%)	34 (37.4%)
Race	White	50 (84.7%)	28 (87.5%)	78 (85.7%)
	Asian	1 (1.7%)	1 (3.1%)	2 (2.2%)
	Mediterranean	4 (6.8%)	2 (6.3%)	6 (6.6%)
	Indigenous	1 (1.7%)	1 (3.1%)	2 (2.2%)
	Other	3 (5.1%)	0 (0.0%)	3 (3.3%)
BMI (kg/m^2)	Mean (SD)	26.4 (5.1)	27.4 (5.4)	26.7 (5.2)
	Median (range)	26.0 (16.0 – 41.0)	28.0 (19.0 - 46.0)	27.0 (16.0 – 46.0)
	Number (missing)	59 (0)	30 (2)	89 (2)
	95% CI of mean	25.0; 27.7	25.4; 29.4	25.6; 27.8
BMI (grouped)	Underweight	2 (3.4%)	0 (0.0%)	2 (2.2%)
	Normal	19 (32.2%)	8 (26.7%)	27 (30.3%)
	Overweight	24 (40.7%)	18 (60.0%)	42 (47.2%)
	Obese	13 (22.0%)	3 (10.0%)	16 (18.0%)
	Morbidly obese	1 (1.7%)	1 (3.3%)	2 (2.2%)
History of smoking	Yes	38 (64.4%)	14 (43.8%)	52 (57.1%)
	No	21 (35.6%)	18 (56.3%)	39 (42.9%)

Source: Section 14, Table 14.1.2.1

Table 16: Primary Operative Procedure (Study 400-08-002, ITT Set)

Procedure	Fibrin Pad N = 59	Standard of Care (N = 32)	Total N = 91
Pulmonary Resection	12 (20.3%)	7 (21.9%)	19(20.9%)
Gastrectomy	8 (13.6%)	1 (3.1%)	9 (9.9%)
Pancreatic duodenectomy, radical	4 (6.8%)	4 (12.5%)	8 (8.8%)
Colectomy with or without primary anastomoses	3 (5.1%)	2 (6.3%)	5 (5.5%)
Cystectomy, radical	4 (6.8%)	1 (3.1%)	5 (5.5%)
Prostatectomy, radical	3 (5.1%)	1 (3.1%)	4 (4.4%)
Esophageal resection	2 (3.4%)	2 (6.3%)	4 (4.4%)
Cholecystectomy	2 (3.4%)	1 (3.1%)	3 (3.3%)
Hysterectomy TAH/BSO[1]	2 (3.4%)	1 (3.1%)	3 (3.3%)
Pancreatectomy	1 (1.7%)	2 (6.3%)	3 (3.3%)
Abdominoperineal resection	1 (1.7%)	1 (3.1%)	2 (2.2%)
Prostatectomy, simple	2 (3.4%)	0 (0.0%)	2 (2.2%)
Retroperitoneal tumor resection	1 (1.7%)	0 (0.0%)	1 (1.1%)
Hysterectomy, total	1 (1.7%)	0 (0.0%)	1 (1.1%)
Nephrectomy, partial	0 (0.0%)	1 (3.1%)	1 (1.1%)
Nephrectomy, radical	1 (1.7%)	0 (0.0%)	1 (1.1%)
Other[2]	12 (20.3%)	8 (25.0%)	20 (22.0%)

[1]Total abdominal hysterectomy with bilateral salpingo-oopherectomy

[2]Details of procedures categorized as 'other' are given in Listing 16.2.5.1

Source: Section 14, Table 14.1.3.1

CSR 400-08-002, Text Table 9

The study included a wide range of major surgical procedures; mean duration of surgery was 208.4 ± 108.5 min. Pulmonary resection, gastrectomy and radical pancreatic duodenectomy were the most common procedures. Gastrectomy represented 13.6% of cases (8/59 subjects) in the FP group, but only 3.1% of cases (1/32) in the SoC group and radical pancreatic duodenectomy accounted for 6.8% of cases (4/58) in the FP group but 12.5% of SoC cases (4/32). There were no other noticeable differences between the treatment groups in the procedures performed.

Procedures classified as 'other' included operations where multiple surgical procedures were performed (e.g. urethrectomy and diverticulectomy). Five cases of decortication of the lung and 2 cases of hepatic resection were also included in the category of 'other'.

Table 17: Anatomical Location of TBS (Study 400-08-002, ITT Set)

Anatomical Location	Fibrin Pad N = 59	Standard of Care (N = 32)	Total N = 91
Abdominal	23 (39.0%)	15 (46.9%)	38 (41.8%)
Thoracic	17 (28.8%)	10 (31.3%)	27 (29.7%)
Pelvic	12 (20.3%)	4 (12.5%)	16 (17.6%)
Retroperitoneal	7 (11.9%)	3 (9.4%)	10 (11.0%)

Source: Section 14, Table 14.1.3.2

Table 18: Tissue Type at TBS (Study 400-08-002, Safety Set)

Tissue Type	Fibrin Pad N = 59	Standard of Care (N = 32)	Total N = 91
Muscle	22 (37.3%)	4 (12.5%)	26 (28.6%)
Fat	12 (20.3%)	8 (25.0%)	20 (22.0%)
Lymph node bed	5 (8.5%)	6 (18.8%)	11 (12.1%)
Loose areolar connective	7 (11.9%)	2 (6.3%)	9 (9.9%)
Lymphatic	2 (3.4%)	2 (6.3%)	4 (4.4%)
Other	11 (18.6%)	10 (31.3%)	21 (23.1%)

Source: Section 14, Table 14.1.3.2

The primary method of at the TBS prior to randomization was cautery in 16.5% of cases (15/91), suture in 5.5% of cases (5/91), ligation in 1.1% of cases (1/91) and 'other' in 18.7% of cases (17/91). 'Other' methods included packing, compression and Surgicel. No hemostatic methods were used at the TBS prior to study treatment in 58.2% of cases (53/91) as they were deemed to be impractical by the surgeon.

Haemostatic Methods in the Control Group

The control group was treated with a composite of techniques/methods typically used by the surgeon to control severe bleeding after conventional methods (e.g. suture, ligature, cautery) were found to be ineffective or impractical. Methods categorized as "other" were one case each of manual compression+ ORC+topical thrombin, cautery+manual compression+ORC, and suture ligation.

Table 19: Hemostatic Methods in the Control Group (Study 400-08-002, ITT Set)

Hemostatic Method	N (%)
Manual compression only	2/32 (6.5%)
Manual compression with topical absorbable hemostat (TAH)	29/32 (90.6%)
Oxidized regenerated cellulose (ORC)	*28/29 (96.6%)*
Collagen	*1/29 (3.4%)*
Other	3/32 (10.0%)

Source: Section 14, Table 14.1.3.2

Numbers analysed

Table 20: Analysis Sets (Study 400-08-002)

	Fibrin Pad	Standard of Care	Total
Intent to Treat (ITT)	59	32	91
Per Protocol (PP)	52	28	80
Safety Set	59	32	91

Source: Section 14, Table 14.1.1.3
CSR 400-08-002 Text Table 7

- **Outcomes and estimation**

Primary efficacy endpoint.

At 4 minutes, after release of manual compression, 52/59 subjects (88.1%) in the FP group had achieved haemostasis as compared to 14/32 (43.8%) in the SoC group. The number of subjects with haemostasis at 4 minutes and no re-bleeding requiring treatment at the TBS any time prior to wound closure was 50/59 (84.7%) in the FP group and 10/32 (31.3%) in the SoC group (with missing data imputed as failures in both treatment groups) as in table 21.

Table 21: Primary Endpoint Results (Study 400-08-002, ITT Set)

Fibrin Pad	Standard of Care	p-value	Treatment Difference
50/59 (84.7%)	10/32 (31.3%)	<0.0001	53.5%

Source: Section 14, Tables 4.2.1.1 and 14.2.1.3
CSR 400-08-002, Text Table 13

Table 22: Primary Endpoint Results (Study 400-08-002, PP Set)

Fibrin Pad	Standard of Care	p-value	Treatment Difference
49/52 (94.2%)	10/28 (35.7%)	<0.0001	58.5%

Source: Section 14, Tables 14.2.1.2 and 14.2.1.3

Additional ITT analyses imputing missing data as successes in both groups (analysis #2), or as failures in the FP group and successes in the SoC group (analysis #3), or as successes in the FP group and failures in the SoC group (analysis #4) are shown in the following Table. These analyses support the robustness of the results for the primary efficacy endpoint.

Table 23: Sensitivity Analysis (Study 400-08-002, ITT Set)

Analysis #	Imputation of Missing Data	Fibrin Pad	Standard of Care	p-value	Treatment Difference
1†	Failure	50/59 (84.7%)	10/32 (31.3%)	<0.0001	53.5%
2	Success	56/59 (94.9%)	12/32 (37.5%)	<0.0001	57.4%
3	FP Failure, SoC Success	50/59 (84.7%)	12/32 (37.5%)	<0.0001	47.2%
4	FP Success, SoC Failure	56/59 (94.9%)	10/32 (31.3%)	<0.0001	63.7%

†Primary efficacy endpoint

Source: Section 14, Tables 4.2.1.1 and 14.2.1.3

CSR 400-08-002, Text Table 15

Secondary efficacy endpoints

Table 24: Hemostatic Success at 10 minutes (Study 400-08-002)

Analysis Set	Fibrin Pad	Standard of Care	Treatment Difference
ITT	58/59 (98.3%)	22/32 (68.8%)	29.5%
PP	51/52 (98.1%)	19/28 (67.9%)	30.2%

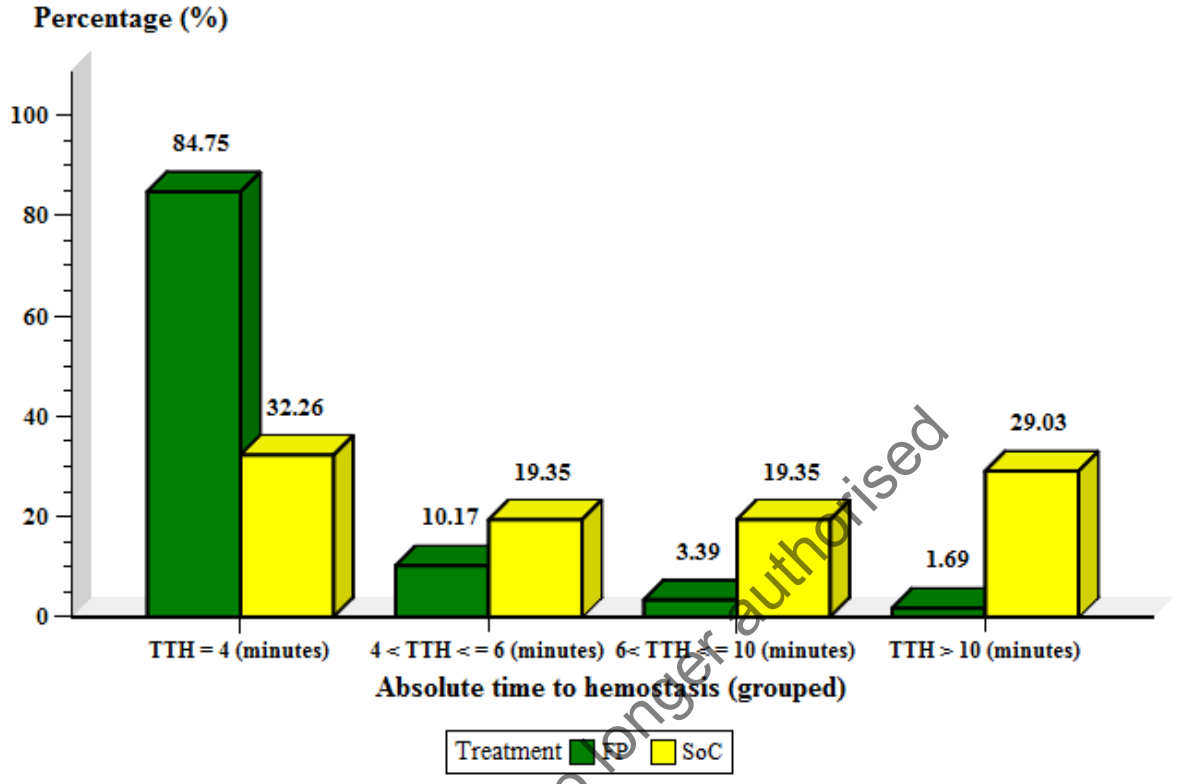
Source: Section 14, Tables 14.2.1.1 and 14.2.1.2.

Table 25: Absolute Time to Haemostasis (minutes)(Study 400-08-002)

Analysis Set		Fibrin Pad	Standard of Care
ITT	N	59	32
	Mean (SD)	6.1 (13.5)	17.8 (32. 0)
	Median (Range)	4.0 (4.0; 107.3)	6.0 (4.0; 130.3)
PP	N	52	28
	Mean (SD)	6.2 (14.3)	19.2 (33.4)
	Median (Range)	4.0 (4.0; 107.3)	7.3 (4.0; 130.3)

Source: Section 14, Tables 14.2.1.1 and 14.2.1.2.

Figure 1: Distribution of Time to Haemostasis (grouped) by Treatment (Study 400-08-002, ITT Set)



Retreatment at the TBS prior to wound closure

In the ITT set, 3/59 subjects (5.1%) treated with FP required re-treatment prior to wound closure, compared to 17/32 (53.1%) in the SoC group. Retreatment in the 3 cases in the FP group consisted of reapplication of FP. In the SoC group, retreatment included the use of suture, ligation, cautery, ORC, manual compression and 'other' methods described as the use of 'felt pieces', gauze and clips.

Blood loss and transfusion requirement

The percentage of subjects requiring a transfusion from the time of surgery until the Day of Discharge was 30.5% (18/59) in the FP group and 34.4% (11/32) in the SoC group. The mean estimated blood loss was 973 mL (range 50 to 10,000 mL) in the FP group and 1,431.5 mL (range 150 to 13,000 mL) in the SoC group.

Interim analyses

The first interim analysis, after the first 90 randomized subjects, revealed that Fibrin Pad treatment was declared superior to Standard of care with a significance level <0.0001. Recruitment to the study was terminated.

• Ancillary analyses

N/A

Study 400-10-001

This was a Phase III Randomized, Controlled, Superiority Study Evaluating the Fibrin Pad versus Standard of Care Treatment in Controlling Parenchymal Bleeding during Elective Hepatic Surgery

Methods

Study participants

Inclusion criteria

Eligible subjects should be aged 18 years or over, requiring elective or urgent open hepatic surgery, willing to participate in the study and provide written informed consent. The presence of an appropriate parenchymal TBS was identified intra-operatively by the surgeon.

Exclusion criteria

Candidates were excluded from the study if any of the following conditions applied:

- Intra-operative findings that could preclude conduct of the study procedure
- TBS was from large defects in arteries or veins where the injured vascular wall required repair with maintenance of vessel patency and which would result in persistent exposure of the FP to blood flow and pressure during healing and absorption of the product
- TBS had major arterial bleeding requiring suture or mechanical ligation
- Subject was admitted for trauma surgery
- Subject was undergoing a liver transplant for fulminant hepatic failure
- TBS was within an actively infected field
- Bleeding site was in, around, or in proximity to foramina in bone, or areas of bony confine
- Subject had known intolerance to blood products or to one of the components of the study product
- Subject was unwilling to receive blood products
- Subject was known, current alcohol and / or drug abuser
- Subject had participated in another investigational drug or device research study within 30 days of enrolment
- Subject was pregnant or nursing.

Control treatment was SoC.

Subsequently, eligible subjects were stratified based on the type of hepatic parenchyma Normal or Abnormal (identified as cirrhotic, steatotic or other).

Treatment

FP was supplied for the study in units of 10.2 x 10.2 cm (4 x 4 inches) in size.

The control group was to be treated with the surgeon's Standard of Care (SoC) methods. Standard of Care is a composite of techniques/methods typically used by the surgeon to control parenchymal

bleeding after conventional methods (e.g. suture, ligature, cautery) are ineffective or impractical. For this study, SoC was to be initiated with continuous firm manual compression with or without gauze or sponge and with or without a topical absorbable hemostat (TAH).

If breakthrough bleeding occurred at the TBS during the initial 4-minute period, the surgeon could apply additional FP if clinically appropriate. If bleeding was due to insufficient coverage of the TBS, the additional units were to be applied so that they overlapped the previously applied product. If bleeding was due to incomplete adherence to the tissue, the previous unit was to be removed and replaced with a new unit. After re-treatment, manual compression was to be applied for 2-3 minutes, after which haemostasis was to be assessed.
If breakthrough bleeding requiring treatment other than FP occurred during the 4-minute treatment period, or during the subsequent observation period at any time prior to wound closure, the surgeon was to revert to SoC and the subject was to be considered a treatment failure for the primary efficacy parameter.

Objectives

The primary objective of this study was to evaluate the safety and hemostatic effectiveness of the FP versus Standard of Care (SoC) treatment in controlling parenchymal bleeding during hepatic surgery.

Outcomes/endpoints

The primary endpoint was the proportion of subjects achieving haemostasis at the TBS at 4-minutes following randomization and with no re-bleeding at the TBS any time prior to initiation of wound closure (last point in time where FP was visible to confirm haemostasis).

Secondary endpoints were: the proportion of subjects achieving hemostatic success at 10 minutes following randomization; absolute time to haemostasis; the proportion of subjects who, after initial hemostatic success at 4 minutes, had breakthrough bleeding requiring treatment

Safety variables included: incidence of all AEs; incidence of AEs potentially related to bleeding at the TBS; incidence of AEs potentially related to thrombotic events;

Follow-Up Visits

Two follow-up visits were scheduled:

a one-month follow-up visit (30 days +14 days post procedure) and a two-month follow-up visit (60 days + 14 days post-procedure).
At both visits, the following information was to be recorded: changes in concomitant medications, including use of any blood products following hospital discharge; blood samples were to be taken for CBC with Differential and Coagulation parameters (PT, APTT, INR, Platelet count, Fibrinogen, and D-Dimer); Adverse events, including any complications potentially related to bleeding and/or thrombotic events.

In addition, at the one-month follow-up visit, a physical examination was performed and blood samples were taken for CBC with differential, liver function tests and coagulation parameters.

Sample size

Due to the sequential study design no fixed sample size was calculated but the maximum sample size for a triangular design with continuous monitoring was contrasted with the sample size for a fixed design. Anticipating a success rate of 50% in the control arm, a success rate of 75% in the treatment arm, a 2-sided type I error of 0.05 and 90% power a maximum sample size of 230 subjects was calculated in case of a continuously monitored triangular test and an 1:1 (active: control) allocation ratio and the corresponding number of subjects in a fixed sample design were about 150. Simulations were performed to assess the impact of the planned discrete study monitoring on the study power.

Randomisation

Subjects were randomized applying a 1:1 (active: control) ratio, randomisation methodology was same as in the other two studies.

Blinding (masking)

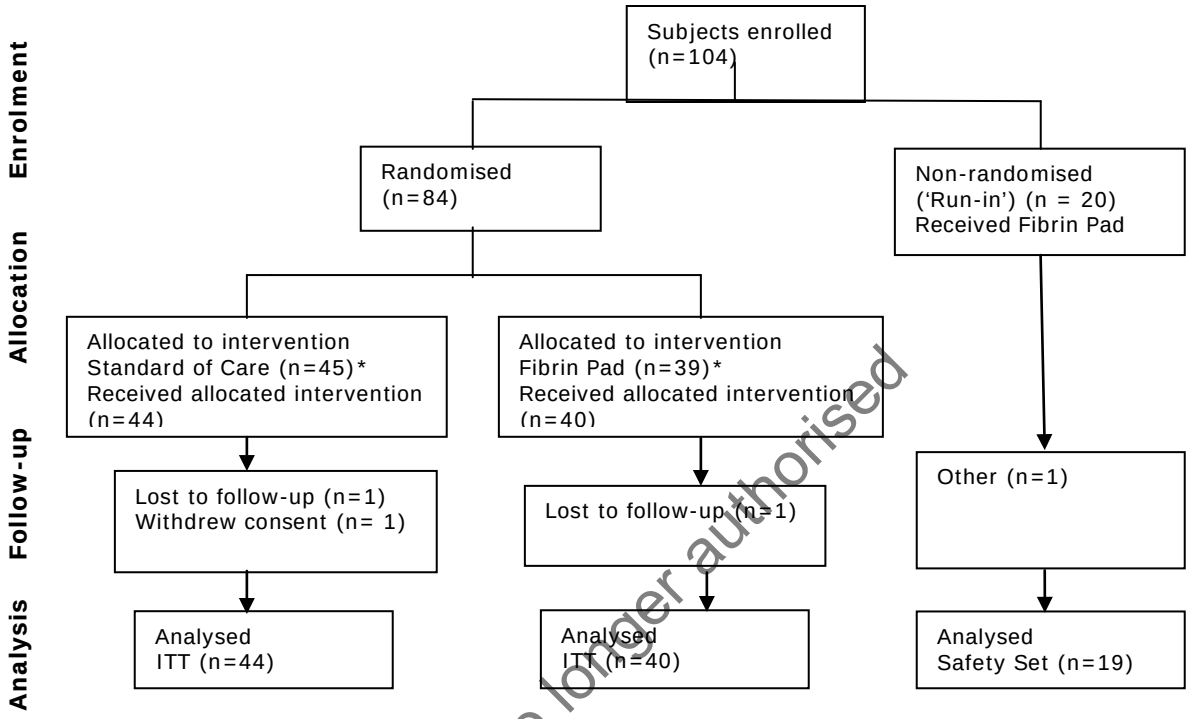
The study was not blinded.

- **Statistical methods**

A sequential triangular test was used to analyse the primary endpoint based on the ITT population of all randomized subjects. For this analysis subjects with missing endpoint information were considered as treatment failures. The first analysis was planned for the first 80 patients with further analyses at completion of every 40 subjects if required. At each interim analysis the value of the appropriate test statistics were calculated and compared with the appropriate stopping boundary (adjusted for discrete monitoring). In case the upper boundary was crossed, the study was stopped and the superiority of FP over the control treatment was concluded. Secondary endpoints analysed by means of logistic regression were: the proportion of subjects achieving hemostatic success at 10 minutes; absolute time to; the proportion of subjects requiring re-treatment at the TBS prior to wound closure and incidence of treatment failure. In addition all categorical data were summarized by frequencies along with associated percentages for each group. Continuous variables were summarized by number of subjects, mean, standard deviation, minimum, and maximum for each group.

Results

- **Participant flow**



Reasons and time for withdrawal (Source: CSR 400-10-001, Listing 16.2.1.1)
Standard of Care:
Subject 10111 withdrew consent 4 days after procedure
Subject 11107 lost to follow-up 15 days after procedure

Fibrin Pad randomized:
Subject 18107 lost to follow-up 48 days after procedure

Fibrin Pad 'Run-in':
Subject 15303 other (hospitalisations) 9 days after procedure

Table 26: Major Protocol Deviations (Study 400-10-001)

Subject #	Treatment	Deviation Category	Details
11-104	Fibrin Pad	Study Procedure	Four minute evaluation of hemostasis performed at 4 min 30 sec.
11-106	Fibrin Pad	Study Procedure	Four minute evaluation of hemostasis performed at 4 min 31 sec.
15-105	Fibrin Pad	Study Procedure	Stopwatch was started when FP opened, not when randomization envelope opened.
18-102	Fibrin Pad	Inclusion/exclusion criteria	Patient was randomized although major arterial bleeding was present at the TBS.
		Other	Absolute TTH was not recorded.
10-302	Fibrin Pad (run-in)	Randomization	Subject was the second non-randomized subject treated by the investigator, whereas the protocol specified only one run-in patient per investigator.
18-301	Fibrin Pad (run-in)	Study Procedure	Stopwatch started when FP applied, not when randomization envelope opened.
13-204	Standard of Care*	Randomization	Randomization envelope taken out of sequence; subject should have received FP but was erroneously treated with SoC.
13-106	Standard of Care	Study Procedure	FP was not prepared and opened in theatre prior to randomization.
18-101	Standard of Care	Randomization	The randomization envelope 18202 was opened in error.

*Analyzed as FP in the ITT Set

Source: Appendix 16.2, Listing 16.2.2

Recruitment

First subject included: June 14, 2010; last subject exit the study: October 17, 2011.

Conduct of the study

The original protocol was dated February 23, 2010. No protocol amendments were required during the study.

The study was conducted at 10 institutions in UK, Germany, The Netherlands, Australia, and New Zealand.

A Data Safety Monitoring Board (DSMB) was established and had responsibility for the review of data and identification of any potential safety issues throughout the duration of the study. In addition, a Clinical Events Committee (CEC) was appointed to adjudicate Adverse Events (AEs), or Serious Adverse Events (SAEs) that were potentially related to TBS bleeding, thrombotic events and transfusion exposure.

Baseline data

Table 27: Subject Demography (Study 400-10-001, ITT Set)

Category	Statistic	Fibrin Pad N = 40	Standard of Care N = 44	Total N = 84
Age (years)	Median (Range)	65 (31 – 82)	65.5 (39 – 82)	65 (31 – 82)
Age (grouped)	18 - <50 years	6 (15.0%)	7 (15.9%)	13 (15.5%)
	50 - <65 years	12 (30.0%)	41 (31.8%)	26 (31.0%)
	65 - <75 years	13 (32.5%)	13 (29.5%)	26 (31.0%)
	≥75 years	9 (22.5%)	10 (22.7%)	19 (22.6%)
Gender	Male	24 (60.0%)	24 (54.5%)	48 (57.1%)
	Female	16 (40.0%)	20 (45.5%)	36 (42.9%)
Race	White	38 (95.0%)	41 (93.2%)	79 (94.0%)
	Asian	2 (5.0%)	0 (0.0%)	2 (2.4%)
	Black/ African American	0 (0.0%)	1 (2.3%)	1 (1.2%)
	Indigenous	0 (0.0%)	1 (2.3%)	1 (1.2%)
	Other	0 (0.0%)	1 (2.3%)	1 (1.2%)
BMI (kg/m^2)	Mean (SD)	27.9 (5.8)	26.7 (5.2)	27.3 (5.5)
	Median (range)	27.0 (15.0 – 41.0)	25.0 (18.0 - 43.0)	26.0 (15.0 – 43.0)
	Number (missing)	40 (0)	43 (1)	83 (1)
	95% CI of mean	26.1; 29.7	25.1; 28.3	26.1; 28.5
BMI (grouped)	Underweight	1 (2.5%)	1 (2.3%)	2 (2.4%)
	Normal	13 (32.5%)	15 (34.9%)	28 (33.7%)
	Overweight	12 (30.0%)	17 (39.5%)	29 (34.9%)
	Obese	13 (32.5%)	9 (20.9%)	22 (26.5%)
	Morbidly obese	1 (2.5%)	1 (2.3%)	2 (2.4%)
History of smoking	Yes	24 (60.0%)	22 (50.0%)	46 (54.8%)
	No	16 (40.0%)	22 (50.0%)	38 (45.2%)

Source: Section 14, Table 14.1.2.1

CSR 400-10-001, Text Table 8

Primary Operative Procedure

The reason for liver resection in the majority of study subjects in the Safety Set (75.0%) was metastatic liver disease. Hepatocellular carcinoma was the other principal reason (14.4%) with cholangiocarcinoma (3.8%), hemangioma (2.9%) and 'other' (3.8%) also reported. The resection of the liver was categorized as 'anatomic', 'non-anatomic' or 'other'. In the Safety Set, approximately two thirds of subjects underwent anatomic resections (FP 38/59, 64.4%; SoC 31/45, 68.9%). The anatomic resections were further classified. The most frequently performed procedure was right lobe resection, which represented almost half of all anatomic procedures (FP 18/59, 47.4%; SoC 15/45, 46.9%). The involvement of the anatomical liver segments I to VIII in the resection was also documented.

Classification of Hepatic Parenchyma

The hepatic parenchyma was examined by the investigator and classified as Normal or Abnormal. Abnormal hepatic parenchyma was then identified as cirrhotic, steatotic or other.

Table 28: Hepatic Parenchyma (Study 400-10-001, Safety Set)

Classification of Hepatic Parenchyma	Fibrin Pad N = 59	Standard of Care N = 45	Total N = 104
Normal	41 (69.5%)	33 (73.3%)	74 (71.2%)
Abnormal	18 (30.5%)	12 (26.7%)	30 (28.8%)
Cirrhotic	*3 (16.7%)*	*5 (41.7%)*	*8 (26.7%)*
Steatotic	*13 (72.2%)*	*3 (25.0%)*	*16 (53.3%)*
Other	*2 (11.1%)*	*4 (33.3%)*	*6 (20.0%)*

Source: Section 14, Table 14.1.3.2a

Firm pressure was applied and held for 30 seconds in both treatment groups. A primary method of haemostasis was not used in approximately half the subjects (FP 20/40, 50%; SoC 20/44, 45.5%). In the remaining subjects, suture, cautery or ligation or 'other' methods were used.

Table 29: Characteristics of Bleeding at the TBS (Study 400-10-001, Safety Set)

Variable	Category	Fibrin Pad N=59	Standard of Care N=45	Total N=104
Predominant source of bleeding	N	59	45	104
	Arterial	3 (5.1%)	2 (4.4%)	5 (4.8%)
	Venous	36 (61.0%)	24 (53.3%)	60 (57.7%)
	Mixed	20 (33.9%)	19 (42.2%)	39 (37.5%)
If arterial:	N	22	20	42
	Non-pulsatile	19 (86.4%)	14 (70.0%)	33 (78.6%)
	Pulsatile, non-spurting	2 (9.1%)	5 (25.0%)	7 (16.7%)
	Pulsatile, spurting	1 (4.5%)	1 (5.0%)	2 (4.8%)
If venous:	N[a]	54	42	96
	n[b]	58	42	100
	Oozing	31 (53.4%)	25 (59.5%)	56 (56.0%)
	Steady	20 (34.5%)	13 (31.0%)	33 (33.0%)
	Brisk	7 (12.1%)	4 (9.5%)	11 (11.0%)
Area of bleeding	N	59	45	104
	Discrete (<1 cm^2)	13 (22.0%)	16 (35.6%)	29 (27.9%)
	Diffuse (> 1cm^2)	46 (78.0%)	29 (64.4%)	75 (72.1%)
If diffuse:	N	44	28	72
	Patchy	27 (61.4%)	17 (60.7%)	44 (61.1%)
	Confluent	17 (38.6%)	11 (39.3%)	28 (38.9%)

[a]N= number of subjects;

[b]n= number of observations. Two descriptions of venous bleeding were recorded for 4 subjects in the FP group. Thus the number of observations is greater than the number of subjects.

Source: Section 14, Table 14.1.3.3a and Appendix 16.2, Listing 16.2.5.3.

Hemostatic Methods in the Control Group

The control group was treated with a composite of techniques/methods typically used by the surgeon to control severe bleeding after conventional methods (e.g. suture, ligature, cautery) were found to be ineffective or impractical.

Table 30: Hemostatic Methods in the Control Group (Study 400-10-001, ITT Set)

Hemostatic Method	N (%)
Manual compression only	27/44 (61.4%)
Manual compression with topical absorbable hemostat (TAH)	15/44 (34.1%)
Oxidized regenerated cellulose (ORC)	*14/15 (93.3%)*
Gelatin	*2/15 (13.3%)*
TachoComb®	*1/15 (6.7%)*
Other	2/44 (4.5%)

Source: Section 14, Table 14.1.3.4

- **Numbers analysed**

The primary endpoint analysis was based on the ITT analysis set. The PP population was used in a supportive analysis of the primary effectiveness variable only. The incidences of subjects with AEs that were potentially related to bleeding at TBS or to thrombotic events were summarized descriptively for the ITT and Safety analysis set, because these secondary endpoints are also safety endpoints. All other secondary endpoints were analyzed using the ITT and Per-Protocol set. The Safety Analysis Set included the subjects who were treated in a run-in phase with Fibrin Pad.

Table 31: Analysis Sets (Study 400-10-001)

	Fibrin Pad	Standard of Care	Total
Intent to Treat (ITT)*	40	44	84
Per Protocol (PP)	35	42	77
Safety Set	59	45	104

Source: Section 14, Table 14.1.1.3a

- **Outcomes and estimation**

Primary efficacy endpoint

At 4 minutes, after release of manual compression, 34/40 subjects (85.0%) in the FP group had achieved haemostasis as compared to 17/44 (38.6%) in the SoC group. The number of subjects with haemostasis at 4 minutes and no re-bleeding requiring treatment at the TBS any time prior to the initiation of wound closure was 33/40 (82.5%) in the FP group and 13/44 (29.5%) in the SoC group (with missing data imputed as failures in both treatment groups).

Table 32: Primary Endpoint Results (Study 400-10-001, ITT Set)

Classification of Hepatic Parenchyma	Fibrin Pad	Standard of Care	p-value	Treatment Difference
All	33/40 (82.5%)	13/44 (29.5%)	<0.0001	53.0%
Normal	23/28 (82.1%)	11/33 (33.3%)	0.0001	48.8%
Abnormal	10/12 (83.3%)	2/11 (18.2%)	0.0009	65.2%

Source: Section 14, Table 4.2.1.1.4

The supportive analysis in the PP set showed similar results. Five subjects in the FP group and 2 subjects in the SoC group had major protocol deviations and were excluded from the PP analysis.

Table 33: Primary Endpoint Results (Study 400-10-001, PP Set)

Classification of Hepatic Parenchyma	Fibrin Pad	Standard of Care	p-value	Treatment Difference
All	33/35 (94.3%)	12/42 (28.6%)	<0.0001	65.7%
Normal	23/24 (95.8%)	10/31 (32.3%)	<0.0001	63.6%
Abnormal	10/11 (90.9%)	2/11 (18.2%)	0.0003	72.7%

Source: Section 14, Table 4.2.1.2.4

Additional ITT analyses imputing missing data as successes in both groups (analysis #2), or as failures in the FP group and successes in the SoC group (analysis #3) are shown in the following Table. These analyses support the robustness of the results for the primary efficacy endpoint.

Table 34: Sensitivity Analysis (Study 400-10-001, ITT Set)

Analysis #	Imputation of Missing Data	Fibrin Pad	Standard of Care	p-value	Treatment Difference
1†	Failure	33/40 (82.5%)	13/44 (29.5%)	<0.0001	53.0%
2	Success	35/40 (87.5%)	13/44 (29.5%)	<0.0001	58.0%
3	FP Failure, SoC Success	33/40 (82.5%)	13/44 (29.5%)	<0.0001	53.0%

†Primary efficacy endpoint

Source: Section 14, Tables 4.2.1.1.4

Secondary efficacy endpoints

The proportion of subjects achieving hemostatic success at 10 minutes following randomization is presented in table 35.

Table 35: Hemostatic Success at 10 minutes (Study 400-10-001, ITT Set)

Classification of Hepatic Parenchyma	Fibrin Pad	Standard of Care	p-value	Treatment Difference
All	38/40 (95.0%)	30/44 (69.8%)	0.0189	25.2%
Normal	27/28 (96.4%)	23/33 (71.9%)	-	24.5%
Abnormal	11/12 (91.7%)	7/11 (63.6%)	-	28.1%

Source: Section 14, Tables 4.2.1.1.1, 4.2.1.1.2, 4.2.1.1.3 and 14.2.2.1.2

Absolute time to haemostasis (TTH), defined as the absolute time to achieve haemostasis at or after 4 minutes from randomization was also evaluated as a secondary endpoint- presented in table 36.

Table 36: Absolute Time to Haemostasis in minutes (Study 400-10-001, ITT Set)

Classification of Hepatic Parenchyma		Fibrin Pad	Standard of Care
All	N	40	44
	Mean (SD)	4.6 (2.0)	10.0 (7.1)
	Median (Range)	4.0 (4.0; 13.2)	9.7 (4.0; 31.3)
Normal	N	28	33
	Mean (SD)	4.3 (1.2)	9.5 (6.6)
	Median (Range)	4.0 (4.0; 10.0)	9.4 (4.0; 29.7)
Abnormal	N	12	11
	Mean (SD)	5.3 (3.0)	11.6 (8.7)
	Median (Range)	4.0 (4.0; 13.2)	10.0 (4.0; 31.3)

Source: Section 14, Tables 4.2.1.1.1, 4.2.1.1.2 and 4.2.1.1.3

Bleeding requiring re-treatment

In the ITT Set, among subjects who had achieved haemostasis at 4 minutes, additional treatment for bleeding was required by 1/38 subjects (2.6%) treated with FP compared to 1/44 (2.3%) subjects in the SoC group. Of subjects who achieved haemostasis at a time-point later than 4 minutes, additional treatment was required by 4/40 (10%) in the FP group as compared to 27/44 (61.4%) in the SoC group (p <0.0001). The percentages in the sub-groups of subjects with normal and abnormal hepatic parenchyma were closely comparable.

Retreatment in the 5 cases in the FP group consisted of reapplication of FP in 3 cases, manual compression in one case and suture and argon beam in one case.

Retreatment methods used for the 28 subjects in the SoC group included the use of suture, cautery, argon beam, gelatin, ORC, manual compression with or without TAH and 'other' methods. Other

methods included the use of diathermy, ligaclips plus diathermy, and other local haemostatic products.

Hemostatic efficacy in the Safety Analysis Set includes additionally the non-randomized subjects treated with Fibrin Pad in the run-in phase.

Table 37: Summary of Haemostasis (Study 400-10-001, Safety Set)

Parameter	Classification of Hepatic Parenchyma	Fibrin Pad N=59	SoC N=45	p-value	Treatment Difference
Hemostasis at 4 min; no rebleeding prior to wound closure	All	53/59 (89.8%)	13/45 (28.9%)	<0.0001	60.9%
	Normal	36/41 (87.8%)	11/33 (33.3%)	<0.0001	54.5%
	Abnormal	17/18 (94.4%)	2/12 (16.7%)	<0.0001	77.8%
	Statistic				
Hemostasis at 10 min; no rebleeding prior to wound closure		57/59 (96.6%)	31/44* (70.5%)	0.0037	26.1%
Absolute Time to Hemostasis (minutes)	N*	56	45		
	Median	4.0	9.9	<0.0001	
	Range	4.0 – 13.2	4.0 – 31.3		
Bleeding requiring retreatment:					
Hemostasis at 4 minutes		1/57* (1.8%)	1/45 (2.2%)		
Hemostasis later than 4 minutes		3/59 (5.1%)	28/45 62.2%)	<0.0001	

* number of available observations in this category

Source: Tables 14.2.1.3.1, 14.2.2.3.1, 14.2.2.3.2 and 14.2.1.3.4

Ancillary analyses

N/A

Summary of main efficacy results

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 38: Summary of efficacy for trial 400-07-002

Title: A Prospective, Randomized, Controlled Superiority Evaluation of Fibrin Patch (Fibrin Pad) as an Adjunct to Control Soft Tissue Bleeding during Abdominal, Retroperitoneal, Pelvic, and Thoracic Surgery				
Study identifier	Protocol Number 400-07-002			
Design	Randomized, controlled, parallel groups, open, sequential, multicenter study			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	March 2008 to April 2009 not applicable not applicable		
Hypothesis	Superiority			
Treatments groups	FP (Fibrin Pad = Evarrest) randomized	FP used to treat one TBS in a single surgical procedure.		
	Surgicel®	Surgicel used to treat one TBS in a single surgical procedure.		
	FP non-randomized	Once superiority was established, subsequent subjects enrolled to be treated with FP		
Endpoints and definitions	Primary endpoint	TBS 4: Success in achieving haemostasis at the target bleeding site (TBS) 4 minutes after randomization with no re-bleeding requiring treatment during a subsequent 6-minute observation period. Haemostasis was defined as no detectable bleeding at the TBS		
	Secondary endpoint	TBS 10: Success in achieving hemostatic success at 10 minutes following randomization (defined as the achievement of haemostasis within 10 minutes and no further bleeding requiring treatment during the final 6-minute observation period)		
	Secondary endpoint	Treatment failure (TF): haemostasis not achieved within 4 minutes or bleeding requiring additional intervention during the 6 minute observation period		
Database lock	July 2, 2009			
Results and Analysis				
Analysis description	**Primary / Secondary Analyses**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	FP randomized	Surgicel	
	Number of subject	60	30	

	TBS 4 n/N (%)	59/60 (98.3%)	16/30 (53.3%)	
	TBS 10 n/N (%)	59/60 (98.3%)	22/30 (73.3%)	
	TF n/N (%)	1/60 (1.7%)	14/30 (46.7%)	

Effect estimate per comparison		Comparison groups	FP vs. surgical
	Primary endpoint: TBS 4	Difference of incidences	45%
		P-value	< 0.0001
	Secondary endpoint: TBS 10	Difference of incidences	25%
		P-value	Not provided
	Secondary endpoint: TF	Difference of incidences	-45%
		P-value	Not provided
Notes	No measures of variability on the original scale are provided with the study report.		

Table 39: Summary of efficacy for trial 400-08-002

Title: A Phase III Randomized, Controlled, Superiority Study Evaluating the Fibrin Pad Versus Standard of Care Treatment in Controlling Severe Soft Tissue Bleeding During Abdominal, Retroperitoneal, Pelvic and Thoracic Surgery			
Study identifier	Protocol Number 400-08-002 EudraCT number 2008-004835-3		
Design	Randomized, controlled, parallel groups, open, sequential, multicenter study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	August 2009 to March 2011 not applicable not applicable	
Hypothesis	Superiority		
Treatments groups	FP (Fibrin Pad = Evarrest)	FP used to treat one TBS in a single surgical procedure.	
	SoC	Surgeons' standard of care to control severe bleeding	
Endpoints and definitions	Primary endpoint	TBS 4: Success in achieving haemostasis at the target bleeding site (TBS) 4 minutes after randomization with no re-bleeding at the TBS any time prior to wound closure. Haemostasis was defined as no detectable bleeding at the TBS	
	Secondary endpoint	TBS 10: Success in achieving hemostatic success at 10 minutes following randomization (defined as the achievement of haemostasis within 10 minutes and no further bleeding requiring treatment prior to wound closure)	
	Secondary endpoint	Time to haemostasis: time to achieve haemostasis at or after 4 minutes from randomization	

	Secondary endpoint	Need for re-treatment at the TBS prior to wound closure
	Secondary endpoint	Treatment failure: haemostasis not achieved within 4 minutes or bleeding requiring additional intervention during the 6 minute observation period
Database lock	April 6, 2011	

Results and Analysis

Analysis description	**Primary / Secondary Analyses**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	FP	SoC	
	Number of subject	59	32	
	TBS 4 n/N (%)	50/59 (84.7%)	10/32 (31.3%)	
	TBS 10 n/N (%)	58/59 (98.3%)	22/32 (68.8%)	
	Time to haemostasis (min) Mean (SD)	6.1 (13.5)	17.8 (32.0)	
	Re-treatment n/N (%)	3/59 (5.1%)	17/32 (53.1%)	
	Treatment failure n/N (%)	9/59 (15.3%)	22/32 (68.8%)	

Effect estimate per comparison		Comparison groups	FP vs. SoC
	Primary endpoint: TBS 4	Difference of incidences	53.4%
		P-value	< 0.0001
	Secondary endpoint: TBS 10	Difference of incidences	29.5%
		P-value	Not provided
	Secondary endpoint: Time to haemostasis (min)	Mean difference	-11.7
		P-value	Not provided
	Secondary endpoint: Re-treatment	Difference of incidences	48.0%
		P-value	Not provided
	Secondary endpoint: treatment failures	Difference of incidences	-53.5%
		P-value	Not provided
Notes	No measures of variability for treatment effects on the original scale are provided with the study report.		

Table 40: Summary of efficacy for trial 400-10-001

Title: A Phase III Randomized, Controlled, Superiority Study Evaluating the Fibrin Pad Versus Standard of Care Treatment in Controlling Parenchymal Bleeding During Elective Hepatic Surgery				
Study identifier	Protocol Number 400-10-001 EudraCT number 2010-019427-58			
Design	Randomized, controlled, parallel groups, open, sequential, multicenter study			
	Duration of main phase:	June 2010 to October 2011		
	Duration of Run-in phase:	One surgery per investigator not familiar with FP		
	Duration of Extension phase:	not applicable		
Hypothesis	Superiority			
Treatments groups	FP (Fibrin Pad = Evarrest)	FP used to treat one TBS during hepatic surgery		
	SoC	Surgeons' standard of care to control severe bleeding		
Endpoints and definitions	Primary endpoint	TBS 4: Success in achieving haemostasis at the target bleeding site (TBS) 4 minutes after randomization with no re-bleeding at the TBS any time prior to initiation of wound closure. Haemostasis was defined as no detectable bleeding at the TBS		
	Secondary endpoint	TBS 10: Success in achieving hemostatic success at 10 minutes following randomization (defined as the achievement of haemostasis within 10 minutes and no further bleeding requiring treatment prior to wound closure)		
	Secondary endpoint	Time to haemostasis (TTH): time to achieve haemostasis at or after 4 minutes from randomization		
	Secondary endpoint	Breakthrough bleed (BB4): Initial hemostatic success at 4 minutes followed by breakthrough bleeding requiring treatment		
	Secondary endpoint	Breakthrough bleed (BB10): Initial hemostatic success after 4 minutes followed by breakthrough bleeding requiring treatment		
Database lock	October 25, 2011			
Results and Analysis				
Analysis description	**Primary / Secondary Analyses**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	FP	SoC	
	Number of subject	40	44	
	TBS 4 n/N (%)	33/40 (82.5%)	13/44 (29.5%)	
	TBS 10 n/N (%)	38/40 (95.0%)	30/44 (69.8%)	
	TTH (min) Median (Range)	4.0 (4.0 to 13.2)	9.7 (4.0 to 31.3)	

	BB4	1/38 (2.6%)	1/44 (2.3%)	
	BB10	4/40 (10.0%)	27/44 (61.4%)	

Effect estimate per comparison		Comparison groups	FP vs. SoC
	Primary endpoint: TBS 4	Difference of incidences	53.0%
		P-value	< 0.0001
	Secondary endpoint: TBS 10	Difference of incidences	25.2%
		P-value	0.019
	Secondary endpoint: TTH (min)	Difference of medians	-5.7
		P-value	< 0.0001
	Secondary endpoint: BB4	Difference of incidences	0.3%
		P-value	Not provided
	Secondary endpoint: BB10	Difference of incidences	-51.4%
		P-value	Not provided
Notes	Except time to haemostasis no measures of variability for treatment effects on the original scale are provided with the study report.		

Analysis performed across trials (pooled analyses and meta-analysis)
Comparison of efficacy parameters

Studies 400-07-002, 400-08-002, and 400-10-001 were similar in design and thus the data on hemostatic efficacy at 4 minutes and 10 minutes can be integrated. Table 40 shows integrated data for all randomized subjects (ITT Set) and for all subjects treated (Safety Set).

Table 41: Hemostatic Efficacy (Integrated Efficacy Data)

	ITT Set		Safety Set	
	FP Randomized (N = 159)	Control (N = 106)	FP-All (N = 229)	Control (N = 107)
Hemostasis at 4 minutes	91.2%	46.2%	93.9%	45.8%
Hemostasis at 10 minutes	98.7%	77.4%	99.1%	77.6%
Bleeding requiring retreatment	5.0%	55.7%	3.5%	56.1%

Source: Module 5.3.5.1, Integrated Summary of Efficacy, Tables 2.1.1 and 2.1.1a

Clinical studies in special populations

No special studies in children, in the elderly or in patients with renal or hepatic impairment have been submitted.

Supportive studies

FL-PN-001-IS

This was a prospective, open-label, phase I study evaluating the safety of fibrin fleece in partial nephrectomy in a single center, performed with fibrin fleece, a predecessor product of Fibrin Pad between December 2006 and August 2007 in 10 patients. The objective of the study was to evaluate the safety of fibrin fleece in open partial nephrectomy surgical procedures. Adult subjects were eligible for inclusion if they were undergoing elective open partial nephrectomy and presented intraoperatively with a bleeding site (mild to moderate bleeding) after conventional surgical techniques had been exhausted and the collection system of the kidney was confirmed to be intact.

The primary evaluations were safety parameters: adverse events, clinically abnormal laboratory and coagulation assessments. Secondary evaluations included time to haemostasis, incidence of treatment failures. All parameters were analyzed descriptively.

In this small cohort of subjects, Fibrin Fleece/Pad was used according to the applied indication. Complete haemostasis was achieved within 4 minutes of application of Fibrin Fleece in all patients and no re-bleeding occurred. No repeat surgeries were required during the 8-week follow-up period.

FL-PN-002-IS

This was a prospective, randomized, single blind, standard care controlled, two-Cohort Phase II Study Evaluating the Safety and Hemostatic Efficacy of Fibrin Fleece (a sterile bio-absorbable combination product consisting of a flexible polyglactin 910 matrix and a coating of Human Thrombin and Human Fibrinogen) in Partial Nephrectomy, performed in 2008 in two centers in Israel. Fibrin Fleece was supplied for the study in units of 4x4 inches (10 x 10 cm) in size. The objective was to evaluate the safety and hemostatic efficacy of Fibrin Fleece as the primary method of haemostasis applied to the actively bleeding site as compared to standard of care in partial nephrectomy surgery. It was planned to recruit 30 subjects and to randomize 20 subjects to Fibrin Fleece and 10 subjects to Standard of care (SOC) which should be suture, cautery, ligature or passive hemostats. Subjects were to be assessed during surgery, until 36 hours post-surgery, daily until hospital discharge, at 2 weeks and at 30 days post-surgery.

Adult subjects could be eligible if they had a renal tumor, smaller than 4 cm in diameter, scheduled to undergo an elective open partial nephrectomy. They had to be excluded intraoperatively if the collection system was damaged or when accumulation of blood by suction exceeded 500 mL not including irrigation liquids and sustained systolic pressure < 80mm Hg, *or* sustained heart rate ≥130 per minutes *or* sustained oxygen saturation (SaO2) <90%.
Eligible subjects were undergoing open partial nephrectomy surgery. Once the resection was complete, the target bleeding site (TBS) was to be identified. Subjects were to be randomized into the study and the time of randomization was to be recorded. Based on the assigned treatment group, the surgeon was required to either apply the Fibrin Fleece directly onto the bleeding site or to control the bleeding by conventional surgical techniques (including suture, ligature and cautery). The starting time of either product application or use of conventional haemostatic techniques was to be recorded.

Primary Efficacy Analysis

Success at 10 minutes was defined as the achievement of haemostasis within 10 minutes and no further bleeding requiring treatment during a 6-minute observation period. The primary endpoint analysis was to be based on the ITT analysis set.

Secondary Efficacy Analyses were: Proportion of successes at 5 minutes, time to haemostasis, and others

The study was terminated prematurely after recruitment of 7 subjects, following a SAE (see Section 2.6 Clinical Safety) and the subsequent decision of the sponsor to discontinue the study secondary to a decision not to proceed towards an indication for the primary treatment of severe arterial haemorrhage.

2.5.3. Discussion on clinical efficacy

The efficacy of EVARREST/Fibrin Pad (FP) has been evaluated in three pivotal clinical studies. Pivotal study 400-07-002 in relation to the development of Fibrin Pad for the indication "*as supportive treatment in surgery for improvement of haemostasis where standard surgical techniques are ineffective of impractical" was discussed at* CHMP Scientific Advice working group (SAWP) as part of an applicant's request for CHMP Scientific Advice. SAWP considered that as study 400-07-002 limited treatment to mild or moderate bleeding, it was insufficient to support the MAA and Fibrin Pad should also be investigated in more challenging surgical settings, according to CPMP/BPWG/1089/00 'Guideline on the clinical investigation of plasma derived fibrin sealant/haemostatic products' which requires that the mainstay of fibrin sealant/ haemostatic product use is in patients who require major surgery or experience major trauma.

CHMP Scientific Advice has been followed by the Applicant who performed two additional pivotal studies (Study 400-08-002 in severe soft tissue bleedings in abdominal, pelvic, retroperitoneal and thoracic surgery and Study 400-10-001 in parenchymal bleeding in liver surgery) with the final product.

Design and conduct of clinical studies

Three prospective, randomized, and controlled studies either versus Surgicel, an oxidised regenerated cellulose (ORC) product widely used in surgery as a haemostatic product (Study 400-07-002) or versus the surgeon's routine Standard of Care (Studies 400-08-002 and 400-10-001), were submitted. The choice of comparator is considered to be according to guideline (standard treatment without fibrin sealant) and is acceptable.

Due to the different appearance of study treatment and control, blinding was not possible. Study 400-07-002 and Study 400-08-002 were both performed to evaluate safety and haemostatic efficacy of Fibrin Pad in soft tissue bleeding in subjects undergoing abdominal, pelvic, retroperitoneal, and (non-cardiac) thoracic surgery, in the first study in mild to moderate bleedings, in the second study in challenging, severe bleedings. Study 400-10-001 was performed in controlling parenchymal bleeding during elective liver surgery.

In total, including application on additional bleeding sites, no more than four units (10.2 x 10.2 cm) of FP were to be left implanted. This limit was determined on the basis of the data in the 90-day subchronic toxicity study in rats, the use being equivalent to the maximum implanted dosage for which safety data were available from studies in animals (see discussion on non-clinical aspects).

In the absence of validated terms classifying bleeding severity and characteristics, the Applicant developed a classification of bleeding severity during clinical studies with Evicel Solutions for Sealant, and this was subsequently used in the pivotal studies for EVARREST.
Patient population was adequately selected and evenly distributed to treatment groups. Some differences are noted with respect to the distribution of the primary operative procedure, tissue type at target bleeding site (TBS) or types of hepatic parenchyma. Exploratory analyses in general did not indicate a major difference of the effect of Evarrest in different tissues (data not shown).

The chosen primary and secondary endpoints are considered to be clinically relevant and appropriate to capture haemostatic efficacy of the products. Similar endpoints have also been used in studies with other fibrin sealants.

The follow-up period of 30 days in the first pivotal study was regarded to be too short, as the absorption of the Fibrin Pad is supposed to be 8 weeks, as derived from animal data. The follow-up period of 8 weeks, as in the next two pivotal studies, is regarded to be adequate.

Efficacy data and additional analyses

Haemostatic success of Fibrin Pad was superior to control treatment in all pivotal studies. The treatment differences are statistically significant and are deemed clinically relevant.

In study 400-07-002 in mild and moderate soft tissue bleeding, the primary efficacy endpoint was haemostasis at 4 minutes and no further bleeding requiring treatment during the additional 6-minute observation period. Haemostasis was defined as no detectable bleeding at the TBS. In the ITT population, this endpoint was reached in 59/60 (98.3%) subjects randomized to Fibrin Pad compared to 16/30 (53.3%) subjects in the Surgicel group. The analysis of all subjects treated with Fibrin Pad, randomized and non-randomized, confirmed this success rate in a total of 109/111 (98.2%) FP treated subjects. It is remarkable, that the success rate was evenly high for Fibrin Pad in mild (31/31; 100%) and moderate (28/29; 96.6%) bleedings, whereas the limitations of the comparator product Surgicel became apparent when comparing the effect in mild (12/15; 80.0%) and moderate (4/15; 26.7%) bleedings. There is a clear statistically significant treatment difference in the total ITT population and in both subsets, the mild and the moderate bleedings, with the highest treatment difference between Fibrin Pad and Surgicel of 69.9% in moderate bleedings. While the oxidized regenerated cellulose product Surgicel had quite acceptable haemostatic efficacy in mild bleedings, defined as a small area of capillary, arteriole or venule oozing, treatment failures became frequent in the attempt to stop moderate bleedings with Surgicel. Interpretation of these data is limited by the small numbers of subjects in the control subgroups (mild/moderate). Overall, the study results demonstrate a clinically relevant superiority of EVARREST over Surgicel in mild to moderate soft tissue bleedings.

In Study 400-08-002 in severe soft tissue bleeding, the ITT analysis for the primary efficacy endpoint, durable haemostasis at 4 minutes, demonstrated a higher success rate in the Fibrin Pad group (50/59 subjects; 84.7%) than in the Standard of Care group (10/32 subjects, 31.3%). Haemostatic success at 10 minutes was achieved in 58/59 subjects (98.3%) in the FP group as compared to 22/32 (68.8%) in the SoC group. This result for the secondary efficacy parameter is consistent with study 400-07-002 in mild and moderate bleedings, where 59/60 subjects (98.3%) in the FP group achieved haemostasis at 10 minutes compared to 22/30 subjects (73.3%) in the Surgicel group. All efficacy parameters of study 400-08-002 are consistent and demonstrate superiority of EVARREST over Standard of Care treatment in severe soft tissue bleeding.

Parenchymal bleeding during liver surgery was investigated in study 400-10-001. The ITT analysis for the primary efficacy endpoint demonstrated a durable haemostatic success at 4 minutes in 33/40 subjects (82.5%) in the Fibrin Pad group compared to 13/44 subjects (29.5%) after SoC treatment. Haemostatic efficacy results are consistent with the two preceding pivotal studies and the treatment differences between EVARREST and Standard of Care are considered to be clinically relevant.

A worst-case reanalysis of the primary efficacy endpoint was performed counting all cases of breakthrough bleeding in the control groups at 4 minutes as success. A highly significant treatment effect in favour of Evarrest was still found in this worst-case analysis for each of the three pivotal studies.

Results for Fibrin Pad are consistent, demonstrating superiority over control treatment Surgicel or Standard of Care in all pivotal studies.

The originally proposed indication emphasised the use in challenging and/or severe bleeding. This does not conform to the Core SmPC for Plasma Derived Fibrin Sealant/Haemostatic Products where the use of the product is not differentiated for severities of bleedings. It is the original purpose of a fibrin sealant/haemostatic product to offer a surgical tool also in more challenging bleeding situations. Moreover, the definition of bleeding severity was generated by the Applicant for clinical study purposes and is not recognized as a validated, generally known tool. The wording of the indication was revised in line with the core SmPC to: *EVARREST is indicated in adults for supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis.*

In all clinical studies with EVARREST (Fibrin Pad, Fibrin Fleece, or Fibrin Patch) the TBS has always been of a size that could be adequately covered by a single 10.2 cm x 10.2 cm Fibrin Pad, with an appropriate overlap as necessary, to achieve haemostasis. The use of up to two units of EVARREST, both at distinct locations and in an overlapping manner with an overlap of 1-2 cm of adjacent pieces of EVARREST, was based on non-clinical data. The applicant agreed to specifically monitor local complication events through pharmacovigilance reporting for 1 year after product approval in EU and 2 years after approval in the US (where a maximum of 4 units with overlap is accepted) and to commit to monitor these events in 2 additional pivotal clinical studies. (see RMP, Annex II). Therefore in Posology section 4.2 it is stated, that '*EVARREST should only be used in a single layer, with an overlap of approximately 1 to 2 cm onto non-bleeding tissue or an adjacent EVARREST sealant matrix'*. As a further safety measure, intraoperative monitoring of the application site to verify that haemostasis is maintained is added to the administration instructions.

2.5.4. Conclusions on the clinical efficacy

With this MAA the Applicant applied for "supportive treatment in surgery, for improvement of haemostasis where standard surgical techniques are ineffective or impractical. EVARREST has also been shown to be effective as an adjunct to haemostasis in challenging and/or severe bleeding."

Results for Fibrin Pad are consistent, demonstrating superiority over control treatment Surgicel or Standard of Care in all pivotal studies.

The initially proposed indication "EVARREST has also been shown to be effective as an adjunct to haemostasis in challenging and/or severe bleeding" is not covered by the Core SmPC. The indication

of fibrin sealants/haemostatics does not differentiate between different grades of severity of bleeding. In general, fibrin sealants/haemostatic products offer a broad indication and the surgeon may choose the best suitable technique or product in an individual surgical situation. Moreover, the bleeding scale used in the trials was developed by the applicant for the purpose of the trials and is not a generally accepted tool. More importantly use in severe bleeding was associated with a severe SAE of post-procedural haemorrhage which was the reason of the discontinuation of the supportive study FL-PN-002-IS and is discussed in the Clinical Safety Section.

In addition, the wording “where standard surgical techniques are ineffective or impractical” is not appropriate as standard surgical techniques should not be deemed a priori as impractical. According to Guideline, fibrin sealant/haemostatic products must not be considered a substitute for surgical hemostatic measures or meticulous surgical technique. It is therefore recommended that the indication for EVARREST should be given according to Core SmPC for “supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis”, in consistency with other products.

Instructions on the handling of the product and in case of re-treatment are included in the SmPC.

2.6. Clinical safety

Patient exposure

Exposure and integration of safety data are presented in tables 42 and 43.

Table 42: Patient exposure

Study no	Surgical procedure	Subjects enrolled	Randomized to active control	Fibrin Pad Randomized	Fibrin Pad Non-randomized	Fibrin Pad Total
400-07-002	Abdominal, pelvic, retroperitoneal, thoracic	141	30	60	51	111
400-08-002	Abdominal, pelvic, retroperitoneal, thoracic	91	32	59		59
400-10-001	Hepatic surgery	104	45	39	20	59
FL-PN-001-IS	Partial nephrectomy	10			10	10
FL-PN-002-IS	Partial nephrectomy	7	3	4		4
Total Safety Set						**243**

Each subject was treated in a single surgical procedure.

The integrated safety set was the total of 243 patients in the 5 trials listed above.

Adverse events

Table 43: AEs occurring in at least 5% of subjects (Integrated Safety Set)

System Organ Class	Preferred Term	Fibrin Pad N = 229	Control N = 107
Blood and Lymphatic System Disorders	Anemia	44 (19.2%)	25 (23.4%)
	Leukocytosis	14 (6.1%)	8 (7.5%)
Cardiac Disorders	Atrial Fibrillation	17 (7.4%)	10 (9.3%)
	Bradycardia	12 (5.2%)	6 (5.6%)
	Tachycardia	27 (11.8%)	12 (11.2%)
Gastrointestinal Disorders	Abdominal Pain	10 (4.4%)	7 (6.5%)
	Constipation	71 (31.0%)	35 (32.7%)
	Diarrhea	19 (8.3%)	9 (8.4%)
	Ileus	11 (4.8%)	6 (5.6%)
	Localized Intra-abdominal Fluid Collection	4 (1.7%)	8 (7.5%)
	Nausea	112 (48.9%)	56 (52.3%)
	Vomiting	47 (20.5%)	25 (23.4%)
General Disorders and Administration Site Conditions	Edema, Peripheral	8 (3.5%)	14 (13.1%)
	Pain	51 (22.3%)	37 (34.6%)
	Pyrexia	48 (21.0%)	37 (34.6%)
Infections and Infestations	Pneumonia	12 (5.2%)	9 (8.4%)
	Urinary Tract Infection	14 (6.1%)	4 (3.7%)
Injury, Poisoning and Procedural Complications	Procedural Hypotension	6 (2.6%)	6 (5.6%)
	Procedural Pain	12 (5.2%)	7 (6.5%)
Metabolism and Nutrition Disorders	Hyperglycemia	29 (12.7%)	12 (11.2%)
	Hypocalcemia	15 (6.6%)	10 (9.3%)
	Hypokalemia	53 (23.1%)	25 (23.4%)
	Hypomagnesemia	53 (23.1%)	19 (17.8%)
	Hyponatremia	13 (5.7%)	5 (4.7%)
	Hypophosphatemia	28 (12.2%)	16 (15.0%)
Musculoskeletal and Connective Tissue Disorders	Arthralgia	10 (4.4%)	7 (6.5%)
Nervous System Disorders	Dizziness	12 (5.2%)	8 (7.5%)
Psychiatric Disorders	Anxiety	13 (5.7%)	5 (4.7%)
	Confusional State	10 (4.4%)	6 (5.6%)
	Insomnia	22 (9.6%)	16 (15.0%)
Renal and Urinary Disorders	Incontinence	0 (0.0%)	6 (5.6%)
	Oliguria	13(5.7%)	7 (6.5%)
Respiratory, Thoracic, and Mediastinal Disorders	Atelectasis	27 (11.8%)	9 (8.4%)
	Pleural Effusion	33 (14.4%)	20 (18.7%)
	Pneumothorax	18 (7.9%)	4 (3.7%)
Skin and Subcutaneous Tissue Disorders	Pruritus	20 (8.7%)	6 (5.6%)
Vascular Disorders	Hypertension	23 (10.0%)	13 (12.1%)
	Hypotension	57 (24.9%)	37(34.6%)

[a] Number and % refers to subjects, not episodes
Source: Module 5.3.5.3, ISS Table 3.1.3

Table 44: Adverse events with potential causal relationship to study treatment (Integrated Safety Set)

Subject #	Treatment Group	Event	SAE?	Causal Relationship
Study 400-07-002				
21-207	FP Randomized	GI hemorrhage	Yes	Possibly related
12-209	FP Non-randomized	Ascites	No	Possibly related
		Infected pancreatic fluid collection	Yes	Possibly related
		Deep vein thrombosis	No	Possibly related
		Suspected pulmonary embolism	Yes	Possibly related
13-102	FP Non-randomized	Operative hemorrhage	Yes	Possibly related
14-207	SURGICEL	Operative hemorrhage	No	Related
16-202	SURGICEL	Operative hemorrhage	No	Possibly related
Study 400-08-002				
16-001	Fibrin Pad	Massive gastric aspiration due to ileus caused by ischemic bowel	Yes	Possibly related
		Distended abdomen	No	Possibly related
22-009	Fibrin Pad	Increased fibrinogen (Discharge)	No	Possibly related
22-010	Fibrin Pad	Pleural effusion/prolonged secretion	No	Possibly related
22-011	Fibrin Pad	Increased fibrinogen (Discharge)	No	Possibly related
22-012	Fibrin Pad	Increased fibrinogen (Discharge)	No	Possibly related
		Increased fibrinogen (Day 60)	No	Possibly related
22-008	Standard of Care	Pleural effusion/prolonged secretion	No	Possibly related
		Increased fibrinogen (Discharge)	No	Possibly related
Study 400-10-001				
11-109	Fibrin Pad	Postoperative bleeding	Yes	Possibly related
15-201	Fibrin Pad	Intra-abdominal bleed with serosanguinous blood in drains	Yes	Possibly Related
15-303	Fibrin Pad (Run-in)	Abdominal collection	Yes	Possibly related

Source: Module 5.3.5.1, Clinical Study Report 400-07-002, Text Table 24, Clinical Study Report 400-08-002, Text Table 26, and Clinical Study Report 400-10-001, Text Table 29

AEs potentially related to re-bleeding at the TBS

Study 400-07-002: 3/30 (10.0%) of subjects treated with Surgicel:
- TBS haemostasis at 10 minutes, but re-bleeding thereafter
- TBS haemostasis at 4 minutes, but re-bleeding during 6-minutes observation period
- TBS haemostasis at 4 minutes, but re-bleeding during 6-minutes observation period

FP treated subjects: One subject in the FP group had an SAE of postoperative re-bleed. The event was related to the surgical procedure but occurred at a site other than the TBS.

Study 400-08-002: None of the subjects in either treatment group experienced AEs that were assessed as potentially related to re-bleeding at the TBS.

Study 400-10-001: 4/59 (6.8%) FP treated subjects:

- one event of post-procedural hemorrhage, potentially related to FP treatment;
- one event of intra-abdominal hemorrhage, potentially related to FP treatment;
- two other events related to intra-operative rather than post-operative bleeding, considered to have no relationship to study treatment

1/45 (2.2%) SoC treated subject:
- one event related to intra-operative rather than post-operative bleeding

Information on SAEs related to bleeding is presented Table 45.

Table 45: SAEs related to bleeding

Table 78-1 SAEs related to bleeding in subjects treated with Fibrin Pad

Study #	Patient Identifier	Event	Outcome	Causal Relationship to Study Treatment[a]	Causal Relationship to Surgical Procedure[a]
400-07-002	13-102/ JCJ	Re-Bleed	Recovered	Possibly related	Related
400-07-002	14-210 /B-K	Retroperitoneal bleed	Death	Not related	Possibly related
400-07-002	21-207/ CFC	Massive GI Bleed	Death	Possibly related	Possibly related
400-08-002	LAJ/16-006	Intra-abdominal hemorrhage	Death	None	Related
400-10-001	11-109	Postoperative bleeding	Recovered	Possibly related	Related
400-10-001	15-106	Intra-abdominal bleed	Resolved	None	Related
400-10-001	15-201	Intra-abdominal bleed	Resolved with treatment	Possibly related	Possibly related
FL-PN-002-IS	2-5	Post procedural hemorrhage	Resolved with treatment	Related	Not assessed

[a] Investigator assessment

AEs potentially related to thrombotic events

In the overall Integrated Safety Set, potential venous thromboembolic events (VTEs) were reported in 9/229 subjects (3.9%) treated with Fibrin Pad, as compared to 4/107 subjects (3.7%) treated with control methods.

From study 400-07-02 a higher frequency of potential thrombosis-related events was reported. In this study, potential thrombosis-related events were reported in 8/111 subjects (7.2%) treated with Fibrin Pad, as compared to 2/30 subjects (6.7%) treated with Surgicel. Of these, 6/111 events (5.4%) in subjects treated with Fibrin Pad were VTEs and 2/111 (1.8%) were arterial events. Both events in subjects treated with Surgicel were VTEs. The two events in the Fibrin Pad group that were potentially related to arterial thrombosis were cerebrovascular accident (stroke) and intestinal infarction. Neither of these was considered by the investigators to be related to use of study product.

One Fibrin Pad subject (12-209) had a suspected but unconfirmed SAE of pulmonary embolism (PE). Based on clinical bedside diagnoses on the evening of surgery, this subject was reported to have had deep venous thrombosis (DVT) (assessed as non-serious) and possible PE (assessed as serious). Both events were assessed as possibly related to study treatment. However, imaging studies undertaken the next day were negative for DVT and PE.

An additional event occurred in the FP group of study 400-08-002 which was of unknown pathology. This subject (subject 16-001) experienced massive gastric aspiration due to ileus caused by ischemic bowel. The event was fatal. The possibility that ischemia was caused by a thrombotic event could not be ruled out. The investigator assessed the event as possibly related to treatment.

Serious adverse event / deaths / other significant events

Deaths

A total of 10 deaths have been reported in subjects treated with Fibrin Pad.

Table 46: Serious adverse events with fatal outcome (Integrated Safety Set)

Subject #	Treatment	SAE	Potential Causal Relationship to: Study Treatment	Surgical Procedure
Study 400-07-002				
14-215	Fibrin Pad	Cardiopulmonary arrest	None	Possibly related
14-218	Fibrin Pad	Retroperitoneal bleed (not TBS)	None	Possibly related
15-203	Fibrin Pad	Sepsis related to perforated jejunum	None	None
21-109	Fibrin Pad	Cardiopulmonary arrest secondary to postoperative ileus	None	Related
21-207	Fibrin Pad	Massive GI bleed (not TBS)	Possibly related	Possibly related
22-116	Fibrin Pad	Stroke	None	Possibly related
		Respiratory failure	None	None
23-201	SURGICEL	Progression of cancer	None	Possibly related
Study 400-08-002				
13-005	Fibrin Pad	Disease progression	None	Possibly related
15-019	Fibrin Pad	Progression of bladder cancer	None	None
16-001	Fibrin Pad	Massive gastric aspiration due to ileus	Possibly related	Related
16-006	Fibrin Pad	Abdominal hemorrhage	None	Related
13-002	SoC	Empyema	None	Possibly related
15-002	SoC	Postoperative hepatorenal syndrome	None	Possibly related
20-007	SoC	Respiratory failure	None	None

Source: Module 5.3.5.1, Clinical Study Report 400-07-002, Table 30 and Module 5.3.5.1, Clinical Study Report 400-08-002

No deaths occurred during studies 400-10-001, FL-PN-001-IS, or FL-PN-002-IS.

Other Serious Adverse Events

A total of 121 SAEs were reported in 71 out of 229 subjects (31.0%) treated with Fibrin Pad during studies 400-07-002, 400-08-002 and 400-10-001, as compared to 55 SAEs in 35 out of 107 control subjects (32.7%).

No SAEs were reported during study FL-PN-001-IS.

Study FL-PN-002-IS was terminated prematurely following a case of severe post-procedural haemorrhage in a subject in the Fibrin Fleece group. The patient had a tumor resection in the

kidney. According to study protocol, no conventional method of haemostasis was applied at the TBS. Fibrin Fleece was applied on the resection area, followed by 3 minutes of manual compression. Haemostasis was not achieved within 3 minutes of application due to incomplete adherence. The first Fibrin Fleece was thus removed and replaced by another Fibrin Fleece, again followed by 3 minutes of manual compression. It is documented that the Fleece was not disturbed during the 3 minutes of compression, that no problems occurred with the application, and that no conventional treatment was needed. Haemostasis was achieved and maintained during the following 6 minutes of observation. TTH was measured to be 8.8 minutes. However, two hours after surgery, blood was noted in the drain and the patient was hemodynamically unstable. The patient had to be re-operated and a severe bleeding from the area under the Fibrin Fleece was stopped by using standard surgical techniques. The blood loss had to be replaced by administration of 10 units of blood (packed red cells or FFP). The investigator and the sponsor assessed this case as related to study treatment.

Laboratory findings

Changes in haematology and in coagulation parameters between the screening visit and the postoperative assessment and between the screening visit and the follow-up visit are consistent with expectations for subjects undergoing major surgical procedures.

Safety in special populations

N/A

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

Study treatment consisted of a single surgical procedure. Discontinuation from the study could occur due to withdrawal of consent, lost to follow-up, death, or other circumstances.

Post marketing experience

No data presented

2.6.1. Discussion on clinical safety

The biological components of EVARREST are the same as in the solutions for sealant Evicel, which is authorised in EU since October 2008.

In total, 243 adult subjects have been exposed in a single surgical procedure to the investigational product Fibrin Fleece/Fibrin Pad in the 3 pivotal and 2 initial clinical studies. Data from studies FL-PN-001-IS and FL-PN-002-IS are included in the overall safety evaluation as the use of Fibrin Fleece/Pad was in both studies very similar to the applied indications and the treatment of severe bleeding in study FL-PN-002-IS as primary haemostatic method is as done in the majority (61%) of subjects treated with FP in study 400-08-002. Safety evaluations were performed in an amended “Integrated Safety Set”, comprising all 243 subjects treated with fibrin pad / EVARREST including the two initial studies.

Clinical studies only provided experience in the use of a single unit of EVARREST. The target bleeding site (TBS) had to be of a size that could be adequately covered with a single unit of Fibrin Pad. The application of multiple units to cover a larger bleeding site has not been investigated which is stated in the SmPC. On the basis of pre-clinical data with exaggerated doses in rats and current use in the US (up to 4 units) it was agreed that administration of up to two units of EVARREST to remain in the body is acceptable, adjacent pieces of EVARREST should be applied with an overlap of 1-2 cm. EVARREST should only be used in a single layer and instructions in case of persistent bleeding, i.e. removal of the ineffective initial Fibrin Pad before application of a second unit, are clearly stated in the SmPC. There is no knowledge about the safety of EVARREST in repeated use, since only single surgical procedures have been investigated. Immunogenicity may be an issue for re-treatment.

Clear identification of the bleeding source and application surface is emphasized in the SmPC. Awareness to the risk of re-bleeding and intraoperative monitoring to verify that haemostasis is maintained is also stated in the SmPC.

Inappropriate use and insufficient efficacy of EVARREST may result in bleedings from the application site. This is the major safety issue identified with this haemostatic product. It is of concern that haemorrhage could still occur after haemostatic success had been confirmed thereby causing serious adverse events. This is documented in the severe SAE of post-procedural haemorrhage in study FL-PN-002-IS, which was clearly assessed as related to Fibrin Pad application and which led to premature termination of the study. The way this event is presented in the Summary of Clinical Safety is not acceptable, since it is misleading and diminishes the clinical relevance of this case. Further cases of post-procedural bleeding are reported, some of them assessed by the investigator as possibly related to study treatment. Clear precautions and instructions for handling have to be added to the SmPC to control this risk of re-bleeding. The need for a primary conventional method e.g. suture, ligature or cautery is of importance.

Eight subjects with SAEs related to bleeding were identified in the group of EVARREST treated patients. The narrative of one subject in study 400-07-002, revealed that this was a case of re-bleeding at the target bleeding site, which had to undergo re-surgery to stop the bleeding and which was assessed by the surgeon as possibly related to treatment with fibrin pad. Despite clear documentation of this case, it was initially reported as “operative haemorrhage at a site other than the TBS”, this was investigated further. Moreover, this second SAE of clinically relevant re-bleeding at the TBS after wound closure, highlighted the need for risk minimisation measures to preclude this identified risk.

Important aspects of risk minimization measures are addressed in the currently proposed SmPC/PL, most importantly the wording of the indication as an adjunct to haemostasis “for supportive treatment in surgery where standard surgical techniques are insufficient”. The use of Evarrest according to the indication would exclude the incorrect application at a bleeding area which would require primary surgical techniques for haemostasis. Details on method of administration, contraindications as well as special warnings and precautions for use are considered to address the critical issues appropriately. There is a general risk of post-operative bleeding in surgery. The RMP lists re-bleeding as an identified risk of the use of Evarrest which is to be monitored and reported as events of special interest in PSURs within routine pharmacovigilance activities.

Another important finding is the occurrence of thromboembolic events mainly in study 400-07-002. Biochemical investigations of the used lot could not explain the safety problem and an increased risk for thrombotic events could not be completely ruled out. This risk is addressed in the RMP and carefully monitored in the post-marketing.

Undesirable effects related to the composite matrix were also identified. Whereas the oxidized regenerated cellulose (ORC) product Surgicel is normally removed after primary haemostasis, EVARREST remains implanted, awaiting the natural process of absorption. It is known (Fagotti 2010) that ORC increases the risk for post-operative abscesses. During the limited follow-up periods of the clinical studies with EVARREST (30 days in 400-07-002; 60 days in 400-08-002 and 400-10-001), a total of six SAEs of abscess have been reported with FP treatment. The risk of abscess formation was thoroughly elaborated in the RMP and will be montored in the post-marketing phase. In this context, also the risk of granuloma formation and foreign body reaction, which are reported with the use of ORC products, is to be monitored. Findings of foreign body reactions in the 90 days subchronic toxicity study in rats support this concern. A review of the clinical benefits and risks of topical haemostats, has found (Tomizawa, 2005) cases of persistence of the ORC product Surgicel, inflammatory reactions and infections, and confusion of diagnostic imaging after local haemostat use due to granuloma formation. This review concludes that only the minimum amount of haemostat should remain implanted and recommends documentation of information on the haemostat used including the site and the amount in the surgical record, as that information may be helpful in the interpretation of future diagnostic images.

The Applicant provided narratives on all SAEs of abscess, empyema and sepsis. However, the site of Evarrest application was not precisely given to confirm or reject a physical relationship to the location of abscess/empyema. Individual risk factors for the development of deep surgical site infection were present in most cases. Abscess formation is given in the RMP as potential risk and should be monitored and reported as event of special interest in PSURs.

Complications of ORC products or known from literature, contraindications, warnings, precautions, and adverse events reported in the product information were included in SmPC of EVARREST as class effects. As formal interaction studies were unfeasible, relevant information from comparable products is included in section 4.5.
The 90-day subchronic toxicity study in rats found foreign body reaction (see discussion on non-clinical aspects). In human studies the longest follow-up period was 60 days and the application of more than one unit of EVARREST was not systematically investigated. Oxidized cellulose has been developed as an absorbable haemostat in 1943 [Frantz 1943] and has been widely used since then. A limitation of the use of EVARREST to two 10.2 x 10.2 cm pads to be applied on distinct locations or overlapping with an adjacent second sealant matrix by 1 to 2 cm, as investigated in a non-clinical model, is considered acceptable. Safety concerns related to the issue of local complications of the matrix, i.e. incomplete absorption, abscess formation, granuloma formation, foreign body reactions, which are unknown for areas of overlapping matrix, are defined in the RMP as potential risks which have to be monitored by routine pharmacovigilance activities and reported as events of special interest in PSURs. Long-term tolerability data from the use of a maximum of 2 units of Evarrest are awaited.

Eight AEs of anaphylactic reaction and hypersensitivity are reported. Estimation on the immunogenic risk associated with re-administration of human thrombin or fibrinogen containing products was discussed. It has been reported that hypersensitivity or allergic reactions may occur

in rare cases in patients treated with fibrin sealants/haemostatics. In isolated cases, 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.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Safety data derive from clinical studies demonstrating haemostasis in mild or moderate soft tissue bleeding in a total of 141 subjects (111 treated with EVARREST and 30 with control) undergoing abdominal, retroperitoneal, pelvic, and (non-cardiac) thoracic surgery; in 91 patients undergoing abdominal, retroperitoneal, pelvic, and (non-cardiac) thoracic surgery (59 treated with EVARREST and 32 with control) demonstrating haemostasis in severe soft tissue bleeding. A clinical study in 104 patients undergoing hepatic surgery (59 treated with EVARREST and 45 with control) demonstrated haemostatic efficacy in persistent parenchymal bleeding.

The following uses are contraindicated in the SmPC section 4.3: treatment of severe bleeding from large defects in large arteries or veins where the injured vascular wall requires repair with maintenance of vessel patency and which would result in persistent exposure of EVARREST to blood flow and/or pressure during healing and absorption of the product; intravascular application; use in closed spaces (e.g., in, around, or in proximity to foramina in bone or areas of bony confine) since swelling may cause nerve or blood vessel compression; use in the presence of active infection or in contaminated areas of the body because infection may occur.

No formal interaction studies have been performed. SmPC section 4.5 'Interaction with other medicinal products and other forms of interaction' states: *'Similar to comparable products or thrombin solutions, the product may be denatured after exposure to solutions containing alcohol, iodine, or heavy metals (e.g., antiseptic solutions). Such substances should be removed to the greatest possible extent before applying the product.'*

Significant safety issues have been identified; most important was the reoccurrence of bleedings from the site of Fibrin Pad application, even after documentation of haemostatic success. Surgeons should not be encouraged to use EVARREST as the primary haemostatic method, when others are deemed "impractical" and without identification of the bleeding source. The indication as agreed in accordance with the Core SmPC is in line with a more cautious approach. Other safety concerns related to thrombogenicity, abscess formation, and immunogenicity, are to be further monitored. The posology reflects the use in single layers or overlapping of adjacent, maximum 2 units. Instructions for handling give clear recommendations on observation of the application site and re-treatment if needed.

Warning statements on hypersensitivity reactions, anaphylaxis, antibodies against components of fibrin sealant/haemostatic with the risk of anaphylactic reaction, are included in section 4.4. The risk of occurrence of thromboembolic complications if the preparation is unintentionally applied intravascularly is highlighted in section 4.4 of the SmPC. Section 4.8 appropriately reflects safety findings from all clinical trials.

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:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1, the PRAC considers by consensus that the risk management system for Human Fibrinogen/Human Thrombin (EVARREST) in adults for supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis is acceptable.

This advice concerns the following content of the Risk Management Plan:

Table 47: Safety concerns

Summary of safety concerns	
Important identified risks	Post-procedural haemorrhage (Re-bleeding lack of expected efficacy)
	Thrombotic & Embolic Events
	Increased Blood Fibrinogen
Important potential risks	Pseudoaneurysm if used to treat large vessel defects
	Hypersensitivity/allergic reactions, including severe anaphylaxis
	Incorrect Product Application
	Immunogenicity of the biological components
	Transmission of adventitious agents
	Nerve or blood vessel compression due to swelling of the matrix within a confined space
	Infection due to use in contaminated areas
	Incomplete absorption
	Abscess formation
	Granuloma formation
	Foreign body reaction
Missing information	Repeat Use
	Use in children and adolescents
	Use in women who are pregnant or lactating

Note: the proposed Table regards the updated RMP v1.2 which followed the v1 assessed by the PRAC.

Table 48: Pharmacovigilance plans

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)**
The Fibrin Pad Paediatric Mild/Moderate Liver and Soft Tissue Bleeding Study	To determine safety and efficacy of Fibrin Pad as an adjunct to control mild to moderate bleeding in a paediatric population.	Use in Children	Planned	Final Report December 2018
Fibrin Pad	To determine safety	Use in	Planned	Final Report August

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)
paediatric severe bleeding study	and efficacy of Fibrin Pad as an adjunct to control severe bleeding in a paediatric population.	Children		2020.
A randomized, controlled, clinical study evaluating the superiority of EVARREST compared to Standard of Care or TachoSil when used as an adjunct to haemostasis during cardiovascular surgery. Phase II	To evaluate the safety and effectiveness of the EVARREST™ Sealant Matrix (Fibrin Pad) as suture support for haemostasis during cardiovascular surgery	Monitor local complication events	Planned	Final Report June 2014 (planned)
A Phase III Randomized, Controlled, Superiority Study Evaluating EVARREST™ Fibrin Sealant Patch Versus Standard of Care Treatment in Controlling Parenchymal Bleeding During Hepatic Surgery	To evaluate the safety and hemostatic effectiveness of EVARREST™ Fibrin Sealant Patch (EVARREST) in controlling parenchymal bleeding during hepatic surgery	Monitor local complication events	Planned	Final Report December 2015 (planned)

Note: the proposed Table regards the updated RMP v1.2 which followed the v1 assessed by the PRAC.

Table 49: Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Post-procedural haemorrhage (Lack of expected efficacy)	Amendments to SPC for Evarrest. Haemorrhage reported as an adverse reaction in SmPC Section 4.8	None
Thrombotic and Embolic events	Amendments to SPC for Evarrest. Warning in SmPC Section 4.4 that life threatening thromboembolic complications may occur if the preparation is unintentionally applied intravascularly. Venous thrombosis and pulmonary embolism	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	reported as adverse reactions in SmPC Section 4.8. Surgeons will be made aware of the potential concern regarding thrombotic / thromboembolic events in association with EVARREST and will be instructed to take appropriate medical action and to report such events. Contact numbers for reporting of these events will be provided.	
Increased Fibrinogen	Amendments to SPC for Evarrest. Blood fibrinogen increased reported as an adverse reaction in SmPC Section 4.8	
Pseudoaneurysm if used to treat large vessel defects	The following contraindication is intended to prevent the use of EVARREST in situations shown in non-clinical studies to present a potential risk for pseudo-aneurysm: *Do not use EVARREST to treat severe bleeding from large defects in large arteries or veins where the injured vascular wall requires repair with maintenance of vessel patency and which would result in persistent exposure of EVARREST to blood flow and pressure during healing and absorption of the product.* (Section 4.3 Contraindications).	None
Hypersensitivity/allergic reactions, including severe anaphylaxis	The following contraindication should be sufficient to minimize the potential risks: *Do not use in individuals known to have anaphylactic or severe systemic reaction to human blood products or to other components of EVARREST. (*Section 4.3, Contraindications*)* Since anaphylaxis is a rare event without known predisposing factors the routine surveillance will be through the education of all health-care providers (HCP) who use the product to report any event using the PV system. The relationship of such an event to the potential product immunogenicity will be assessed by the HCP	None
Incorrect Product application • Application of the inactive side of EVARREST to the bleeding surface could represent a potential risk • Application of insufficient EVARREST to	The inactive side has an embossed wave pattern to aid differentiation. The SPC contains the following wording: *The active side of the Matrix is powdery, and the non-active side has an embossed wave pattern.* (Section 3, Pharmaceutical Form) The SPC contains the following wording:	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
adequately cover the entire target bleeding site, with an overlap of 0.5 to 1 in. (1 to 2 cm). • Incomplete apposition /contact of the product to tissue (e.g. due to wrinkles or folds or displacement of EVARREST during the surgical procedure	*Apply an appropriately sized piece, or number of units, of EVARREST to adequately cover the entire bleeding area, with an overlap of approximately 1 to 2 cm to assist with adherence to tissue.* (Section 6.6, Instructions for Use, Handling and Disposal) The SPC contains the following wording: *EVARREST should be applied so it extends approximately 1 to 2 cm beyond the margins of the target bleeding area. It can be cut to the size and shape required to fit the size of the bleeding area* *Multiple units of EVARREST can be applied (overlapped by approximately 1 to 2 cm) if needed, to cover the target bleeding area.* (Section 4.2, Posology and Method of Administration)	
Transmission of Infectious agents	As part of the educational program, surgeons will be instructed of the potential immunogenicity of the product and the related events that could occur. Amendments to SPC for Evarrest. Warning in section 4.4 of SmPC stating: 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 infectious 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 as HIV, hepatitis C virus, hepatitis B virus, and for the non-enveloped virus hepatitis A virus. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or abnormal erythropoiesis (e.g., haemolytic anaemia). It is strongly recommended that every time EVARREST is administered to a patient, the	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product	
Nerve or blood vessel compression due to swelling of the Matrix within a confined space	Amendments to SPC for Evarrest. Contraindication in SmPC Section 4.3 against use in closed spaces (e.g., in, around, or in proximity to, foramina in bone or areas of bony confine) where swelling may cause nerve or blood vessel compression.	None
Infection due to use in contaminated areas	Amendments to SPC for Evarrest. Contraindication in SmPC Section 4.3 against application to contaminated areas of the body, or in the presence of active infection.	None
Incomplete absorption	Routine risk minimisation measures	None
Abscess formation	Routine risk minimisation measures	None
Granuloma formation	Routine risk minimisation measures	None
Foreign body reaction	Amendments to SPC for Evarrest. Warning in SmPC Section 4.4 that foreign body reactions may occur.	None
Off Label use	The following contraindication is included in the SPC: *Do not use EVARREST to treat severe bleeding from large defects in large arteries or veins where the injured vascular wall requires repair with maintenance of vessel patency and which would result in persistent exposure of EVARREST to blood flow and pressure during healing and absorption of the product.* (Section 4.3, Contraindications) In addition, the following warning is included: *EVARREST should not be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial bleeding.* (Section 4.4, Special Warnings and Precautions for Use)	None
Repeat Use	Routine risk minimisation measures	None
Pediatric Use	A Pediatric Investigation Plan has been agreed with EMA (Module 1.10, Information Relating to Pediatrics). Amendments to SPC for Evarrest. Section 4.2 of the SmPC states that The safety and efficacy of EVARREST in children from birth to 18 years has not yet been established.	None
Risks in Pregnant or Lactating Patients	The SPC states: *The safety of fibrin sealants/haemostatics for use in human pregnancy or during breast-feeding has not been established in controlled clinical trials. Experimental animal*	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	studies are insufficient to assess the safety with respect to reproduction, development of the embryo or foetus, the course of gestation, and peri- and postnatal development. *Therefore, EVARREST should be administered to pregnant and lactating women only if clinically indicated.* (Section 4.6, Pregnancy and Lactation)	

Note: the proposed Table regards the updated RMP v1.2 which followed the v1 assessed by the PRAC.

The CHMP endorsed this advice with changes.

These changes concerned the following elements of the Risk Management Plan:

In the safety specification "Incorrect Product Application" was included as main potential risk.

The MA, during the OE committed to specifically monitor local complication events through PV reporting for 1 year after product approval in EU and 2 years after EVARREST™ US BLA approval (with max. of 4 units and overlap); indeed such events would have been monitored in 2 additional pivotal clinical studies. The latest RMP (v1.2) has been therefore updated to address this commitment.

2.9. 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 the pivotal studies, EVARREST has been shown to be superior to control treatment in terms of achieving haemostasis defined as no detectable bleeding at the target bleeding site (TBS) at 4 minutes after application with no re-bleeding requiring treatment during a defined observation period of 6 minutes or longer, until wound closure. In mild and moderate soft tissue bleedings (Study 400-07-002), 59 out of 60 (98.3%) subjects treated with EVARREST reached the primary efficacy endpoint compared to 16 out of 30 (53.3%) subjects randomized to the oxidized regenerated cellulose product Surgicel. Treatment difference of 45.0% was statistically significant with p-value <0.0001. Analysis of the subgroup with mild bleedings revealed haemostatic efficacy in 31/31 (100%) subjects treated with EVARREST compared to 12/15 (80%) subjects treated with Surgicel. This treatment difference of 20.0% was statistically significant with a p-value of 0.03. A treatment difference of 69.9% was found when comparing the primary efficacy endpoint in the subgroup of moderate soft tissue bleedings. EVARREST was clearly more effective demonstrating

haemostatic success in 28/29 (96.6%) of subjects compared to 4/15 (26.7%) of subjects treated with Surgicel (p<0.0001).

Haemostatic efficacy and superiority to Standard of Care was demonstrated in severe soft tissue bleeding (Study 400-08-002). Severe bleeding was defined as a bleeding (arterial, venous, or mixed) that is rapidly flowing, pulsatile or spurting that in the surgeon's judgment requires rapid control to prevent hemodynamic consequences (e.g. hypovolaemia, tachycardia, or hypotension) and could involve major volume loss which if not treated rapidly could be life threatening. Fibrin Pad should not be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial bleeding. The study included a wide range of major surgical procedures with pulmonary resection, gastrectomy, and radical pancreatic duodenectomy being the most common procedures. Standard of Care (SoC) was a composite of techniques/methods typically used to control severe bleeding after conventional methods (e.g. suture, ligature, cautery) were found to be ineffective or impractical. SoC was initiated with 4 minutes of continuous manual compression with or without gauze or sponge and with or without a topical absorbable hemostat (TAH). The primary endpoint, number of subjects with haemostasis at 4 minutes and no re-bleeding requiring treatment at the TBS any time prior to wound closure was 50/59 (84.7%) in the FP group and 10/32 (31.3%) in the SoC group (ITT population).

Treatment difference of 53.5% was statistically significant with p-value <0.0001. Mean absolute time to haemostasis was 6.1 minutes (SD 13.5) in the EVARREST group and 17.8 minutes (SD 32.0) in the control group. Haemostatic success at 10 minutes was reached in 98.3 % (58/59) of subjects treated with EVARREST and in 68.8% (22/32) of subjects with control treatment.

In study 400-10-001 EVARREST demonstrated superiority over SoC in controlling parenchymal bleeding during hepatic surgery. The number of subjects with haemostasis at 4 minutes and no re-bleeding requiring treatment at the TBS any time prior to the initiation of wound closure was 33/40 (82.5%) in the FP group and 13/44 (29.5%) in the SoC group. The treatment difference of 53.0% was statistically significant (p-value <0.0001). Patients had been stratified for normal and abnormal (cirrhotic, steatotic, or other) hepatic parenchyma with reach of primary endpoint in 23/28 (82.1%) and 10/12 (83.3%) of EVARREST treated subjects compared to 11/33 (33.3%) and 2/11 (18.2%) of subjects treated with SoC, respectively. At 10 minutes following randomization, 38/40 (95.0%) of subjects treated with EVARREST had durable haemostasis compared to 30/44 (69.8%) of control subjects. Treatment difference of 25.2% was statistically significant with p-value<0.0189. Mean (SD) absolute time to haemostasis was 4.6 (2.0) minutes in the EVARREST group and 10.0 (7.1) minutes in the SoC group.

Uncertainty in the knowledge about the beneficial effects.

None

Risks

Unfavourable effects

In 243 subjects treated with Fibrin Pad, a total of eight SAEs related to bleeding were reported, four of them assessed as possibly related and one assessed as related to treatment. A severe post-procedural haemorrhage occurred after haemostasis had been confirmed from the site of EVARREST application and after finalization of the surgery, leading to blood loss, haemodynamic

instability and re-operation of the subject. This event was clearly assessed as related to study treatment Fibrin Pad. A second case of severe re-bleeding at the target bleeding site was identified during the procedure, which had been reported in the dossier as “operative hemorrhage at a site other than the TBS”. The bleeding was classified as a bleeding from a site other than the TBS, as they assessed the bleeding to originate from alongside the site of Fibrin Pad placement.

A cluster of thromboembolic events has occurred in the first pivotal study. A causal relation could not be clarified but it was not reproduced in the two following studies. Some adverse events of hypersensitivity were reported. Immunogenicity investigations revealed a few cases of increased anti-thrombin antibody levels. For topical absorbable haemostats like the oxidized regenerated cellulose product Surgicel, local complications are reported in the literature and contraindications, warnings and precautions in the product information reflect them. Surgicel with its decades of experience in clinical use is recommended to be removed after haemostasis is reached. As EVARREST’s matrix is basically made of oxidized regenerated cellulose and actually remains implanted in the body, these precautions were also considered for EVARREST (see below).

Uncertainty in the knowledge about the unfavourable effects

Risks associated with the use of local haemostats are reported in the literature. There are reports of persistence of oxidized regenerated cellulose (ORC) at sites of implantation; infection, fluid retention, abscess formation, foreign body reaction, and granuloma formation mimicking a tumor are reported. It is therefore common practice to remove ORC after haemostasis or to leave only a minimum amount in situ. For EVARREST, no data exist from humans on the duration of the absorption procedure. The follow-up periods were designed assuming a complete absorption within 56 days as derived from animal studies. This may be too short in human to capture complications occurring in the long-term. Cases of abscess formation are reported. Target bleeding sites in clinical studies had to be of a size that could be covered by one single unit, however on the basis of the results of a 90-days subchronic toxicity study in rats the possibility of use of a maximum of 2 units of Evarrest within one surgery procedure to remain in the body should be accepted, not only on different bleeding sites but also in an overlapping manner (1-2 cm) to cover a larger bleeding area. Clinical studies did not investigate the simultaneous use of more than one Fibrin Pad, and there is a risk that the absorption may be delayed and complications may occur, when EVARREST is applied in more than one layer therefore further monitoring is warranted through the RMP. A safety concern relates to the issue of local complications of the matrix, i.e. incomplete absorption, abscess formation, granuloma formation, foreign body reactions, which are unknown for areas of overlapping matrix. These complications are defined in the RMP as potential risks which have to be monitored by routine pharmacovigilance activities and reported as events of special interest in PSURs.

There is no knowledge about the safety of EVARREST in repeated use. Immunogenicity may be an issue when administering EVARREST or another product containing human fibrinogen and/or thrombin at a later occasion. Association between hypersensitivity reactions reported as AE and increased anti-thrombin antibody titres is possible, relevant warning statements are included in the SmPC.

Benefit-risk balance

Importance of favourable and unfavourable effects

Haemostasis is an essential part of surgical procedures. While a secure haemostasis is the prerequisite for finalization of the surgery, time consuming difficulties in reaching haemostasis are often causal for prolongation of the intervention and anaesthesia, for blood loss, and possible complications in the post-operative period. EVARREST has demonstrated to be superior to pure oxidized regenerated cellulose, in reaching haemostasis in mild and moderate soft tissue bleedings. Having a haemostatic product with high efficacy in moderate bleedings would be an important and clinically relevant benefit. A large beneficial effect was also demonstrated in the treatment of severe soft tissue bleedings and in hepatic parenchyma bleedings, where conventional methods of control (e.g. suture, ligation, cautery) were deemed ineffective, impractical, or inappropriate and an alternative method was required to achieve haemostasis. Standard of care methods consisted of manual compression with or without topical haemostat. Although a variety of techniques and products is available for haemostasis during surgical procedures, EVARREST could add a valuable alternative.

Inappropriate use on a bleeding site that has not been investigated and treated with all surgical efforts but would require mechanical suture, ligation or cautery, can result in severe haemorrhage, which, unfortunately, may initially be masked by the Fibrin Pad. This risk has been emphasized in the SmPC through strict contraindications and warnings and in the risk management plan.

Benefit-risk balance

The indication "*EVARREST is indicated in adults for supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of heamostasis"* reflects the clinical trials submitted, is in accordance with the core SmPC and is covered by an overall positive benefit / risk of the product.

EVARREST should not be used to treat bleeding in place of sutures or other forms of mechanical ligation when appropriate for the treatment of major arterial bleeding. EVARREST should not be used to treat severe bleeding from large defects in large arteries or veins where the injured vascular wall requires repair with maintenance of vessel patency and which would result in persistent exposure of EVARREST to blood flow and pressure during healing and absorption of the product.

Discussion on the benefit-risk balance

Clinical studies demonstrating haemostasis in mild, moderate or severe soft tissue bleeding were conducted in subjects undergoing abdominal, retroperitoneal, pelvic, and (non-cardiac) thoracic surgery and haemostatic efficacy in persistent parenchymal bleeding in hepatic surgery.

The management of intraoperative bleedings is often a challenging, time consuming and crucial task for the surgeon. A haemostatic product superior to oxidized regenerated cellulose or superior to standard of care could offer a therapeutic alternative, which, when used with precaution as an adjunct to meticulous surgical haemostatic techniques could provide clinically relevant benefit.

The product could provide surgeons with an effective tool in the treatment of bleedings.

The safety data for EVARREST reflect the types of post-operative complication generally related to the surgical settings in which the trials were conducted and the underlying disease of the patients. In clinical trials, the most frequently reported adverse reactions were haemorrhage and increased

fibrinogen, and the most serious adverse reactions were aspiration, pulmonary embolism, and haemorrhage.

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 EVARREST in the supportive treatment in surgery in adults 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 products on "restricted" medical prescription, reserved for use in certain specialised areas (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 the first periodic safety update report for this product within 6 months following authorisation. Subsequently, 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.

In addition, 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.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

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