14 September 2017
EMA/734511/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

VeraSeal

International non-proprietary name: human fibrinogen / human thrombin

Procedure No. EMEA/H/C/004446/0000

Note

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

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemica
B19V	parvovirus B19
CBC	complete blood count
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
FDA	Food and Drug Administration
FS	fibrin sealant
FS Grifols	Fibrin Sealant Grifols
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HTC	haemostatic time category
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
Ig	immunoglobulin
INN	International Non-proprietary Name
INR	international normalized ratio
IRB	Institutional Review Board
ISS	integrated summary of safety
ITT	intent-to-treat
MC	manual compression
MedDRA	Medical Dictionary for Regulatory Activities
NAT	nucleic acid testing
$NHTC_{>10}$	non-haemostatic time category: persistent bleeding at the TBS beyond the 10-minute observational period
PP	per protocol
PTFE	polytetrafluoroethylene
RBC	red blood cell
REB	Research Ethics Board
RR	risk ratio

SAE	serious adverse event
SAF	subject authorization form
SAP	statistical analysis plan
S/D	solvent/detergent
SmPC	summary of product characteristics
SOC	system organ class
SWFI	sterile water for injection
T_0	time of randomization
T3, T4, T5, T7, and T10	haemostatic assessment of the TBS at 3, 4, 5, 7, and 10 minutes following TStart
$T_{Closure}$	time of completion of the surgical closure by layers of the exposed surgical field containing the TBS (when the last skin closure stitch is put in)
$T_{Completion}$	time of completion of surgical incision closure (when the last skin closure stitch is put in) of the last exposed field, regardless of whether it was the field containing the TBS
T_{end}	time of the end of FS Grifols application
T_{off}	time of the proximal clamp release 1 minute after the end of FS Grifols application
T_{on}	time of clamps reapplication after identifying the TBS
T_{Start}	time of the start of the study treatment (FS Grifols or MC) application
TBS	target bleeding site
TEAE	treatment-emergent adverse event
TTH	time to haemostasis
ULN	upper limit of normal
US	United States
WBC	White Blood Cell
WHO-DD	World Health Organization Drug classification Dictionary

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Instituto Grifols, S.A. submitted on 28 November 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for VeraSeal, 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 28 April 2016. 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:

Supportive treatment in adults where standard surgical techniques are insufficient:

- for improvement of haemostasis.

- as suture support in vascular surgery.

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 test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0289/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0289/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Andrea Laslop Co-Rapporteur: Ewa Balkowiec Iskra

- The application was received by the EMA on 28 November 2016.
- The procedure started on 23 December 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 March 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 March 2017.
- During the meeting on 21 April 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 July 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 17 August 2017.
- During the PRAC meeting on 1 September 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 14 September 2017, 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 VeraSeal on 14 September 2017.

2. Scientific discussion

2.1. Problem statement

The human fibrin adhesion system constitutes the last phase of the physiological blood coagulation system leading to the formation of a semi-rigid fibrin clot. In the coagulation pathway, fibrinogen, the main structural protein in the blood responsible for forming clots, is proteolytically cleaved and converted into fibrin monomers by thrombin and the fibrin monomers then polymerize to form insoluble fibrin. Thrombin also activates endogenous factor XIII that catalyses the formation of covalent bonds between molecules of fibrin to form a cross-linked clot capable of resisting dissolution. Calcium ions (Ca++) are required for most reactions that lead to the generation of active thrombin. The clot adheres to a variety of proteins, such as collagen, fibronectin, von Willebrand factor, and cell surface receptors, contributing to anchoring the fibrin clot to the injured site. As wound healing progresses, increased fibrinolytic activity is induced by plasmin and decomposition of fibrin to fibrin degradation products is initiated.

The use of human plasma proteins as tissue sealants dates back to early last century. The concept of using plasma fibrinogen mixed with thrombin to form a biological adhesive was reported approximately 70 years ago. Commercial concentrates rich in clottable fibrinogen became available in Europe in the late 1970s, and, more recently, commercial fibrin sealant (FS) products were licensed for use in the United States of America (USA). Fibrin sealants may be used in various diseases and clinical situations, and actual products may differ in their composition, application sets, and technique of use. These products have been used in a large variety

of surgical fields, including but not limited to, cardiac and vascular surgery, thoracic surgery, neurosurgery, plastic and reconstruction surgery, gastrointestinal surgery, hepatic and splenic surgery, and dental surgery. Practical applications of fibrin sealant products in orthopaedic surgery, interventional radiology, and minimally invasive endoscopy are growing.

Intended benefit of the FS application is to support local haemostasis, to “glue” surface of injured tissues in order to obtain adaptation or sealing of surfaces, to support sutures, or to improve repair or healing.

2.1.1. Disease or condition

Surgical approaches are receiving increasing attention as a way to solve many global public health problems. Data from the World Bank reported that in 2002, an estimated 164 million disability-adjusted life years, representing 11% of the entire disease burden, were attributable to surgically treatable conditions. In practice, fibrin sealants have been demonstrated to be efficacious in controlling slowly bleeding foci, diffuse oozing, bleeding from needle puncture sites, lymphatic leaks, serous fluid collections, and diffuse parenchymal organ haemorrhage.

2.1.2. Epidemiology

Worldwide volume of surgery is large. In view of the high death and complication rates of major surgical procedures, surgical safety should now be a substantial global public health concern. In a study which obtained surgical data for 56 (29%) of 192 WHO member states, they estimated that 234.2 (95% CI 187.2–281.2) million major surgical procedures are undertaken every year worldwide or approximately one operation annually for every 25 human beings alive. Many risk factors have been associated with surgery. Some are preoperative patient characteristics, others are related to the type and severity of the disease itself and a third group are related to the type and extent of the surgical procedure.

2.1.3. Clinical presentation

The fibrin adhesion system initiates the last phase of physiological blood coagulation. Conversion of fibrinogen into fibrin occurs by the splitting of fibrinogen into fibrin monomers and fibrinopeptides. The fibrin monomers aggregate and form a fibrin clot. Factor XIIIa, which is activated from factor XIII by thrombin, cross links fibrin. Calcium ions are required for both, the conversion of fibrinogen and the cross linkage of fibrin. As wound healing progresses, increased fibrinolytic activity is induced by plasmin and decomposition of fibrin to fibrin degradation products is initiated.

2.1.4. Management

Conventional procedures used to control bleeding include the use of direct pressure, sutures, pledges, and/or electrocautery. Absorbable haemostatic agents such as bovine gelatine power and sponges, and haemostatics agents made from bovine collagen and oxidised cellulose are also used for stopping bleeding. Additionally products containing thrombin and/or fibrinogen are used to assist body´s natural clotting mechanism to achieved haemostasis. The versatility of fibrin sealant is due to its capacity to cause blood to clot, creating a sealing barrier as well as gluing tissues together.

The use of human plasma proteins as tissue sealants dates back to early last century. The concept of using plasma fibrinogen mixed with thrombin to form adhesive was reported approximately in the 1930s (Cronkite E *et al* JAMA 1944; 124: 976-978. (S2) 3-10). Commercial concentrates rich in clottable fibrinogen became available in Europe in the late 1970s.

Fibrin sealant products are particularly in use, when:

- application of mechanical pressure is not possible,

- suturing is difficult or tight tissue sealing/adhesion is required,

- reliable haemostasis is critical, or

- where the patient's own physiological coagulation system is impaired.

About the product

VeraSeal is a frozen, solvent/detergent (S/D) treated and double-nanofiltered fibrin sealant (FS) consisting of two components: Fibrinogen and Thrombin; both derived from pooled human plasma. Thrombin contains human Albumin as excipient. The product is presented in a two syringes, each syringe contains equal amounts of frozen Fibrinogen and Thrombin (total volume package sizes are 2ml, 4ml, 6ml and 10ml) which are held together by a syringe holder designed by Grifols. An applicator tip is supplied. A spray applicator (Gas-assisted spray applicator) is an optional accessory and is provided separately.

The newly developed FS Grifols is intended for local application and a local effect. It imitates the final stage of blood coagulation, i.e. the natural process of clot formation: soluble Fibrinogen is cleaved by Thrombin and consequently forms an insoluble network of fiber bundles – the fibrin clot.

The volume of VeraSeal to be applied and the frequency of application should always be oriented towards the underlying clinical needs for the patient. The dose to be applied is governed by variables including, but not limited to, the type of surgical intervention, the size of the area and the mode of intended application, and the number of applications. Application of the product must be individualised by the treating physician. In clinical trials, the individual dosages have typically ranged from 0.3 to 12 ml. For other procedures, larger volumes may be required.

2.2. Quality aspects

2.2.1. Introduction

VeraSeal is a solution for sealant, containing two active substances: Human fibrinogen 80 mg/ml and Human thrombin 500 IU/ml (total volume package sizes are 2ml, 4ml, 6ml and 10ml).

VeraSeal (human plasma-derived fibrin sealant (FS)) is supplied as a single-use kit with two separate pre-filled syringes containing sterile frozen solutions of human fibrinogen (Component 1) and human thrombin with calcium chloride (Component 2) assembled on a syringe holder. A single use sterile applicator tip is also supplied with the product. The applicator spray (Gas-assisted spray applicator, CE-marked) is an optional accessory and provided separately.

VeraSeal mimics the last stage of the human coagulation system. Fibrin generation is the final stage of the coagulation system inducing the formation of a semi-rigid fibrin clot: fibrinogen, the primary protein responsible for the clot formation, is proteolytically cleaved into fibrin monomers by the action of thrombin. The fibrin monomers polymerise to form soluble fibrin. Thrombin activates the endogenous FXIII, which catalyses the formation of covalent bonds between the Fibrin molecules resulting in the formation of a stable clot. The presence of calcium ions is required for most reactions that lead to the generation of active Thrombin.

The product is intended for epilesional use only and is used as a biodegradable tissue sealant to control haemorrhages in supportive treatment in surgery where standard surgical techniques are insufficient for improvement of haemostasis, and as a suture support in vascular surgery.

2.2.2. Active Substance

General information

The active substances human fibrinogen (component 1) and human thrombin (component 2) are isolated from human plasma and the information referring to the human plasma used for the manufacture of blood products at Instituto Grifols, S.A. is detailed in the Instituto Grifols Plasma Master File. Both active substances Human Fibrinogen (component 1) and Human Thrombin (component 2) comply with the Ph. Eur. monograph “Fibrin Sealant Kit” (0903).

As there is no distinct intermediate active substance stage, not all active substance (AS) sections have been included in the active substance part. Further detailed information can be found in the finished product part.

Manufacture, characterisation and process controls

Manufacture

Both components of VeraSeal are manufactured based on Cohn’s fractionation process. Due to the continuous manufacturing process of both components from fractionation to the final component, there is no distinct intermediate active substance stage as such. Therefore detailed information on the manufacturing process of both components can be found in the finished product (FP) section.

Instituto Grifols, S.A. (C/ Can Guasch, 2, Pol. Ind. Levante, Parets del Vallés, 08150 Barcelona, Spain) is responsible for the whole manufacturing process, i.e. from plasma starting material to packaged, labelled, quality control tested and batch released finished product.

Characterization

- ***Fibrinogen (component 1)***

Biochemical characterization was extensively performed on a total of three commercial lots using different test methods. The experimental design covers the analysis of product-related parameters, excipients, product-related impurities and process related impurities.

Characterization revealed that fibrinogen is a highly purified protein. The SDS-PAGE band analysis and the immunoblotting show, under reducing conditions, the presence of three main bands corresponding to fibrinogen dimer chains: α chain β chain and γ chain. Under non-reducing conditions, a major band

corresponding to fibrinogen is detected. The analysis of the integrity of the fibrin chains shows the formation of a stable clot in the presence of calcium demonstrating the proper functionality of the fibrinogen molecule.

The fibrinogen component of VeraSeal FS has been extensively characterized, showing a high degree of purity, and maintaining its functional properties.

- ***Thrombin (component 2)***

An extensive list of test methods which were performed in order to characterize Thrombin has been presented. A total of three industrial lots of thrombin were studied.

The conclusion of this characterization study is that thrombin is a highly purified protein. The electrophoretic profile indicates that the thrombin concentrate is mainly α-thrombin.
The determination of process-related impurities shows that these are not detected or are at trace level.
The thrombin component of VeraSeal has been extensively characterized, showing a high degree of purity, and maintaining its functional properties.

- ***VeraSeal (both components)***

The characterization studies of VeraSeal FS also evaluated the clot structure, the mechanical properties of formed clots (tensile strength) and also included the macroscopic study of clot polymerization and fibrinolysis.

Clot structure

Special focus was laid on the clot structure and its characterization. As fibrin sealants are used as biodegradable tissue sealants to control haemorrhages, demonstration of appropriate clot formation of the product is essential.
As a result, the following *in vitro* characterization studies were performed in order to demonstrate clot formation:

- Tensile strength: mechanical properties of formed clots

- Clot structure by microscopy

- Macroscopic study of clot polymerization and fibrinolysis

  Clot polymerization
  Three different turbidity methods were used:
  - Polymerisation according to Bollinger-Stucki
  - Polymerization with different concentrations of Thrombin
  - Polymerization after product fixed dilution

Fibrinolysis kinetics

The characterization studies are appropriately performed and give sufficient information on the fibrin sealant components. The functionality test shows appropriate clot formation once the two components (fibrinogen and thrombin of FS) are mixed. Results of the characterisation studies demonstrated the robustness of the clot characteristics.

Process controls

Details on process controls can be found in the Finished Product section

Specification

Please refer to the finished product section for further details.

Stability

Stability studies have been performed with the defined process intermediates for both components. No significant changes in any parameters were observed. The proposed holding times have been justified. The proposed storage periods are justified based on the respective data of adequate stability investigations.

Fibrinogen (component 1)

A stability study was conducted on three lots of each process intermediate in order to verify their stability profile.
The samples were stored at ≤ -20°C in a temperature-controlled chamber or freezer, simulating the storage conditions during the production process.

Thrombin (component 2)

Three lots of each process intermediate were studied. Long term stability data show that this component of VeraSeal is stable for 2 years when stored at ≤ -18ºC. After thawing, it can be maintained for not more than 48 hours stored at 2 – 8ºC or 24 hours at room temperature before use.

Container closure system

The material used in the manufacture of the containers complies with the compositional requirements of the Pharmacopoeia monographs listed relating to polyolefins for medico-pharmaceutical use.
Absence of a cytotoxic potential of the containers used for intermediates storage was demonstrated.
Potential toxicity was investigated in two *in vivo* studies and the results revealed no toxicological concern for the materials used. Extractables testing into aqueous and fatty simulants also showed and confirmed that the containers comply with the relevant standards and are deemed adequate as container closure system.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Description

VeraSeal is a two-component frozen sterile solution manufactured by Instituto Grifols, S.A., Barcelona, Spain. The two components, human fibrinogen and human thrombin, generate a cross-linked fibrin clot in a process that mimics the last stage of the human coagulation process. It is intended for local application and local effect.
The active substances, fibrinogen and thrombin of VeraSeal are derived from human plasma.

VeraSeal is available in the following pack sizes:
- VeraSeal 2 ml (containing 1 ml of human fibrinogen and 1 ml of human thrombin)
- VeraSeal 4 ml (containing 2 ml of human fibrinogen and 2 ml of human thrombin)
- VeraSeal 6 ml (containing 3 ml of human fibrinogen and 3 ml of human thrombin)
- VeraSeal 10 ml (containing 5 ml of human fibrinogen and 5 ml of human thrombin)

The choice of excipients has been justified and their functions adequately explained. Adequate and sufficient information has been provided in relation to the human albumin used as excipient in component 2 (thrombin).

Container closure system

VeraSeal is supplied as a single-use kit containing one fibrinogen syringe and one thrombin syringe (glass type I) assembled on a syringe holder. The packaging material in contact with the product consists of glass syringe barrels, tip caps and plunger stoppers, complying with the European Pharmacopoeia specifications. A single use sterile applicator tip intended for dripping application is also provided (is a CE-marked cannula).

The possible presence of leachables and extractables in the final product from the plunger stoppers and tip capsused has been adequately assessed. No levels of potentially toxic leachables were detected in the final product analysed.

Results showed that the container closure system, the tip caps and the plunger stopper are compatible with VeraSeal Fibrin Sealant.

The functionality of the application systems has been adequately studied. Tests of mixing of the components, consistency, homogeneity and viability of the application have been performed using both tip and spray applicators.

A validation study was performed to demonstrate the integrity of the container closure. According to the results obtained in the integrity test, it is considered that the container closure system guarantees correct product integrity without leaks that may result in product loss and/or product contamination.

Optionally, the product may also be applied by spraying. For this purpose, a spray applicator is supplied separately and adequate information has been provided. To avoid the risk of potentially life-threatening air or gas embolism VeraSeal is recommended to be sprayed using pressurised CO_2 and it has to be ensured that the pressure and the distance from the tissue are within the ranges recommended in the SmPC. The instructions for use are also described in the healthcare professionals' package leaflet part.

Sufficient and adequate information about the container closure system for VeraSeal has been provided.

Pharmaceutical development

Fibrinogen (component 1)

The starting material of Fibrinogen comes from plasma fractionation. Initial development stages included clarification by centrifugation. Later on, centrifugation was replaced by filtration step in order to reduce process time. Chemical treatment was implemented immediately after clarification as a pathogen inactivation step. Precipitation step following chemical treatment are performed. This step allows the reversible precipitation of fibrinogen. The fibrinogen precipitate is separated by centrifugation and re-suspended in saline solution and clarified. Nanofiltration is implemented as a second pathogen safety step. The product is then adjusted for concentration and formulation by ultrafiltration. Finally, a sterile bulk filtration is performed before aseptic filling into syringes. Fibrinogen formulation was evaluated in several studies in order to achieve the optimal composition of excipients for a liquid formulation. Reproducibility and consistency of the Fibrinogen production process for use as a component of Fibrin adhesive at a final scale was performed at commercial scale.

Thrombin (component 2)

Thrombin is obtained from concentrated prothrombin complex (PTC) captured with ion exchange resin from a supernatant of the fractionation of pooled plasma. The activation of thrombin is performed by incubation in presence of activation excipients. Then a chemical treatment for pathogen inactivation is performed. Thrombin was then adsorbed and purified by ion exchange resin. Several optimizations on that process step were performed during the whole development phase. The eluted fraction is formulated before nanofiltration

Finally, a sterile bulk filtration is performed before aseptic filling into syringes.

Manufacture of the product and process controls

Manufacture

VeraSeal FS consists of two highly purified plasma proteins: fibrinogen and thrombin.
Fibrinogen (VeraSeal component 1) is obtained from frozen plasma fractionation. Thrombin (VeraSeal component 2) is obtained from frozen fresh plasma fractionation.
The production of the human fibrinogen and thrombin, as a component 1 and component 2 of VeraSeal FS, involves several separation and purification steps. The combination of these process steps results in a product with an adequate level of purification and recovery.
With the aim to ensure the product safety, the fibrinogen and thrombin production process includes two specific steps with virus removal/inactivation capacity.

Fibrinogen (component 1)

The Fibrinogen manufacturing process starts from the Cohn fractionation process and includes two dedicated viral inactivation/removal steps (S/D treatment, double nanofiltration), followed by formulation, sterile filtration, aseptic filling, assembling to the syringe holder and package into a blister pack which is then sterilized. Each packed unit is stored frozen at ≤ -20°C.
Equivalence of both manufacturing scales has been demonstrated.

Full descriptions for each manufacturing step have been provided, as well as process times and in process controls (IPC).
Filter integrity tests are performed and if the integrity tests of the 0.22µm sterile filters fail the product solutions are filtered through new filter sets. Critical process steps have been defined and are appropriately controlled.

Thrombin (component 2)

Thrombin (VeraSeal component 2) is obtained from the prothrombin complex concentrate (PTC), captured by ionic exchange resin from a supernatant of frozen fresh plasma fractionation. After obtaining the PTC eluate, activation of thrombin by incubation in the presence of activation excipients is performed. Afterwards, a chemical treatment for pathogen inactivation is carried out. Next, adsorption and purification of thrombin by ionic exchange resin is performed. The eluted fraction is formulated before nanofiltration, followed by sterile filtration, aseptic filling, assembling to the syringe holder and package into a blister pack. Each packed unit is stored frozen.

Sufficient information on materials and reagents used during the manufacturing process has been provided. A list of filters used during the process and their handling before and after the use has been submitted. An explanation of using equivalent filter types in the production of thrombin has been also presented. Criteria were defined by the company if equivalent filter types will be established in the production of VeraSeal.

If the post-use integrity test of the sterile filters fails after its use, the product solution will be re-filtered through new filter sets. This procedure has been validated and acceptable. No further re-processing is intended.
In-process controls of intermediate products and critical process steps have been defined and are appropriately controlled.

VeraSeal

Overages

VeraSeal is filled with a minimal overfill aiming to ensure the effective delivery of the nominal dose of the product.
Definition of the dose control specifications for both components was evaluated in respective studies, based on the calculation of the volume.

Batch consistency

Reproducibility and batch consistency for both components at a final scale was performed in the fibrin sealant facilities with six process runs, resulting in representative lots for each product presentation.
A batch numbering system is in place and is sufficiently described.

Microbiological attributes

Both components of VeraSeal undergo a purification process including viral safety steps and are sterile filtered before aseptic filling into syringes. The syringes are sterilized and frozen at ≤ -20°C. The applicant has a system in place to control microbiological contamination throughout the manufacturing process of VeraSeal.

Process controls

Fibrinogen (component 1)

The in-process controls performed during the production process of human fibrinogen (component 1) have been adequately detailed and justified.

In-process intermediate product controls

A detailed method description has been provided.

Thrombin (component 2)

The in-process controls performed during the production process of human thrombin (component 2) have been adequately detailed and justified.

In-process intermediate product controls

A detailed method description has been provided.

Process validation

Validation studies were performed to demonstrate that the consistency and quality criteria of the fractionation process are properly maintained in routine production processes. After evaluating the overall results, it is demonstrated that the fractionation process is under control and capable of manufacturing consistently, batches of plasma fractions with adequate quality.
Each manufacturing step was validated for both components and pre-defined parameters were tested in order to demonstrate adequate process qualification. Validation reports for all steps are available.
Extractables studies were performed for both processes, i.e. fibrinogen and thrombin manufacture, and it was demonstrated that the extractables present in the filter material give no reason for toxicological concern.
Cleaning validation of the mobile ultrafilters was performed as well in order to demonstrate that appropriate cleaning and storage of equipment is ensured.
Container closure integrity was sufficiently demonstrated.
Sterilization of the VeraSeal applicator system as well as sterilization of the syringes was shown to be successfully validated.
In order to demonstrate the reproducibility of the manufacturing process with regard to the characteristics of the degree of purification, yield and recovery, in both intermediate process steps and the final product, a study was conducted on the processes of fibrinogen and thrombin for fibrin adhesive at the final industrial scale.
An extensive biochemical characterisation was performed to demonstrate that the finished product produced by the established manufacturing process meets all release requirements for functionality and safety.
The manufacturing process of the fibrinogen and thrombin components seems to be appropriately validated, taking into consideration worst case conditions as applicable. Production of a product that meets its predefined acceptance criteria was demonstrated.
In summary, the manufacturing process for fibrinogen and thrombin has been validated for consistency and for removal of impurities. The extensive testing performed have shown that manufacture is well controlled, and the results obtained demonstrate consistency in yield and production, as well as consistency in degree of purity, quality and safety of the final product.

Product specification

VeraSeal complies with the Ph. Eur. monograph “Fibrin sealant kit” 0903, current edition and will always be adapted to the edition in force. The specification includes appropriate tests for immuno-chemical, physico-chemical, microbiological and biological control of the product.

Specifications were established in order to maintain uniformity of the final product to meet the parameters established in final formulation studies, such as excipient concentrations for tonicity and product stability, potency and appearance. In addition, specifications were established to demonstrate that process-impurities are adequately removed. Specifications meet with all the requirements detailed in the Fibrin Sealant kit European Pharmacopoeia monograph 0903.

The specifications meet the Pharmacopoeia requirements and ensure the safety and efficacy of the finished product. Adequate tests were established according to the formulation and process and ranges are based on analytical variability, safety and guidelines regulations and/or recommendations.
In addition to the fibrinogen and thrombin specifications, a functionality test to assess that the mixture of both components is functionally correct, has been also included, related with properties of the final fibrinogen and thrombin mixtures once delivered (identification and functionality). The functionality of each batch is checked in all cases.
Batch analyses data from recently processed batches have been provided, demonstrating process consistency.

Reference standards

Fibrinogen (component 1)
The fibrinogen content (clottable protein) is defined as protein.

Thrombin (component 2)
Thrombin potency (IU) is measured with an in-house standard.Preparation and qualification of this in-house standard has been adequately described.

Stability of the product

VeraSeal (both components)

Stability investigations have been performed on both components according to current ICH guidance.

Long term stability

Under long term storage all tested parameters remained within their acceptance criteria for the clinical as well as for the commercial scale batches.
Stress conditions revealed that polymers tend to increase over the storage period which is expected, but they are within specification over the whole study period.

In use stability

Stability after thawing was evaluated at the end of shelf life on five batches VeraSeal, representing all fibrin sealant (FS) kit presentations.

Fibrinogen content and thrombin activity showed no trends and remained within their acceptance criteria throughout the whole study period at both storage conditions. No out-of-specification (OOS) results occurred.

Human Albumin 20% Grifols – excipient of component 2
A summary report of stability results of the human albumin 20% Grifols was provided. Based on the results provided a shelf-life for three years at 5±3ºC and 30°C is acceptable.

Shelf life for VeraSeal

A shelf life of 2 years when stored at ≤ -18°C is claimed for VeraSeal.
After thawing, it can be maintained not more than 48 hours stored at 2-8°C or 24 hours at room temperature before use if it remains sealed in the original packaging. Once the outer pouch is opened, VeraSeal should be used immediately.

Based on the data provided the claimed shelf life and in use stability can be accepted.

Adventitious agents

Viral safety

A thorough risk assessment on viral safety was compiled including all relevant considerations, starting from the selection of the starting material, i.e. human plasma, including dedicated and contributory virus safety steps in the manufacturing process, and finally a calculation of the potential remaining risk of the final finished product.

Detailed discussion and evaluation on the starting material can be found in the Grifols Plasma Master File. The manufacturing process of both components was evaluated for its capacity to remove/inactivate potential viral contaminants.

A comprehensive list of all factors that contribute to the viral safety for both components of VeraSeal Fibrin Sealant has been provided, starting from donor selection until the residual risk calculation for the final finished product.

Fibrinogen (component 1)

For Fibrinogen two specific steps are implemented in the manufacturing process:

- Solvent/Detergent (S/D) treatment
- Double nanofiltration

Glycine precipitations were shown to contribute to the overall safety of the product.
All validation studies were conducted in downscale; comparability to the commercial scale process was demonstrated.
Cytotoxicity and interference studies were adequately performed.

S/D treatment

BVDV and WNV were inactivated below the limit of detection (LoD), HIV was below the detection limit and PRV was inactivated after incubation with S/D reagents.
Robustness: Effective inactivation was demonstrated for PRV under worst case conditions with regard to S/D reagents concentration.

Double nanofiltration

The results show that all viruses larger than 35nm (i.e. PRV, HIV, BVDV, WNV) are retained by the filter with no infectivity detected in the filtrate. Filtration increases the safety of the step with respect to these viruses. No infectivity was found in the filtrate.

With regard to HAV and PPV as models for small, non-enveloped viruses, filtration showed effective removal for both viruses.

Sodium heparin (material used in the manufacturing process of component 1)

Sodium heparin is of porcine origin, hence there is no TSE safety concern. However, the manufacturing process of heparin has implemented two virus inactivation steps.

Thrombin (component 2)

The thrombin manufacturing process includes two dedicated virus inactivation/removal steps, S/D (Solvent/Detergent) treatment and double nanofiltration. Additionally two process steps were assessed for virus removal.

In summary, the validation studies performed are considered sufficient and it can be concluded that the manufacturing process of thrombin is effective for inactivation/removal of enveloped and non- enveloped viruses.

Albumin 20 % Grifols (excipient of component 2)

Relevant virus inactivation steps were investigated. The virus validation studies performed are adequate and considered sufficient to demonstrate the viral safety of the product.

TSE safety

Fibrinogen (component 1)

The capacity of the VeraSeal fibrinogen production process to remove a hypothetical contamination by TSE agents was estimated, based on in-house research and bibliographic information.
Two different types of spikes with prion were used in the respective validation studies and two process steps were evaluated for their capacity to remove prion agents.

Thrombin (component 2)

Two studies were conducted in order to estimate the capacity of the production process of Fibrin Sealant components (human fibrinogen and human thrombin) to remove Transmissible Spongiform Encephalopathies (TSE)-causing agents.

Different manufacturing steps of thrombin from which a reduction in the prion load was expected was experimentally tested in laboratory scale studies.

The results reveal that the different production steps are effectively capable to remove TSE agents and can therefore be considered as relevant prion reduction steps in the manufacturing process of thrombin. The TSE studies are in accordance to the relevant guidelines.

Albumin Grifols (excipient of component 2)

A summary report was provided where the potential prion-removal capacity of the manufacturing process of Grifols 20% human albumin was estimated. Based on Grifols own experiments on precipitation and the most relevant bibliographical information relating to the other production steps, TSE safety was calculated and was considered acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The development of the product has been described, the choice of excipients has been adequately justified and their functions explained.
The process validation was sufficiently performed for the different manufacturing steps. Several product specific parameters and process variables were investigated and the data provided demonstrate fulfilment of all predefined acceptance criteria.
The control tests and specifications have been adequately justified and the product specifications cover appropriate parameters for the dosage form. The batch analysis results show that the finished product meets the specifications proposed. The established manufacturing process allows purifying fibrinogen and thrombin for fibrin sealant in a reliable way, achieving a high purity product free of process and product-related impurities.
The stability studies were conducted in accordance with the ICH guidance. The proposed shelf life is acceptable.
Appropriate safety with regard to adventitious agents has been sufficiently demonstrated. In summary, the manufacture of VeraSeal seems to be properly performed and controlled adequately.

VeraSeal is supplied as a single-use kit containing one fibrinogen syringe and one thrombin syringe assembled on a syringe holder. A single use sterile applicator tip) is supplied together with the VeraSeal kit.

Alternatively VeraSeal can be applied via a gas-assisted spray applicator (CE-marked) which is supplied separately from the VeraSeal kit.

The risk of gas embolism by using the spray applicator was appropriately discussed and is justified. The instructions for use are clearly described in the SmPC and in the healthcare professionals' package leaflet part.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality part of VeraSeal was presented in a well-structured and organized manner, reports for all relevant studies have been provided together with adequate and sufficient supporting documentation. Based on the quality data provided in Module 3 it can be expected that the manufacturing process of VeraSeal performs consistently and delivers a product of constant quality. Adventitious agents' safety has been appropriately demonstrated.

2.3. Non-clinical aspects

2.3.1. Introduction

Primary pharmacodynamic studies were conducted *in-vitro* and in two different animal species *in vivo* in its indication as adjuvant to haemostasis in surgery. Single dose toxicity studies with the fibrinogen component of the Fibrin Sealant (FS) Grifols VeraSeal were conducted.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro coagulation after application of FS Grifols seemed to be immediate and satisfactory. The *in vivo* haemostatic effect was tested in cardiac, vascular and liver surgery in pigs and 2 vascular surgery studies in rabbits. In 1 study of each species FS Grifols was compared to other already licensed fibrin sealants

***In-vitro* study**

In-vitro coagulation time of FS Grifols

The objective of this study was to assess the coagulation time of the fibrin sealant in vitro using double cannula application needles.

Results: No differences in coagulation time were observed among the fill volumes, fibrinogen or thrombin lots

***In vivo* studies**

Vascular surgery

The objective of this study was to evaluate the safety and efficacy of FS Grifols applied to a termino-terminal anastomosis of the abdominal aorta. After surgery, animals were observed for 14 days. After this period, a further surgery was done to evaluate the evolution of the anastomosis. Following evaluations were performed: reduction in the number of stitches and bleeding in anastomoses of small arteries, saving surgical time, production of stenosis if applied before unclamping and local tolerance.

Three study groups (9 rabbits each) were used:

Group A – control (no test article used)

Group B1 – FS application after unclamping the abdominal aorta (test article applied to a bleeding vessel)

Group B2 – FS application before unclamping the abdominal aorta (test article applied to a non-bleeding vessel)

Results: Out of 27 rabbits included in the study, 7 rabbits died during the first surgery from bleeding or in the post-surgery before the sacrifice (4 from Group A, 1 from Group B1 and 2 from Group B2).

The surgical operation took less time for groups with FS than for the control group (Group A = 103.8 ± 8.5 min, Group B1 = 92.0 ± 9.8 min, Group B2 = 83.6 ± 7.4 min), the difference between group B2 and group A being statistically significant (p = 0.0001). Bleeding was lower in groups with FS (Group A = 4.86 ± 2.73 g,

Group B1 = 3.00 ± 1.91 g, Group B2 = 0.72 ± 0.83 g), with a statistically significant difference in bleeding Group B2 and Group A (p = 0.001).

Two rabbits of Group A and two of Group B2 showed occlusion or stenosis of the anastomosis. The FS reabsorption occurred in all animals..

Cardiac and vascular surgery

The aim of this study was to assess the safety and efficacy of FS Grifols in cardiac and vascular surgery in pigs. The test article was applied to sutures made in the heart, arteries and veins as well as a incision into the upper right pulmonary lobe. Weeks after surgery, they underwent a second surgical procedure to check the sutures and evolution of the anastomoses.

Following evaluations were performed: reduction of the number of stitches in cardiac and vascular surgery without increasing the number of stitches due to bleeding; reduction of bleeding sites and the number of reoperations; occurrence of false aneurysms (in addition of FS); saving of time when performing sutures; production of stenosis in arteriovenous sutures; efficiency in reducing the time of bleeding at the suture-derived orifices of the polytetrafluoroethylene (PTFE) grafts; development of local or systemic modifications (vital signs); local tolerance.

Following sutures or anastomoses were carried out: Transversal on the external jugular vein; Longitudinal on the carotid artery; Transversal on the subclavian artery; Carotid-carotid bypass with PTFE graft; Carotid-subclavian bypass on jugular vein; Innominate venous truncus; Ascending aorta; Right atrium; Each pig served as its own control.

Incision of the right upper pulmonary lobe: 5 cm parallel and 1 cm from the anterior border. FS application (no Control Group because of the risk of postoperative pneumothorax).

The sutures were classified into 2 groups, Group A and Group B, and each pig served as its own control.

- Group A: fewer stitches with application of FS to the sutures and anastomosis.
- Group B: normal number of stitches without application of the FS to the sutures and anastomosis.

Results:. The administration of FS did not cause any haemodynamic, acid-base balance or ECG modification. No significant difference between the amount of leukocytes was found before sacrifice and during the first surgery. The need for supplementary stitches and compression for haemostasis was lower for the FS group than for the control in all sutures. The FS sealed the suture holes produced in the PTFE, with no need of compression in any instance. The suture time was shorter for the FS group, differences being found in all cases that were more evident in the PTFE grafts sutures. No significant differences were found in flows and resistance indexes between the FS group and the control group in the transversal sutures of the external jugular vein and the longitudinal suture of the carotid artery. No false aneurysm was observed. After weeks, all sutures remained pervious, except the carotid-carotid graft with PTFE was occluded in some animals. In all cases, the sutures histology shows a foreign substance granulomatous inflammatory reaction, without difference between sutures with and without FS. Dystrophic calcification of the collagen fibres and eosinophils in the inflammatory infiltrate was found in some sutures, more frequently with FS application, but without significant differences between the FS group and the control group. Except for 2 sutures, no persistence of FS after weeks was observed. After FS application to the pulmonary resection, no aerial loss occurred. None of the animalsshowed pneumothorax.

Hepatic surgery:

The aim of this study was to assess the safety and efficacy of FS Grifols in hepatic surgery in pigs.

After a liver resection of central liver segments causing major venous and arterial haemorrhage, FS were applied to the haemorrhages using a spray system fitted with external compressed air. The test animals were maintained for weeks after surgery, to perform a new surgery for observation of the evolution of the resection and to take a biopsy of the liver site upon which FS had been applied..

Following objectives were investigated: post-operative haemorrhage during the first hours; coagulation time from application; FS reabsorption after weeks; pathological anatomy of the hepatic surface; check of haemodynamic and respiratory constants

Results: all animals survived. No haemodynamic or respiratory alterations were recorded. Spray application of FS with medicinal O_2 showed effective haemostasis of the hepatectomy surface in). After weeks, remains of the FS were still existent. The biopsy of the hepatic surface showed granulomatous formation with amorphous eosinofil material infiltrated by polymorphonuclears and scar fibrous tissue on the periphery. In the internal hepatic tissue, inflammatory cells infiltrating the liver connective tissue were seen.

Vascular surgery:

The aim of this study was to assess the safety and efficacy of FS Grifols in rabbits when applied with cannula (in drops) to a termino-terminal anastomosis of the infra-renal abdominal aorta in comparison to 3 already licensed fibrin sealants). Animals were maintained for 2 and 4 weeks after surgery. After that time, the animals were re-operated for documentation of the evolution of anastomosis.

Following evaluations were performed: reduction of the number of stitches; blood loss reduction; saving of surgery time; haemodynamic implications; development of stenosis when applied before unclamping and reabsorption of the FS after two and four weeks; occurrence of false aneurysms; product reabsorption.

Results: No modifications of vital signs occurred during or after the study and the anastomosis quality was not affected. Moderate adherences (adherences that extend the dissection time of the abdominal aorta) were detected in some animals) at re-surgery. Pulse-anterograde filling, curve morphology and flow rate values of the second surgery were comparable to those of the first surgery. No false aneurysm has been detected after the first surgery. In all cases, no FS has been found in necropsy.

Haemostasis in hepatic surgery

The objective of this study was to compare the spray application of 4 different fibrin sealants in hepatic resection of pigs (5 for each group) from a commercial hybrid. A liver resection of the central hepatic segments () was performed. Without direct primary haemostasis, of one of the four test articles was applied upon the resection using a spray system with medicinal O_2. Four weeks later, animals were re-opened for evaluation of the resection and to perform biopsies of the hepatic surface where the test articles had been applied. Each animal served as its own control.

Following evaluations were performed: Post-operative haemorrhage; time to haemostasis; coagulation time; product reabsorption after 4 weeks post-surgery; Pathological anatomy of the hepatic resection on fibrin sealant area and comparison to normal liver; safety checking of haemodynamic and respiratory signs.

Results: All animals survived. Effective haemostasis of the haepatectomy surface was reached. No significant differences between the 4 products were detected. No immediate reactions in the monitored parameters were observed during the use of any of the products and no long-term surgical complications were observed. The

postoperative hematic loss was very low and no loss was observed in several animals. No haemodynamic or respiratory changes were monitored. After re-opening, no residual hematomas or haemorrhagic rests were observed. Five infections of the operation injury and 3 laparoceles were observed. In most of the cases, the fibrin sealant was still found on the liver surface. In some animals group, no remains of the product were observed. Biopsies of the hepatic surface upon which the products were applied showed a granulomatous formation with eosinophilic material infiltrated by PMNs and cicatricial fibrous tissue in the periphery. In the internal hepatic tissue, inflammatory cells appeared which infiltrated the liver connective tissue.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were performed.

Safety pharmacology programme

No safety pharmacology studies were performed.

Pharmacodynamic drug interactions

No studies on pharmacodynamic drug interactions were performed.

2.3.3. Pharmacokinetics

No pharmacokinetic studies have been performed.

2.3.4. Toxicology

Single dose toxicity

Six single dose toxicity studies with the fibrinogen component of the Fibrin Sealant (FS) Grifols VeraSeal were conducted.

Table 1

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)	Testing Facility	GLP Compliance[1]
Single-Dose Toxicity	Mouse, Swiss	Intravenous	Single dose	360	Toxicology Service Centro de Investigacion en Farmacobiologia Aplicada (CIFA) University of Navarra C/Irunlarrea, s/n 31008 Pamplona Spain	GLP Compliant
Single-Dose Toxicity	Mouse, Swiss	Intravenous	Single dose	360		GLP Compliant
Single-Dose Toxicity	Mouse, Swiss	Intravenous	Single dose	360		GLP Compliant
Single-Dose Toxicity	Rat, Wistar	Intravenous	Single dose	360		GLP Compliant
Single-Dose Toxicity	Rat, Wistar	Intravenous	Single dose	360		GLP Compliant
Single-Dose Toxicity	Rat, Wistar	Intravenous	Single dose	360		GLP Compliant

VeraSeal is intended for topical use, although in the single dose toxicity studies, fibrinogen was administered by the intravenous (i.v.) route to guarantee systemic exposure of the product and thereby evaluate a possible worst-case-scenario in the clinical setup.

The test article was administered i.v. at one nominal dose during one preliminary study and two main acute toxicity studies. The main single dose toxicity studies were designed to evaluate haematology, clinical chemistry, necropsy, and histopathology data after a single administration, with further evaluations conducted weeks later to assess delayed toxicity and/or recovery.

The two main studies only vary in using different lots of fibrinogen.

No toxicity studies have been performed with thrombin, the second component of the FS Grifols, because thrombin is a thrombogenic protein that cannot be directly administered by the intravenous route.

Neurobehavioral data was generated by the Irwin test through all acute toxicity studies. A complete evaluation of the symptomatology, the intensity thereof, the time of appearance and reversibility produced by the test article was considered in order to obtain the toxicological profile of the product, taking into account the characteristics of the topical-use of the product in humans.

Overall, the presented findings of the toxicological studies do not provide evidence for enhanced toxicological potential of fibrinogen, one of the two components of VeraSeal used in the acute toxicity studies.

The toxicological studies of VeraSeal evaluated: (1) test product toxicity after single-dose intravenous administration in two different rodent species by intravenous route and (2) the symptomatology, the intensity thereof, the time of appearance and reversibility produced by the test article.

No mortality occurred.

Repeat dose toxicity

No repeat dose toxicity was performed.

Genotoxicity

No genotoxicity study was performed.

Carcinogenicity

No carcinogenicity study was performed.

Reproduction Toxicity

No reproductive toxicity study was performed.

Local Tolerance

The local tolerance studies of Fibrin Sealant Grifols were included in the nonclinical efficacy and safety studies performed with FS Grifols, The Fibrin Sealant was well tolerated without causing local or systemic reactions (changes in vital signs).

Other toxicity studies

Not applicable.

2.3.5. Ecotoxicity / environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Fibrinogen and Thrombin are not expected to pose a risk to the environment in accordance with the Guideline on environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00).

2.3.6. Discussion on non-clinical aspects

Single dose toxicity

One *in vitro* study and five *in vivo* studies in pigs and rabbits characterized haemostatic efficacy of FS Grifols. The effects observed were comparable to other fibrin sealants. Overall, the presented findings of the toxicological studies do not provide evidence for enhanced toxicological potential of fibrinogen, one of the two components of VeraSeal used in the acute toxicity studies. No mortality occurred.

Repeat dose toxicity

Given the nature of the product and its intended clinical use no repeated dose toxicity study was performed which is considered acceptable considering that the repeated administration of human proteins in studies conducted in animals is likely to produce a natural immunogenic response. These species-specific immune responses to human proteins may cause direct or indirectly adverse effects by, for example, cross reactivity between endogenous protein and the therapeutic product that could be misinterpreted as a toxicity effect. A repeated dose toxicity study may not be, thus, predictive of an effect on humans.

Genotoxicity

No genotoxicity studies were performed which is considered acceptable since the active substances are naturally expressed human plasma proteins (fibrinogen and thrombin). As indicated in the ICH S6 consensus guideline “Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (CPMP/ICH/302/95)”, direct interaction between peptides or proteins and DNA or other chromosomal material is not expected to occur. These studies are only relevant in the case of new molecular products.

Carcinogenicity

No carcinogenicity studies were performed since there are no carcinogenic potential for this product considering that both components are naturally expressed human proteins.

Reproductive and developmental toxicity

No studies on reproductive toxicity and toxicity during foetal development were performed since both components are naturally expressed human proteins hence this does not justify to conduct such study.

Local tolerance

The results of the preclinical studies support the local tolerance of the product.

Environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Fibrinogen & Thrombin are not expected to pose a risk to the environment and the applicants approach to waive environmental toxicity studies is accepted.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical testing strategy is regarded as appropriate in view of the facts that the product is a preparation of a human protein, clinical experience has already been obtained and data for other Fibrinogen Sealant products is available. The applicable regulatory guidelines were taken into consideration adequately. The non-clinical data submitted are considered appropriate and supportive of the MA for VeraSeal.

2.4. Clinical aspects

2.4.1. Introduction

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.

Table 2 Tabular overview of clinical studies

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered / compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
IG1101	42/USA, Hungary, Serbia, Russia	Phase III, prospective, sigle-blind, randomized 2:1	FS Grifols at the TBS vs MC	Safety, efficacy of FS Grifols vs MC safety, virus safety, and immunogenicity	Total:193/166 FS Grifols: 109/106 MC:57/56	02.08.2012 to 26.12.2015	FS Grifols: 76/33; Age:64y MC: 31/26; Age:61y	Peripheral vascular surgery	Haemostasis at the TBS by 4 min.
IG1102	38/USA, Hungary, Serbia, Russia	Phase III, prospective, single blind, Randomized 1:1 Non-inferiority	FS Grifols vs Surgicel at the TBS	Safety, efficacy of FS Grifols vs Surgicel safety, virus safety, and immunogenicity	Total: 325/300 FS Grifols:163/147 Surgicel:162/153	22.03.2013 to 28.12.2015	FS Grifols:85/78 Age:61y Surgicel:85/77 Age: 61y	Parenchymous tissue surgery	Haemostasis at the TBS by 4 min
IG1103	36/USA, Hungary, Serbia	Phase III, prospective, single blind, randomized 1:1 Non-inferiority	FS Grifols vs Surgicel at the TBS	Safety, efficacy of FS Grifols vs Surgicel safety, virus safety, and immunogenicity	Total:327/290 FS Grifols: 167/151 Surgicel:160/139	19.11.2012 to 04.06.2015	FS Grifols: 53/114 Age:46y Surgicel: 46/114 Age:46,5y	Soft tissue surgery	Haemostasis at the TBS by 4 min

2.4.2. Pharmacokinetics

No pharmacokinetics studies were performed.

2.4.3. Pharmacodynamics

No pharmacodynamics studies were performed.

Mechanism of action

The fibrin adhesion system initiates the last phase of physiological blood coagulation. Conversion of fibrinogen into fibrin occurs by the splitting of fibrinogen into fibrin monomers and fibrinopeptides. The fibrin monomers aggregate and form a fibrin clot. Factor XIIIa, which is activated from factor XIII by thrombin, crosslinks fibrin. Calcium ions are required for both, the conversion of fibrinogen and the crosslinkage of

fibrin. As wound healing progresses, increased fibrinolytic activity is induced by plasmin and decomposition of fibrin to fibrin degradation products is initiated.

2.4.4. Discussion on clinical pharmacology

No pharmacokinetics and pharmacodynamics studies were performed which is considered acceptable as VeraSeal provided as a kit, comprises of two syringes containing sterile frozen solutions of human fibrinogen (component 1) and human thrombin (component 2) assembled on one syringe holder, and is intended for epilesional use only. Therefore, PK/PD evaluations are not applicable.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology for VeraSeal is considered appropriate and supportive of the MA for VeraSeal.

2.5. Clinical efficacy

2.5.1. Dose response studies and main studies

Summary of main efficacy results

Three phase III trials were performed by the Applicant in different surgical indications:

- IG1101 peripheral vascular surgery
- IG1102 parenchymous organ surgery
- IG1103 soft tissue surgery.

Study G1101: A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis during Peripheral Vascular Surgery

Methods

This clinical study consisted of 2 parts: a Preliminary Part (I) and a Primary Part (II).

All subjects enrolled in the Preliminary Part (I) were treated with FS Grifols. The main objective of this part of the clinical study was to ensure that local study teams familiarized themselves with the technique for FS Grifols application and with intra-operative procedures required by the protocol of the clinical study. In addition, safety and efficacy data were collected from the subjects participating in the Preliminary Part (I) of the study. For each study centre participating in the study, the first 2 subjects were to be enrolled in the Preliminary Part (I).

Subjects in the Primary Part (II) were to be randomized in a 2:1 ratio into FS Grifols or Manual Compression treatment groups. This part of the clinical study had 2 main objectives: 1) to assess the safety of FS Grifols and 2) to assess the efficacy of FS Grifols. For each study center, the Primary Part (II) of the study was to start only after enrolments of 2 subjects in the Preliminary Part (I).

In both parts of the clinical study, subjects undergoing an elective (non-emergency), open (non-laparoscopic, non-endovascular) peripheral vascular surgical procedure, wherein a target bleeding site (TBS) was identified and a topical haemostat was indicated, were initially eligible to participate. A specific bleeding area/site was defined as the TBS when it was determined by the investigator (the surgeon) that control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) was ineffective or impractical and required an adjunct treatment to achieve haemostasis.

When the TBS was identified, the investigator was to rate the intensity of the bleeding at the TBS according to a 3-point scale (mild, moderate, severe). In both parts of the study, only subjects with a TBS with bleeding of moderate intensity could be enrolled as detailed in Intra-operative inclusion criteria 7.

Study Participants

Inclusion criteria

1. Signed the written ICF, or the subject's parent or legal guardian signed the ICF and Subject Authorization Form where applicable. Paediatric subjects, as defined by local regulations, were asked to sign an age-appropriate assent form.

2. Were male or female.

3. No lower or upper age limit.

4. Must have had haemoglobin (Hgb) ≥ 9.0 g/dL. Following the incorporation of Protocol Versions 4.0 and 4.1 (both dated 16 Dec 2014), the Hgb levels criterion was decreased from ≥ 9.0 g/dL to ≥ 8.0 g/dL at baseline (within 24 hours prior to surgical procedure) to allow the enrolment of subjects with lower Hgb levels.

5. Required an elective (non-emergency), open (non-laparoscopic, non-endovascular) peripheral vascular surgical procedure.

6. Required 1 of the peripheral vascular procedures listed below involving an end-to-side arterial anastomosis utilizing polytetrafluoroethylene (PTFE) grafts:

    a. Femoral-femoral bypass grafting.

    b. Femoral-popliteal bypass grafting.

    c. Femoral-distal bypass grafting.

    d. Ilio-iliac bypass grafting.

    e. Ilio-femoral bypass grafting.

    f. Ilio-popliteal bypass grafting.

    g. Aorto-iliac bypass grafting.

        ◦ Following the incorporation of Protocol Version 2.0 (dated 23 Aug 2013), this criterion was added to include testing of FS Grifols in bypass grafting at additional anatomic locations with larger vessels.

    h. Aorto-femoral bypass grafting.

◦ Following the incorporation of Protocol Version 2.0 (dated 23 Aug 2013), this criterion was added to include testing of FS Grifols in bypass grafting at additional anatomic locations with larger vessels.

i. Axillo-femoral bypass grafting.

◦ Following the incorporation of Protocol Version 2.0 (dated 23 Aug 2013), this criterion was added to include testing of FS Grifols in bypass grafting at additional anatomic locations with larger vessels.

j. Upper extremity vascular access for haemodialysis (arteriovenous graft formation). The percentage of subjects enrolled with upper extremity vascular access for haemodialysis (arteriovenous graft formation) should not have been >15% in the Primary Part (II) of the clinical study.

7. Intra-operative inclusion criteria:

A target bleeding site (TBS) could have been identified according to the investigator's judgment, and

a. The TBS had a moderate arterial bleeding according to the investigator's judgment.

-Following the incorporation of Protocol Version 1.1 (dated 11 Jun 2012), subjects with a mild bleeding TBS were excluded (ie, no subjects were enrolled in the study with a mild bleed).

b. The intensity of the arterial bleeding at the TBS was rated by the investigator using a predefined 3-point scale:

- Mild: bleeding that affected <25% of the suture line or that consisted of <5 suture-line bleeds (non-pulsatile, non-spurting bleeding).

- Moderate: non-spurting bleeding that affected at least 25% of the suture line or consists of at least 5 suture-line bleeds or consists of one pulsatile suture-line bleed.

- Severe: bleeding that consisted of >1 pulsatile suture-line bleed or consisted of at least 1 spurting (ie, continuous) suture-line bleed.

Exclusion criteria

1. Undergoing a re-operative procedure defined as a second, or successive, surgical procedure on the same anatomic location (ie, same anastomotic site).

2. Undergoing other vascular procedures during the same surgical session (stenting and/or endarterectomy of the same artery were allowed).

3. Had an infection in the anatomic surgical area.

4. Had a history of severe (eg, anaphylactic) reactions to blood or to any blood-derived (human or animal) product.

5. Had a previous known sensitivity to any FS Grifols, heparin, or protamine component.

6. Had a known (documented) previous exposure to thrombin-containing (bovine, human, or recombinant) products. Following the incorporation of Protocol Version 2.0 (dated 23 Aug 2013), this exclusion was removed.

7. Were unlikely to adhere to the protocol requirements or to be cooperative during the study conduct.

8. Females who were pregnant or nursing a child. Following the incorporation of Protocol Version 2.0 (dated 23 Aug 2013), clarification was provided for this exclusion. Females who were pregnant or nursing a child at baseline (within 24 hours prior to surgical procedure) were excluded from the study.

9. Were currently participating or had participated in another clinical study in the context of which they had received investigational drug or device within 3 months from the Screening Visit, or were scheduled to participate during the course of this study.

10. Had undergone a therapeutic surgical procedure within 30 days from the Screening Visit.

11. Previously enrolled in clinical studies with FS Grifols.

12. Intra-operative exclusion criteria:

    a. A TBS could not be identified according to the investigator's judgment.

    b. The TBS had mild or severe bleeding according to the investigator's judgment.

    c. Occurrence of major intra-operative complications that required resuscitation or deviation from the planned surgical procedure.

    d. Intraoperative change in planned surgical procedure which resulted in a subject no longer meeting preoperative inclusion and/or exclusion criteria (eg, abandonment of PTFE graft placement or change in the procedure to a different artery, not included in the acceptable procedures list).

Treatments

Subjects were treated intra-operatively with FS Grifols or manual compression (MC) application.

For subjects randomized to the FS Grifols group, 2 kits of 6 mL (total volume) each were allotted for peripheral vascular procedures. The kits were available and ready for use in the operating room at the time of surgery, but the maximum total volume of FS Grifols allowed to be applied at the TBS was approximately 6 mL (equivalent to the full content of 1 FS Grifols kit). Five units of applicator tips for dripping were available for each subject. Any applicator tips clogged by the biologic mix should have been replaced.

Objectives

The purpose of this study was to demonstrate that FS Grifols was both safe and effective in achieving haemostasis during peripheral vascular surgery and as suture support.

The efficacy objective of the study was to evaluate the haemostatic efficacy of FS Grifols in peripheral vascular surgery and as suture support.

The safety objectives of the study included clinical safety, virus safety, and immunogenicity.

Outcomes/endpoints

For surgical procedures in both the Preliminary Part (I) and the Primary Part (II) of the clinical study, the following data including haemostatic assessment when appropriate were collected and recorded to assess the efficacy of haemostasis by the investigator (surgeon) at the following time points:

1. TOn.
2. T0 (Primary Part [II], only).
3. TStart.
4. TEnd.
5. TOff.
6. TStart2.
7. TEnd2.
8. T4.
9. T5.
10. T7.
11. T10.
12. TClosure.
13. TCompletion; it may or may not have coincided with TClosure.

Following the incorporation of changes made in Protocol Versions 1.1 (dated 11 Jun 2012) and 1.2 (dated 24 Oct 2012), TEnd2 and TStart2 respectively, were added to capture the start and end times of study drug reapplication, if applicable.

The primary efficacy variable was the proportion of subjects in the Primary Part (II) of the study achieving haemostasis (Yes/No) at the TBS by T4 without occurrence of re-bleeding and reapplication of study treatment after T4 and until TClosure and without brisk bleeding and use of alternative haemostatic treatment after TStart and until TClosure.

Secondary efficacy variables

- Time to Haemostasis
- Cumulative Proportion of Subjects Achieving Haemostasis at the Target Bleeding Site by Each of the Following Time Points: T5, T7, and T10
- Prevalence of Treatment Failures

Sample size

The sample size for the Primary Part (II) of the study was estimated to provide sufficient power (at least 80%) to detect a difference between the proportion of subjects achieving haemostasis by a fixed time point (by 4 minutes after the start of treatment application), where it was assumed that 35% of the MC group and 60% of the FS Grifols group could be expected to exhibit haemostasis. Using a 2-group Fisher Exact test (2-

sided at the 5% level) it was determined that with a 2:1 ratio, a total of 156 subjects would provide 80% power (104 FS Grifols and 52 MC). To allow for a 5% drop-out rate after randomization, a total of 165 subjects (110 FS Grifols and 55 MC) would need to be randomized in this part of the study.

Randomisation

Subjects in the Primary Part (II) of the clinical study were randomized in 2:1 ratio into the FS Grifols or MC treatment groups. All study centres were provided with sealed opaque envelopes containing a treatment group assignment. For each subject undergoing a surgery, the first, sequential, available randomization envelope for the appropriate type of procedure (peripheral arterial bypass or upper extremity vascular access or haemodialysis) was taken. Randomization was stratified by study centre and type of intervention (peripheral arterial bypass or upper extremity vascular access for haemodialysis).

Blinding (masking)

Data from subjects participating in the Primary Part (II) of the study, including treatment assignment and accumulating efficacy data, were blinded from the sponsor, except for personnel from study drug supply groups.

Statistical methods

Analysis Data Sets

The ITT population was defined as follows:

- For the Preliminary Part (I) of the study, the ITT population included all subjects who met the intra-operative inclusion criterion and whom the investigator therefore intended to treat with FS Grifols.
- For the Primary Part (II) of the study, the ITT population included all subjects randomized to FS Grifols or MC.

Per-protocol (PP) population: The PP population included all subjects in the ITT population excluding any subject for whom there was at least 1 major protocol deviation that might have an impact on the primary efficacy assessment.

Primary Efficacy Analysis

The efficacy analysis was performed using the ITT population and data from the Primary Part (II) of the study only. Additionally, the primary efficacy endpoint of the proportion of subjects achieving haemostasis by 4 minutes at TBS was analysed using the PP population.

The primary efficacy variable was the proportion of subjects achieving haemostasis by T4 based on its nominal scheduled time point at TBS and was analysed by using a 2×2 Fisher Exact test for the treatment difference. The status of haemostasis was checked and recorded four minutes following TStart (T4). The ratio of the proportion of subjects meeting the primary efficacy endpoint in the 2 treatment groups (FS Grifols relative to MC) and its 2-sided asymptotic 95% confidence interval (CI) will also be provided.

Secondary Efficacy Analysis

Analyses relating to secondary efficacy variables, as the cumulative proportions of subjects achieving haemostasis at other individual assessment times (T5, T7, and T10), were also analysed using a 2×2 Fisher Exact test (Primary Part [II]). The TTH quantified in minutes according to its nominal time point was tested by using Log Rank test, and its Kaplan-Meier plot was provided.

The null hypotheses for the secondary endpoints were only tested if the null hypothesis for the primary efficacy endpoint was rejected. A fixed-sequence testing method was employed to address the multiplicity issue for multiple secondary efficacy endpoints. The order in which the null hypotheses were tested was predetermined as below for all secondary efficacy endpoints:

1. Time to haemostasis.

2. Cumulative proportion of subjects having achieved haemostasis at the TBS by T5.

3. Cumulative proportion of subjects having achieved haemostasis at the TBS by T7.

4. Cumulative proportion of subjects having achieved haemostasis at the TBS by T10.

Each subsequent hypothesis was tested only if all previously tested null hypotheses were rejected at a 2-sided significance level of 5%.

Missing Data

If an observation was missing at a specific scheduled visit/time point, the value at that visit was not imputed and was set to missing. Haemostasis assessment was an exception. A missing haemostasis assessment at a time point was deemed not to have achieved haemostasis at that specific time point only.

Results

Participant flow

Preliminary Part

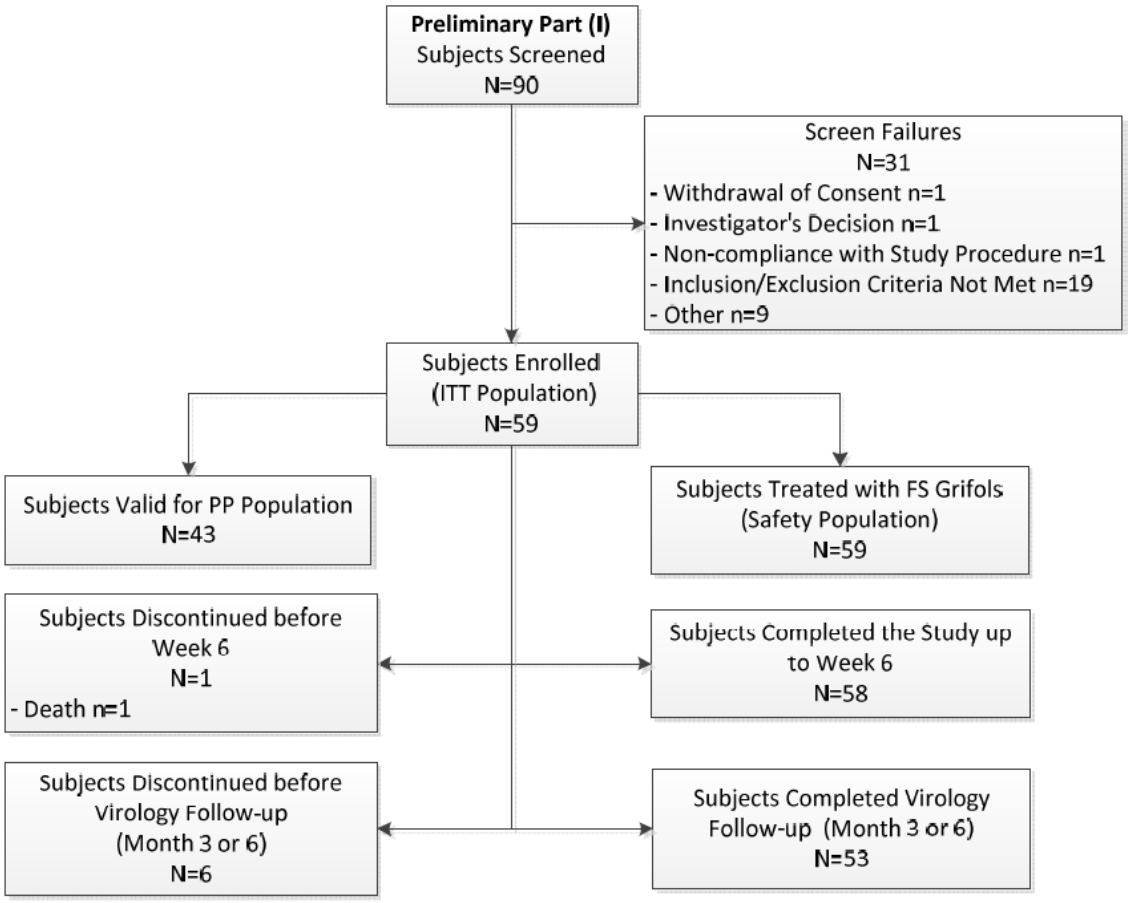

Figure 10-1 Disposition of Subjects during Preliminary Part (I)

Primary Part

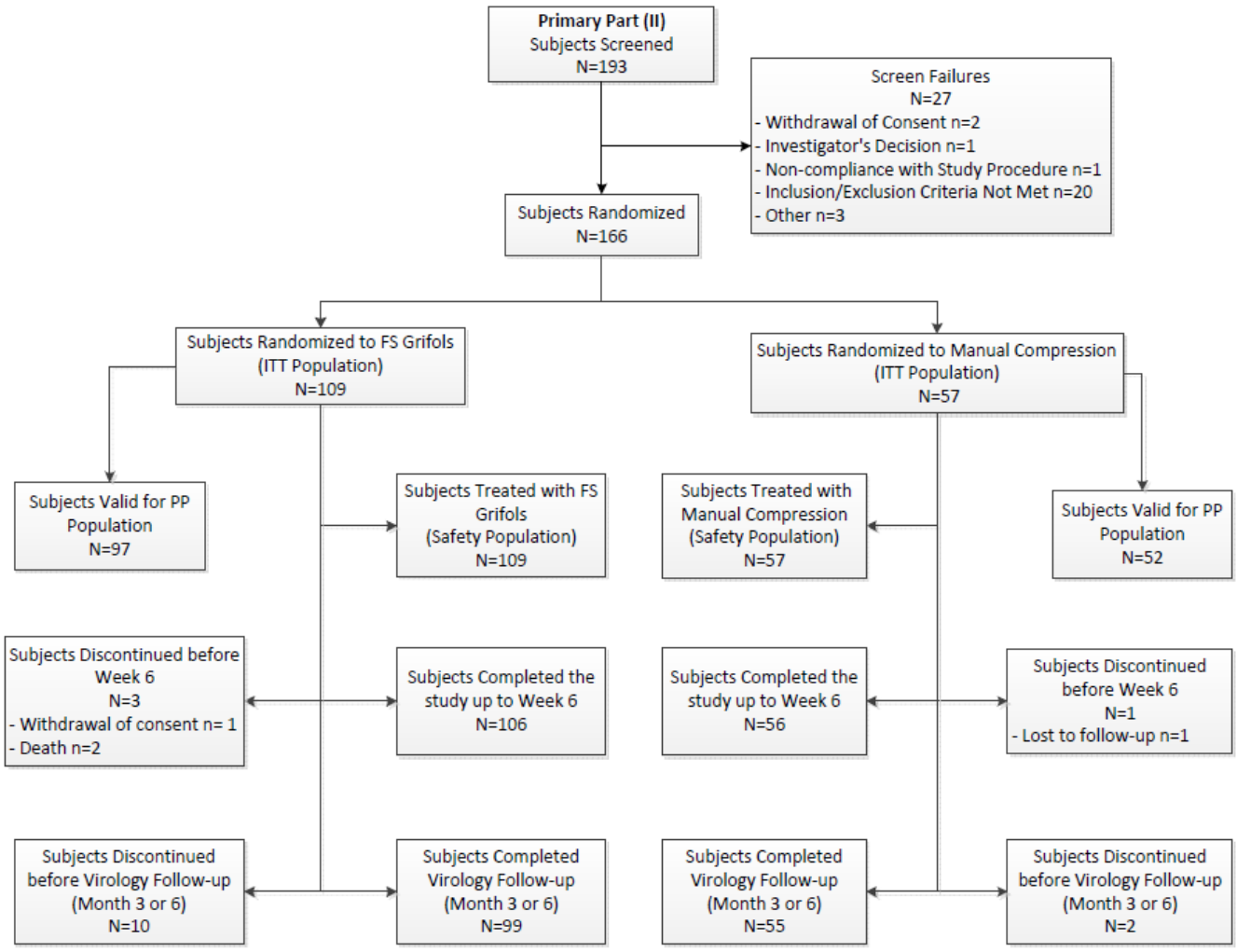

Figure 10-2 Disposition of Subjects during Primary Part (II)

Recruitment

Studied Period (years): approximately 3.3 years

(date of first enrolment) 02 Aug 2012

(date of last completed) 26 Dec 2015

Conduct of the study

8 **protocol amendments** occurred during the study, which mainly updated requirements with regard to paediatric subjects, introduced new eligible surgery procedures or clarified laboratory tests or visits to be done.

Table 3: Protocol Violations

Characteristics	Preliminary Part (I) FS Grifols (N=59) n (%)	Primary Part (II) FS Grifols (N=109) n (%)	Primary Part (II) Manual Compression (N=57) n (%)	Part (I) + Part (II) FS Grifols (N=168) n (%)	Total[a] (N=225) n (%)
Subjects without any protocol deviations	13 (22.0)	20 (18.3)	13 (22.8)	33 (19.6)	46 (20.4)
Subjects with at least one protocol deviation[b]	46 (78.0)	89 (81.7)	44 (77.2)	135 (80.4)	179 (79.6)
Subjects without any major protocol deviations	28 (47.5)	71 (65.1)	40 (70.2)	99 (58.9)	139 (61.8)
Subjects with at least one major protocol deviation[b]	31 (52.5)	38 (34.9)	17 (29.8)	69 (41.1)	86 (38.2)
Type of major protocol deviations[b]					
Inclusion criteria	4 (6.8)	4 (3.7)	1 (1.8)	8 (4.8)	9 (4.0)
Exclusion criteria	0	1 (0.9)	1 (1.8)	1 (0.6)	2 (0.9)
Study treatment	12 (20.3)	10 (9.2)	3 (5.3)	22 (13.1)	25 (11.1)
Assessment safety	12 (20.3)	9 (8.3)	4 (7.0)	21 (12.5)	25 (11.1)
Assessment efficacy	7 (11.9)	3 (2.8)	1 (1.8)	10 (6.0)	11 (4.9)
Informed consent	5 (8.5)	15 (13.8)	8 (14.0)	20 (11.9)	28 (12.4)
Other	2 (3.4)	2 (1.8)	3 (5.3)	4 (2.4)	7 (3.1)

[a] Total includes all subjects from both treatments in Preliminary Part (I) and Primary Part (II).

[b] Protocol deviations are not mutually exclusive.

Table 4: Baseline data

Characteristics	Preliminary Part (I) FS Grifols (N=59) n (%)	Primary Part (II) FS Grifols (N=109) n (%)	Primary Part (II) Manual Compression (N=57) n (%)	Part (I) + Part (II) FS Grifols (N=168) n (%)	Total[a] (N=225) n (%)
Sex - n (%)					
Male	41 (69.5)	76 (69.7)	31 (54.4)	117 (69.6)	148 (65.8)
Female	18 (30.5)	33 (30.3)	26 (45.6)	51 (30.4)	77 (34.2)
Age (years)					
Mean (SD)	63.53 (9.343)	63.72 (8.908)	62.04 (10.734)	63.65 (9.036)	63.24 (9.496)
Median	64.00	64.00	61.00	64.00	63.00
Min, Max	41.0, 82.0	44.0, 84.0	22.0, 82.0	41.0, 84.0	22.0, 84.0
Age Category (years) – n (%)					
≤11	0	0	0	0	0
12-17	0	0	0	0	0
18-64	32 (54.2)	58 (53.2)	32 (56.1)	90 (53.6)	122 (54.2)
≥65	27 (45.8)	51 (46.8)	25 (43.9)	78 (46.4)	103 (45.8)
65-84	27 (45.8)	51 (46.8)	25 (43.9)	78 (46.4)	103 (45.8)
≥85	0	0	0	0	0
Ethnicity - n (%)					
Hispanic or Latino	3 (5.1)	3 (2.8)	2 (3.5)	6 (3.6)	8 (3.6)
Not Hispanic or Latino	56 (94.9)	106 (97.2)	55 (96.5)	162 (96.4)	217 (96.4)
Race – n (%)					
White (Caucasian)	44 (74.6)	101 (92.7)	49 (86.0)	145 (86.3)	194 (86.2)
Black or African American	13 (22.0)	6 (5.5)	8 (14.0)	19 (11.3)	27 (12.0)
Asian	0	2 (1.8)	0	2 (1.2)	2 (0.9)
Native Hawaiian or Other Pacific Islander	1 (1.7)	0	0	1 (0.6)	1 (0.4)
Multi-racial (no primary race)	1 (1.7)	0	0	1 (0.6)	1 (0.4)
Height (cm)					
Mean (SD)	170.7 (9.31)	170.6 (9.50)	167.3 (7.75)	170.7 (9.41)	169.8 (9.12)
Median	173.0	170.0	169.0	171.0	170.0
Min, Max	150, 188	152, 195	152, 184	150, 195	150, 195
Weight (kg)					
Mean (SD)	79.6 (16.66)	77.2 (17.00)	73.6 (14.99)	78.1 (16.87)	76.9 (16.49)
Median	79.0	76.0	74.0	77.0	77.0

Characteristics	Preliminary Part (I)	Primary Part (II)		Part (I) + Part (II)	
	FS Grifols (N=59) n (%)	FS Grifols (N=109) n (%)	Manual Compression (N=57) n (%)	FS Grifols (N=168) n (%)	Total[a] (N=225) n (%)
Min, Max	50, 118	41, 130	46, 116	41, 130	41, 130
Type of Surgery – n (%)					
Aorto-Femoral Bypass Grafting	2 (3.4)	5 (4.6)	1 (1.8)	7 (4.2)	8 (3.6)
Aorto-Iliac Bypass Grafting	0	2 (1.8)	1 (1.8)	2 (1.2)	3 (1.3)
Axillo-Femoral Bypass Grafting	3 (5.1)	4 (3.7)	1 (1.8)	7 (4.2)	8 (3.6)
Femoral-Distal Bypass Grafting	0	2 (1.8)	0	2 (1.2)	2 (0.9)
Femoral-Femoral Bypass Grafting	8 (13.6)	6 (5.5)	4 (7.0)	14 (8.3)	18 (8.0)
Femoral-Popliteal Bypass Grafting	29 (49.2)	53 (48.6)	31 (54.4)	82 (48.8)	113 (50.2)
Ilio-Femoral Bypass Grafting	4 (6.8)	20 (18.3)	8 (14.0)	24 (14.3)	32 (14.2)
Ilio-Iliac Bypass Grafting	0	2 (1.8)	0	2 (1.2)	2 (0.9)
Ilio-Popliteal Bypass Grafting	0	1 (0.9)	1 (1.8)	1 (0.6)	2 (0.9)
Upper Extremity Vascular Access For Hemodialysis (Arteriovenous Graft Formation)	13 (22.0)	14 (12.8)	10 (17.5)	27 (16.1)	37 (16.4)

[a] Total includes all subjects from both treatments in Preliminary Part (I) and Primary Part (II).

Table 5: Numbers analysed

Subject Disposition	Preliminary Part (I)	Primary Part (II)		Part (I) + Part (II)	
	FS Grifols n (%)	FS Grifols n (%)	Manual Compression n (%)	FS Grifols n (%)	Total[a]
Subjects screened	90	193		--	283
Subjects randomized (ITT Population)[b]	59	109	57	168	225
Subjects valid for Safety Population	59 (100.0)	109 (100.0)	57 (100.0)	168 (100.0)	225 (100.0)
Subjects valid for PP Population	43 (72.9)	97 (89.0)	52 (91.2)	140 (83.3)	192 (85.3)
Subjects completed the study up to Week 6	58 (98.3)	106 (97.2)	56 (98.2)	164 (97.6)	220 (97.8)
Subjects discontinued prematurely before Week 6	1 (1.7)	3 (2.8)	1 (1.8)	4 (2.4)	5 (2.2)
Withdrawal of consent	0	1 (0.9)	0	1 (0.6)	1 (0.4)
Lost to follow-up	0	0	1 (1.8)	0	1 (0.4)
Death	1 (1.7)	2 (1.8)	0	3 (1.8)	3 (1.3)
Subjects completed the study up to Virology Follow-up[c]	53 (89.8)	99 (90.8)	55 (96.5)	152 (90.5)	207 (92.0)
Subjects discontinued before Virology Follow-up[c]	6 (10.2)	10 (9.2)	2 (3.5)	16 (9.5)	18 (8.0)

[a] Total includes all subjects from both treatments in Preliminary Part (I) and Primary Part (II).

[b] In Preliminary Part (I), there was no randomization. All subjects enrolled were to be treated with FS Grifols.

[c] Virology Follow-up is either Month 3 or Month 6 visit.

Note: Percentages are based on the number of subjects in the ITT Population as the denominator.

Efficacy analysis was performed using the ITT population and data from the Primary Part (II) of the study.

Outcomes and estimation

Primary efficacy analysis of haemostasis

The primary efficacy analysis of haemostasis at the TBS by T4 based on nominal time points in the ITT population in the Primary Part (II) of the study is presented in Figure 11-1. The rate of haemostasis by T4 was 76.1% (83/109 subjects) in the FS Grifols treatment group and was 22.8% (13/57 subjects) in the MC treatment group.

Inferential analyses of the ratio and 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to MC was 3.339 (2.047, 5.445). The rate of haemostasis by T4 was statistically and significantly higher in the FS Grifols treatment group compared to the MC treatment group (p-value <0.001), indicating that FS Grifols is superior to MC and that the primary efficacy objective was achieved in the ITT population.

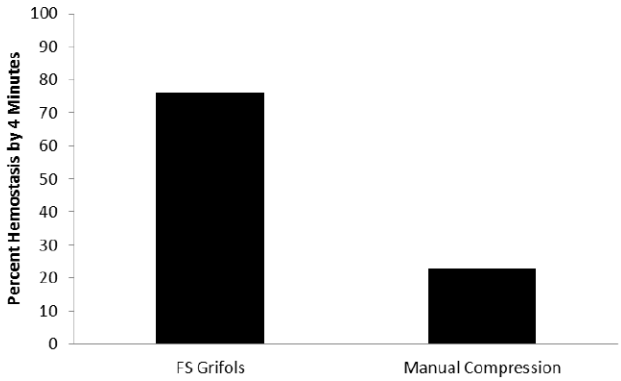

Figure 11-1 Analysis of Hemostasis by T_4 at Target Bleeding Site (ITT Population)

Source: Post-text Table 14.2.1/1

Analysis of the primary efficacy endpoint of haemostasis at the TBS by T4 in the PP population in the Primary Part (II) of the study is presented in Figure 11-2. Similar to the ITT population, the rate of haemostasis by T4 was 77.3% (75/97 subjects) in the FS Grifols treatment group and was 23.1% (12/52 subjects) in the MC treatment group.

Inferential analyses of the ratio and 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to MC was 3.351 (2.016, 5.567). The rate of haemostasis by T4 was statistically and significantly higher in the FS Grifols treatment group compared to the MC treatment group (p-value <0.001), indicating that FS Grifols is superior to MC and that the primary efficacy objective was achieved in the PP population.

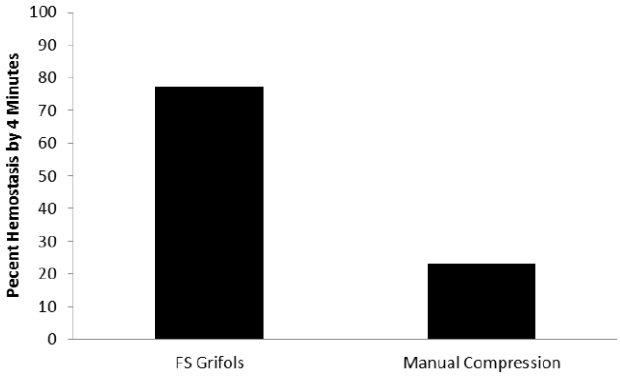

Figure 11-2 Analysis of Hemostasis by T_4 at Target Bleeding Site (PP Population)

Source: Post-text Table 14.2.1/2

Sensitivity Analysis

A sensitivity analysis of haemostasis at the TBS based on the exact (actual) assessment time at the first and last haemostatic assessment selected within the time window was performed. For the primary efficacy endpoint of haemostasis by T4, the results were the same for when the first and last haemostatic assessment was selected, and they were similar to those of the primary efficacy analysis using the nominal assessment time.

The rate of haemostasis by T4 was 75.2% (82/109 subjects) in the FS Grifols treatment group and was 22.8% (13/57 subjects) in the MC treatment group. Inferential analyses of the ratio and 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to MC was 3.299 (2.022, 5.382). The rate of haemostasis by T4 was statistically and significantly higher in the FS Grifols treatment group compared to the MC treatment group (p-value <0.001), demonstrating that FS Grifols is superior to MC and supporting the primary efficacy endpoint.

Secondary Efficacy Analyses of Haemostasis

Time to Haemostasis

Table 6: Analysis of Time to Hemostasis at Target Bleeding Site (ITT Population)

	Primary Part (II)		
Statistics	FS Grifols N=109	Manual Compression N=57	P-value[a]
Mean (SE)	5.1 (0.21)	8.2 (0.35)	<0.001
Q25	4.0	5.0	
Median (95% CI)	4.0 (NA, NA)	NA (10.00, NA)	
Q75	4.0	NA	

Note: Time to hemostasis was measured in minutes

[a] P-value was calculated from Log-rank test.

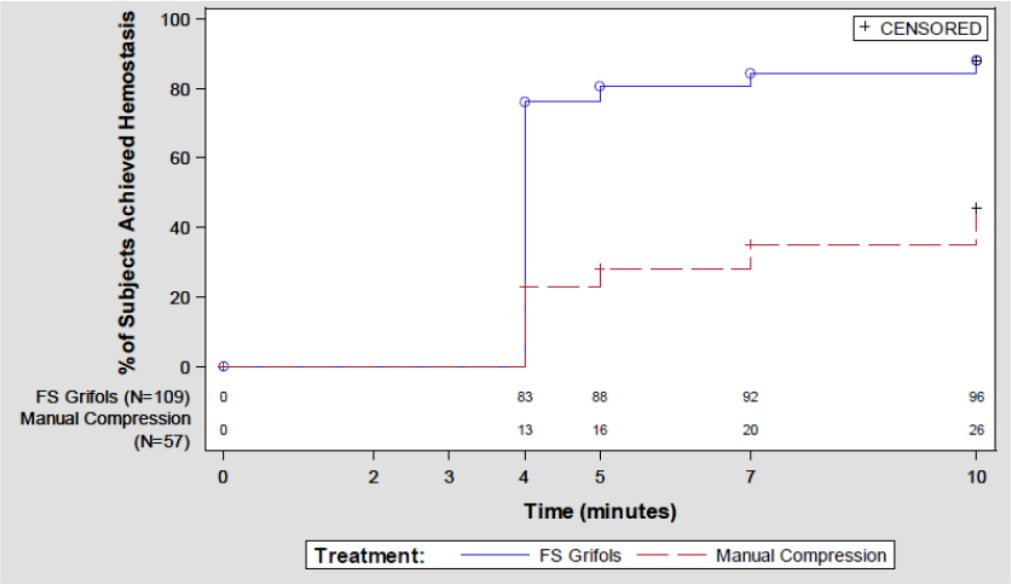

Figure 11-3 Time to Hemostasis at Target Bleeding Site (ITT Population)

Source: Post-text Figure 14.2.1

In the Preliminary Part (I) of the study, the median (95% CI) TTH in the FS Grifols treatment group was 4.0 (4.00, 7.00) minutes. An identical median (95% CI) TTH was observed with the analysis of TTH in actual clock time at the TBS.

Table 7: Cumulative Proportion of Subjects Achieving Haemostasis at the Target Bleeding Site by T5, T7, and T10

	Primary Part (II)			
	FS Grifols N=109 n (%)	Manual Compression N=57 n (%)	RR (95% CI)[a]	P-value[b]
Hemostasis by 5 minutes	88 (80.7)	16 (28.1)	2.876 (1.879, 4.402)	<0.001
Hemostasis by 7 minutes	92 (84.4)	20 (35.1)	2.406 (1.675, 3.455)	<0.001
Hemostasis by 10 minutes	96 (88.1)	26 (45.6)	1.931 (1.442, 2.585)	<0.001

[a] RR was the ratio of proportion of subjects meeting the efficacy endpoint in the two treatment groups in Primary Part (II) (FS Grifols relative to MC).

[b] P-value was calculated from Fischer Exact Test.

Table 8: Analysis of Hemostasis by Each Time Point at Target Bleeding Site (TBS) Population: Intent-to-Treat

	Preliminary Part (I)	Primary Part (II)			
	FS Grifols (N=59) n (%)	FS Grifols (N=109) n (%)	Manual Compression (N=57) n (%)	RR (95% CI) [1]	P-value [2]
Primary Efficacy Endpoint					
Hemostasis by 4 Minutes	33 (55.9)	83 (76.1)	13 (22.8)	3.339 (2.047, 5.445)	<0.001
Secondary Efficacy Endpoints					
Hemostasis by 5 Minutes	36 (61.0)	88 (80.7)	16 (28.1)	2.876 (1.879, 4.402)	<0.001
Hemostasis by 7 Minutes	37 (62.7)	92 (84.4)	20 (35.1)	2.406 (1.675, 3.455)	<0.001
Hemostasis by 10 Minutes	41 (69.5)	96 (88.1)	26 (45.6)	1.931 (1.442, 2.585)	<0.001

Treatment Failures

The rate of treatment failure was statistically and significantly lower (p-value <0.001) in the FS Grifols treatment group (26/109 [23.9%] subjects) compared to the MC treatment group (44/57 [77.2%] subjects).

In the FS Grifols treatment group, the most common cause of treatment failure was persistent bleeding (22.9%, 25/109 subjects). Of the 26 subjects with treatment failure in the FS Grifols treatment group, 96.2% (25/26) of the subjects had persistent bleeding. In accordance with the protocol, no FS Grifols-treated subjects had treatment re-applied after T4 and before TClosure.

In the MC treatment group, the most common causes of treatment failure were persistent bleeding (77.2%, 44/57 subjects) and re-applied treatment after T4 and before TClosure (42.1%, 24/57 subjects). Of the 44 subjects with treatment failure in the MC treatment group, 44/44 (100.0%) subjects had persistent bleeding.

Table 9: Analysis of Treatment Failure at Target Bleeding Site (ITT Population)

	Primary Part (II)			
	FS Grifols N=109 n (%)	Manual Compression N=57 n (%)	RR (95% CI)[a]	P-value[b]
Treatment failure	26 (23.9)	44 (77.2)	0.309 (0.215, 0.445)	<0.001
Reason[c]				
Persistent bleeding	25 (22.9)	44 (77.2)		
Breakthrough bleeding	4 (3.7)	2 (3.5)		
Re-bleeding	1 (0.9)	3 (5.3)		
Use of alternative hemostatic treatment or maneuvers	2 (1.8)	6 (10.5)		
Re-applied treatment[d]	0	24 (42.1)		

[a] RR was the proportion of subjects meeting the efficacy endpoint in the two treatment groups in Primary Part (II) (FS Grifols relative to Manual Compression).

[b] P-value was calculated from Fisher Exact Test.

[c] The reasons were not mutually exclusive.

[d] For the MC treatment group only, treatment could be reapplied beyond T_4 and until the completion of the surgical closure, but would be considered a treatment failure.

In the Preliminary Part (I) of the study, the rate of treatment failure in the FS Grifols treatment group was 44.1% (26/59 subjects). The most common causes of treatment failure were persistent bleeding (39.0%, 23/59 subjects) and use of alternative haemostatic treatment or manoeuvres (25.4%, 15/59 subjects).

Ancillary analyses

In the subgroup analyses of the primary efficacy endpoint, study centres, age group, surgery type, and gender were used as stratifying variables in order to control for the effect of these covariates. The primary efficacy variable was analysed using the CMH test stratified by these covariates, respectively, providing the p-value along with the pooled estimate of the ratio of proportion of subjects meeting the primary efficacy endpoint and its 95% CI.

Table 10: Analysis of Hemostasis by T_4 at Target Bleeding Site Stratified by Investigational Study Centres (ITT Population)

Study Center	Primary Part (II)			
	FS Grifols n/N (%)	Manual Compression n/N (%)	RR (95% CI)[a]	P-Value[b]
Hemostasis by 4 minutes			3.325 (2.041, 5.418)	<0.001
Pooled sites[c]	16/25 (64.0)	2/13 (15.4)		
100	3/5 (60.0)	1/3 (33.3)		
148	7/9 (77.8)	1/4 (25.0)		
500	17/19 (89.5)	3/10 (30.0)		
501	4/8 (50.0)	1/5 (20.0)		
502	13/16 (81.3)	2/8 (25.0)		
521	23/27 (85.2)	3/14 (21.4)		

[a] Risk ratio (RR) was the estimated common ratio of the proportion of subjects meeting the efficacy endpoint in the two treatment groups in Primary Part (II) (FS Grifols relative to Manual Compression).

[b] P-value was calculated from Cochran-Mantel-Haenszel Test.

[c] All small sites, defined as <3 subjects in either treatment group of the Primary Part (II), were pooled together for efficacy analyses. Sites 119, 407, 544, 132, 402, 541, 543, 129, 139, 149, 522, and 102 were pooled (Post-text Table 14.1.1/2).

Source: Post-text Table 14.2.1/4

Table 11: Analysis of Hemostasis by T_4 at Target Bleeding Site Stratified by Age Group (ITT Population)

Age Group	Primary Part (II)			
	FS Grifols n/N (%)	Manual Compression n/N (%)	RR (95% CI)[a]	P-value[b]
Hemostasis by 4 minutes			3.349 (2.052, 5.464)	<0.001
18-64 years	45/58 (77.6)	8/32 (25.0)		
≥65 years	38/51 (74.5)	5/25 (20.0)		

[a] Risk ratio (RR) was the estimated common ratio of the proportion of subjects meeting the efficacy endpoint in the two treatment groups in Primary Part (II) (FS Grifols relative to Manual Compression).

[b] P-value was calculated from Cochran-Mantel-Haenszel Test.

Source: Post-text Table 14.2.1/3.2

Table 12: Analysis of Hemostasis by T_4 at Target Bleeding Site Stratified by Surgery Type (ITT Population)

Surgery Type	Primary Part (II) FS Grifols n/N (%)	Manual Compression n/N (%)	RR (95% CI)[a]	P-value[b]
Hemostasis by 4 minutes			3.197 (1.956, 5.227)	<0.001
Aorto-femoral bypass grafting	5/5 (100.0)	1/1 (100.0)		
Axillo-femoral bypass grafting	2/4 (50.0)	1/1 (100.0)		
Femoral-femoral bypass grafting	3/6 (50.0)	1/4 (25.0)		
Femoral-popliteal bypass grafting	42/53 (79.2)	6/31 (19.4)		
Ilio-femoral bypass grafting	18/20 (90.0)	0/8		
Upper extremity vascular access for hemodialysis (arteriovenous graft formation)	7/14 (50.0)	3/10 (30.0)		
Other surgeries pooled[c]	6/7 (85.7)	1/2 (50.0)		

[a] Risk ratio (RR) was the estimated common ratio of the proportion of subjects meeting the efficacy endpoint in the two treatment groups in Primary Part (II) (FS Grifols relative to Manual Compression).

[b] P-value was calculated from Cochran-Mantel-Haenszel Test.

[c] Surgery types with <3 subjects in either treatment group in Primary Part (II) were pooled together (surgeries included aorto-iliac bypass grafting, femoral-distal bypass grafting, ilio-iliac bypass grafting, ilio-popliteal bypass grafting).

Source: Post-text Table 14.2.1/3.1

Table 13: Analysis of Hemostasis by T_4 at Target Bleeding Site Stratified by Gender (ITT Population)

	Primary Part (II) FS Grifols n/N (%)	Manual Compression n/N (%)	RR (95% CI)[a]	P-value[b]
Hemostasis by 4 minutes			3.514 (2.093, 5.899)	<0.001
Male	59/76 (77.6)	4/31 (12.9)		
Female	24/33 (72.7)	9/26 (34.6)		

[a] Risk ratio (RR) was the estimated common ratio of the proportion of subjects meeting the efficacy endpoint in the two treatment groups in Primary Part (II) (FS Grifols relative to Manual Compression).

[b] P-value was calculated from Cochran-Mantel-Haenszel Test.

Source: Post-text Table 14.2.1/3.3

Summary of main studies

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 14 Summary of efficacy for trial IG1101

Title: A Prospective, Single-blind, Randomized, Phase JJI Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis during Peripheral Vascular Surgery	
Study identifier	IG1101

Design	This trial consists of 2 parts: a Preliminary Part (I) and a Primary Part (II). Preliminary Part (I): All subjects enrolled in the Preliminary Part (I) were treated with FS Grifols. The main objective of this part of the trial was to ensure that local study teams familiarized themselves with the technique of FS Grifols application and with the intra-operative procedures required by the protocol. For each study center participating in the study, the first 2 subjects were to be enrolled in the Preliminary Part (I). Primary Part (II): Subjects in this part were randomly allocated in a 2:1 ratio to treatment with FS Grifols or manual compression (MC). The two main objectives of this part were as follows: 1) Assessment of the safety of FS Grifols. 2) Assessment of the efficacy of FS Grifols.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Intraoperatively: 10 minutes; Post-Operative assessments were performed on Days 1, 2, 3, 7, 14, and Week 6. Viral safety follow-up at month 4 (earlier protocol versions: month 6) not applicable not applicable
Hypothesis	Superiority		
Treatments groups	FS Grifols preliminary		N=59
	FS Grifols primary		N=109
	Manual Compression		N=57
Endpoints and definitions	Primary endpoint	Haemostasis at T4	Proportion of subjects in the Primary Part (II) of the study achieving haemostasis (Yes/No) at the TBS by T4 without occurrence of re-bleeding and reapplication of study treatment after T4 and until TClosure and without brisk bleeding and use of alternative haemostatic treatment after TStart and until TClosure.
	Secondary	TTH	Time to Haemostasis
	Secondary	T5 T7 T10	Cumulative Proportion of Subjects Achieving Haemostasis at the Target Bleeding Site by Each of the Following Time Points: T5, T7, and T10
	Secondary	Treatment Failure	Treatment Failures

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	FS Grifols preliminary	FS Grifols primary	Manual Compression
	Number of subject	59	109	57

	Haemostasis at T4	55.9% (33/59)	76.1% (83/109)	22.8% (13/57)
	TTH median	4.0	4.0	NA (≥10.0)
	95% CI	4.00, 7.00	NA, NA	10.00, NA
	Haemostasis by T5	61.0% (n=36)	80.7% (n=88)	28.1% (n=16)
	Haemostasis by T7	62.7% (n=37)	84.4% (n=92)	35.1% (n=20)
	Haemostasis by T10	69.5% (n=41)	88.1% (n=96)	45.6% (n=26)
	Treatment Failure	44.1% (n=26)	23.9% (n=26)	77.2% (n=44)
Effect estimate per comparison	Primary endpoint Haemostasis at T4	FS Grifols primary vs. Manual Compression		
		RR	3.339	
		95% CI	2.047, 5.445	
		P-value	<0.001	
	Secondary endpoint Treatment Failure	FS Grifols primary vs. Manual Compression		
		RR	0.309	
		95% CI	0.215, 0.445	
		P-value	<0.001	

Study IG1102: A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis During Parenchymous Tissue Open Surgeries

Methods

This clinical study consisted of 2 parts: a Preliminary Part (I) and a Primary Part (II).

Subjects in the Preliminary Part (I) were to be randomized in 1:1 ratio into 1 of 2 treatment groups: FS Grifols or Surgicel. The main objective of this part of the clinical study was to ensure that local study teams familiarized themselves with the technique for FS Grifols application and with intra-operative procedures required by the protocol of the clinical study. In addition, safety and efficacy data were collected from the subjects participating in the Preliminary Part (I) of the study. Efficacy data from subjects enrolled in the Preliminary Part (I) of the study were reviewed to verify the sample size assumptions for the Primary Part (II) of the study. For each study centre participating in the study, the first 4 subjects were to be enrolled in the Preliminary Part (I).

Subjects in the Primary Part (II) were to be randomized in 1:1 ratio into FS Grifols or Surgicel treatment groups. This part of the clinical study had 2 main objectives: (1) to assess the safety of FS Grifols and (2) to assess the efficacy of FS Grifols. For each study centre, the Primary Part (II) of the study was to start only after enrolment of 4 subjects in the Preliminary Part (I).

In both parts of the clinical study, subjects undergoing an elective (non-emergency), open (non-laparoscopic) parenchymous tissue surgical procedure, wherein a target bleeding site (TBS) was identified and a topical haemostat was indicated, were initially eligible to participate. A specific bleeding area/site was defined as the TBS when it was determined by the investigator (the surgeon) that control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) was ineffective or impractical and required an adjunct treatment to achieve haemostasis.

When the TBS was identified, the investigator was to rate the intensity of the bleeding at the TBS and the approximate size of the bleeding surface according to a 3-point scale (mild, moderate, severe for the intensity of the bleeding and small, medium, large for the bleeding surface). In both parts of the study, only subjects with a TBS with bleeding of moderate intensity could be enrolled as detailed in Intra-operative inclusion criteria 6.

- **Study participants**

Inclusion Criteria

Trial IG1102

Male or female patients of any age were eligible for the study if they fulfilled the following criteria:

1. Signed the written ICF, or the subject's parent or legal guardian signed the ICF and Subject Authorization Form where applicable. Paediatric subjects, as defined by local regulations, were asked to sign an age-appropriate assent form.

4. Must have had haemoglobin (Hgb) ≥ 9.0 g/dL. Following the incorporation of Protocol Versions 5.0 and 5.1 (both dated 16 Dec 2014), the Hgb levels criterion was decreased from ≥ 9.0 g/dL to ≥ 8.0 g/dL at baseline (within 24 hours prior to surgical procedure) to allow the enrollment of subjects with lower Hgb levels.

5. Required an elective (non-emergency), open (non-laparoscopic) hepatic resection (wedge or anatomic resections of at least one anatomical hepatic segment, or equivalent tissue volume) procedure where the TBS was identified on cut raw liver surface (resection area).

6. Intra-operative inclusion criteria:

a. A TBS (parenchymous: raw cut liver surface bleeding) could be identified according to the investigator's judgment, and the approximate size of the TBS was rated by the investigator (the surgeon) using a 3-point scale:

- Small: TBS ≤ 10 cm2.
- Medium: 10 cm2 <TBS ≤ 100 cm2.
- Large: TBS >100 cm2.

b. The TBS had a moderate bleeding according to the investigator's judgment.

- Following the incorporation of Protocol Version 2.0 (dated 16 Jul 2012), subjects with a mild bleeding TBS were excluded (i.e. no subjects were enrolled in the study with a mild bleed).

c. The intensity of the bleeding at the TBS was rated by the investigator using a predefined 3-point scale.

- Mild: oozing and capillary.

- Moderate: gradual and steady.
- Severe: brisk and forceful.

Exclusion Criteria

Patients were excluded from the study if one of the following criteria applied:

1. Required hepatic resection due to trauma.

2. Had an infection in the anatomic surgical area.

3. Had a history of severe (eg, anaphylactic) reactions to blood or to any blood-derived (human or animal) product.

4. Had previous known sensitivity to any FS Grifols component or any Surgicel component.

5. Had known (documented) previous exposure to thrombin-containing (bovine, human or recombinant) products. Following the incorporation of Protocol Version 3.0 (dated 23 Aug 2013), this exclusion was removed.

6. Were unlikely to adhere to the protocol requirements or to be cooperative during the study conduct.

7. Females who were pregnant or nursing a child. Following the incorporation of Protocol Version 3.0, clarification was provided for this exclusion. Females who were pregnant or nursing a child at baseline (within 24 hours prior to surgical procedure) were excluded from the study.

8. Were receiving an organ transplant during the same surgical procedure.

9. Were undergoing another concurrent major surgical intervention beyond the liver. Following the incorporation of Protocol Version 4.0, clarification was provided for this exclusion. Concurrent interventions on the pancreas, gall bladder, bile duct, or intestines were allowed.

10. Were currently participating or had participated in another clinical study in the context of which they had received investigational drug or device within 3 months from the Screening Visit or were scheduled to participate during the course of this study.

11. Had undergone a therapeutic surgical procedure within 30 days from the Screening Visit.

12. Were previously enrolled in clinical studies with FS Grifols. Following the incorporation of Protocol Version 4.1 (dated 25 Mar 2014), subjects enrolled in Hungary could not have a known (documented) history of thrombophilia or IgA deficiency, as required by Hungary's national competent authority.

13. Intra-operative exclusion criteria:

    a. A TBS could not be identified according to the investigator's judgment.

    b. The TBS had mild or severe bleeding according to the investigator's judgment.

    c. Occurrence of major intra-operative complications that required resuscitation or deviation from the planned surgical procedure.

    d. Application of any topical haemostatic material on the resection surface of the liver prior to application of the study treatment.

- **Treatments**

Subjects were treated intra-operatively with FS Grifols or Surgicel.

FS Grifols is a 2-component frozen sterile FS solution manufactured and supplied by Instituto Grifols, S.A., Barcelona, Spain. FS Grifols is composed of frozen solutions of human fibrinogen and human thrombin with calcium chloride. Fibrinogen and thrombin solutions were supplied in separate type I glass syringes, each containing 3 mL frozen solution. Both fibrinogen and thrombin syringes were assembled on a syringe holder and sealed in a double plastic pouch (inner pouch and outer pouch). The syringe holder was a plastic device consisting of 1 syringe holder and 1 plunger link. This device allowed for the simultaneous application of equal amounts of fibrinogen and thrombin. The kit containing 6 mL of solution in total was packaged in a cardboard case.

For subjects randomized to the FS Grifols group, 3 kits of 6 mL (total volume) each were allotted for parenchymous tissue surgical procedures /soft tissue surgical procedures (18 mL of solution in total). The kits were available and ready for use in the operating room at the time of surgery, but the maximum total volume of FS Grifols allowed to be applied at the TBS was approximately 12 mL (equivalent to the full content of 2 FS Grifols kits).

Four units of applicator tips for spraying were available for each subject undergoing parenchymous organ surgery.

Any applicator tips clogged by the biologic mix should have been replaced.

In subjects randomized to the FS Grifols group, study drug was applied immediately after opening the randomization envelope. The initial volume of FS Grifols applied to the target surface area was sufficient to entirely cover the intended application area by a thin, even layer.

For every subject undergoing parenchymous organ surgery, FS Grifols was administered by spraying on the TBS surface.

Before application of FS Grifols to the TBS, the target area should have been as dry as possible. When FS Grifols was applied by spraying, the recommended distance between the spray applicator and the surface of the target area was 10 cm and the sterile gas pressure must have been regulated at a pressure of 15 psi (1 bar) to 25 psi (1.75 bar).

Surgicel 4” × 8” sheets for use in this clinical study were provided by Instituto Grifols, S.A. Surgicel is a sterile, absorbable, knitted fabric prepared by the controlled oxidation of regenerated cellulose. Each sheet of Surgicel was for single use only. Surgicel Original was supplied as knitted fabric strips in envelopes and stored according to manufacturer’s instructions (Surgicel package insert).

For subjects randomized to the Surgicel group, four 4” × 8” Surgicel Original sheets were allotted for parenchymous tissue surgical procedures. The sheets were available and ready for use in the operating room at the time of surgery.

- **Objectives**

The purpose of this study was to demonstrate that FS Grifols was both safe and effective in achieving haemostasis during parenchymous tissue open surgeries.

The efficacy objective of the study was to evaluate the haemostatic efficacy of FS Grifols in parenchymous tissue open surgeries.

The safety objectives of the study included clinical safety, virus safety, and immunogenicity.

- **Outcomes/endpoints**

Efficacy Variables

Efficacy variables and endpoints were identical for both studies.

For surgical procedures in both the Preliminary Part (I) and the Primary Part (II) of the clinical study, the data including haemostatic assessment when appropriate was collected and recorded at the following time points:

1. TStart.
2. T2.
3. T3.
4. T4.
5. T5.
6. T7.
7. T10.
8. TClosure.
9. TCompletion; it may or may not have coincided with TClosure.

Primary Efficacy Variable

The primary efficacy variable was the proportion of subjects in the Primary Part (II) of the study achieving haemostasis (Yes/No) at the TBS by T4 without occurrence of re-bleeding and re-application of study treatment after T4 and until TClosure and without brisk bleeding and use of alternative haemostatic treatment after TStart and until TClosure. Haemostasis was defined as an absence/cessation of bleeding at the TBS according to the investigator's (surgeon's) judgment, so that the surgical closure of the exposed field could be started. Re-bleeding was defined as bleeding from the TBS requiring further haemostatic intervention (eg, manual pressure) after haemostasis was previously achieved at the TBS.

Secondary Efficacy Variables

Time to Haemostasis

The TTH was measured from TStart to the achievement of haemostasis at the TBS, or to the end of the 10-minute observational period when haemostasis had not yet been achieved. In the latter case, the TTH was considered as censored at the end of the 10-minute observational period. The TTH was quantified in minutes according to its nominal time point. If the TBS re-bled but cessation of bleeding was again achieved at a later time point, the effective haemostatic time point was considered to be the time point when the cessation of rebleeding occurred. The TTH was the time from TStart to that last effective haemostatic time point.

The TTH was an incremental time. If haemostasis was not achieved at an assessment time point but was achieved at the next assessment time point, it was inferred that the true TTH was between the 2 assessment time points. Therefore, TTH, although not observed directly, was ascertained as falling into the following haemostatic time categories (HTCs):

- ≤ 2 minutes from TStart to haemostasis (HTC ≤ 2).
- >2 minutes to ≤ 3 minutes from TStart to haemostasis (HTC >2 to ≤ 3).
- >3 minutes to ≤ 4 minutes from TStart to haemostasis (HTC >3 to ≤ 4).
- >4 minutes to ≤ 5 minutes from TStart to haemostasis (HTC >4 to ≤ 5).
- >5 minutes to ≤ 7 minutes from TStart to haemostasis (HTC >5 to ≤ 7).
- >7 minutes to ≤ 10 minutes from TStart to haemostasis (HTC >7 to ≤ 10).

In addition, 1 non-haemostatic time category (NHTC) was defined:

• Persistent bleeding at TBS beyond the 10-minute observational period (more than 10 minutes from TStart) (NHTC >10).

If any of the following events occurred, the TTH was considered as censored at the end of the 10-minute observational period:

• Any brisk bleeding during the 10-minute observational period and until TClosure.

• Use of alternative haemostatic treatments or manoeuvres during the 10-minute observational period and until TClosure.

• Re-application of study treatment after T4 and until TClosure.

• Any re-bleeding after the 10-minute observational period and until TClosure.

Cumulative Proportion of Subjects Achieving Haemostasis at the Target Bleeding Site by Each of the Following Time Points: T2, T3, T5, T7, and T10

The cumulative proportion of subjects achieving haemostasis at the TBS by other time points (T2, T3, T5, T7, and T10) was defined as an absence/cessation of bleeding at the TBS by that time point without occurrence of re-bleeding, brisk bleeding, use of alternative haemostatic treatment, and re-application of study treatment after T4 and until TClosure.

Prevalence of Treatment Failures

The following cases were considered treatment failures:

• Persistent bleeding at the TBS beyond T4.

• The event of breakthrough (brisk and forceful) bleeding from the TBS that jeopardized subject safety according to the investigator's judgment at any moment during the 10-minute observational period and until TClosure.

• Re-bleeding at the TBS after the assessment of the primary efficacy endpoint at T4 and until TClosure.

• Use of alternative haemostatic treatments or manoeuvres (other than the study treatment) at the TBS during the 10-minute observational period and until TClosure or use of study treatment at the TBS beyond T4 and until TClosure.

In the event of breakthrough (brisk and forceful) bleeding that jeopardized subject safety according to the investigator's judgment at the TBS at any moment during the 10-minute observational period and until the completion of the surgical closure by layers of the exposed surgical field, the surgeon may have used any other haemostatic measures at his/her discretion if deemed necessary (use of FS Grifols or other plasma-derived haemostatic agents was not allowed in this case). In such a case, the subject was considered a treatment failure. The alternative treatment used was recorded in the subject's source documents and eCRF.

- **Sample size**

The sample size for the Primary Part (II) of the study was estimated to provide sufficient power to show non-inferiority of FS Grifols relative to Surgicel in the proportion of subjects achieving haemostasis by 4 minutes after the start of treatment application. Non-inferiority was defined in terms of the lower limit of a 2-sided 95% CI for the ratio of the response rates in the 2 randomized groups (FS Grifols relative to Surgicel) in the Primary Part (II) of the study. If this limit fell above 80%, then non-inferiority would be deemed to have been demonstrated. It was assumed that 60% of the Surgicel group and 65% of the FS Grifols group could be expected to exhibit haemostasis. It could be determined that with a 1:1 ratio, a total of 212 subjects (106 in FS Grifols and 106 in Surgicel) would provide 80% power. To allow for approximate 5% drop-out rate after randomization, a total of 224 subjects would be needed to be randomized in this part of the study.

- **Randomisation**

Subjects were randomized in 1:1 ratio into the FS Grifols or Surgicel treatment groups. All study centres were provided with sealed opaque envelopes containing a treatment group assignment. The first sequential, available randomization envelope was taken to the operating room.

- **Blinding (masking)**

Data from subjects participating in the Primary Part (II) of the study, including treatment assignment and accumulating efficacy data, were blinded from the sponsor, except for personnel from study drug supply groups.

- **Statistical methods**

The statistical analysis was performed according the Statistical Analysis Plan 2.0, dated Dec 04th, 2015 (IG1102) and Version 2.0, dated Aug 28th, 2015 (IG1103).

Analysis Data Sets

The ITT population included all subjects randomized to FS Grifols or Surgicel. The PP population included all subjects in the ITT population excluding any subject for whom there was at least 1 major protocol deviation that might have an impact on the primary efficacy assessment.

Primary Efficacy Analysis

The efficacy analysis was performed using the ITT population and data from the Primary Part (II) of the study only. Additionally, the primary efficacy endpoint of the proportion of subjects achieving haemostasis by 4 minutes at TBS was analyzed using the PP population.

The primary efficacy variable was the proportion of subjects achieving haemostasis by T4 based on its nominal scheduled time point at TBS and was analysed by providing the ratio of proportion of subjects meeting the primary efficacy endpoint in the 2 treatment groups (FS Grifols relative to Surgicel) and its 2-sided asymptotic 95% confidence interval (CI). The CI was calculated as:

Exp(log(RR) +/- Z(alpha/2) * sqrt((1-p1)/(n1*p1) + (1-p2)/(n2*p2)))

where p1 was the successful rate in the FS Grifols treatment group and p2 was the successful rate in the Surgicel treatment group, risk ratio (RR)=p1/p2. n1 was the number of subjects in FS Grifols treatment group and n2 was the number of subjects in Surgicel treatment group.

For the primary efficacy analysis, only the data from the Primary Part (II) of the study were used. FS Grifols would be deemed non-inferior to Surgicel if the lower limit of the 95% CI exceeded 0.8. If non-inferiority was established, superiority may have been additionally claimed if the 95% CI was entirely above 1.

Secondary Efficacy Analysis

Analyses relating to secondary efficacy variables, as the cumulative proportions of subjects achieving haemostasis at other individual assessment times (T2, T3, T5, T7, and T10), were also analyzed by providing the ratio of proportion of subjects meeting the secondary efficacy endpoints and its 95% CI for subjects in the Primary Part (II) of the study. The TTH quantified in minutes according to its nominal time point was tested by using the Log Rank test, and a Kaplan-Meier plot was provided.

The superiority for the secondary endpoints would have only been tested if the non-inferiority for the primary efficacy endpoint was demonstrated. For secondary efficacy endpoints, a fixed-sequence testing method was employed for handling the multiplicity issue to maintain the overall familywise alpha level at 0.05. Each subsequent hypothesis was tested only if the superiority for the previous comparisons was shown at a 2-sided significance level of 5%. The order in which the null hypotheses were tested was predetermined as below for the secondary efficacy variables:

1. Cumulative proportion of subjects having achieved haemostasis at the TBS by T3.

2. Time to haemostasis.

3. Proportion of subjects having achieved haemostasis at the TBS by T2.

Missing Data

If any missing haemostatic assessment at TBS at T4 for a randomized subject occurred, it was treated as non-haemostasis at TBS at T4.

Results

- **Participant flow**

Trial IG1102

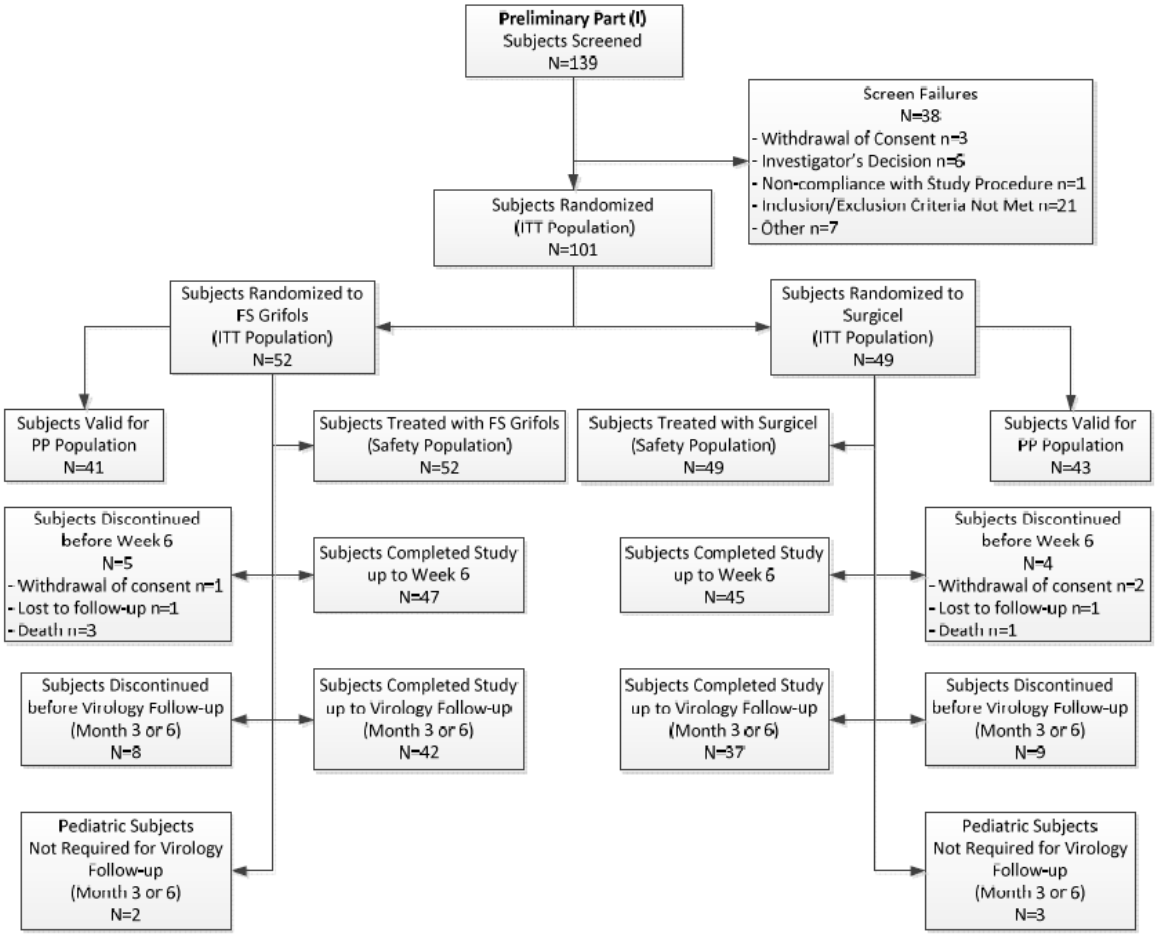

Figure 10-1 Disposition of Subjects during Preliminary Part (I)

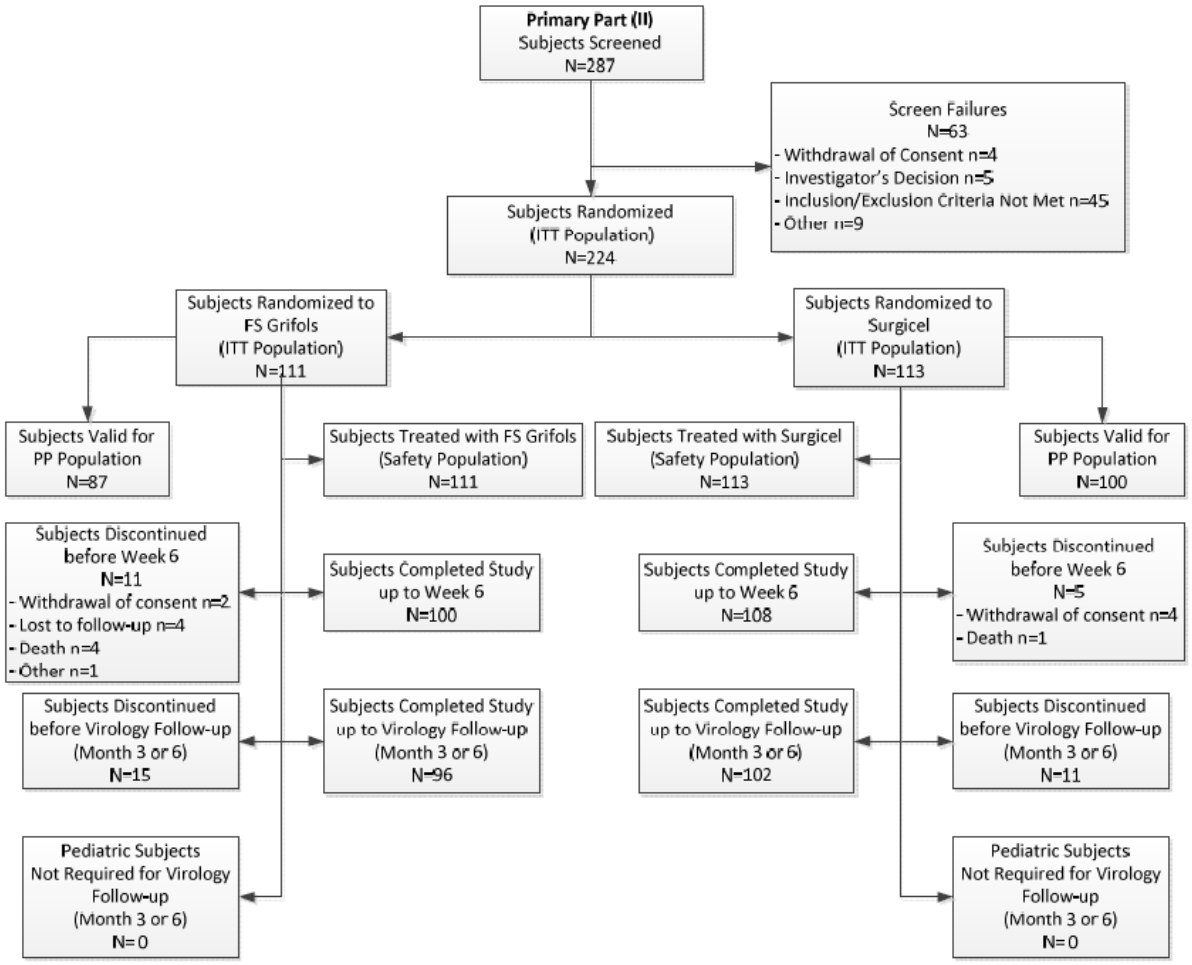

Figure 10-2 Disposition of Subjects during Primary Part (II)

- **Recruitment**

Trial IG1102

Study period: approximately 2.8 years

date of first enrolment: 22 Mar 2013

date of last completed: 28 Dec 2015

- **Conduct of the study**

Trial IG1102

Protocol Amendments

8 protocol amendments occurred during the study, which mainly clarified in- or exclusion criteria or procedures to be done during the study.

Protocol Deviations

Table 15: Protocol Deviations (ITT Population)

Characteristics	Preliminary Part (I)		Primary Part (II)		Part I + Part II		
	FS Grifols (N=52)	Surgicel (N=49)	FS Grifols (N=111)	Surgicel (N=113)	FS Grifols (N=163)	Surgicel (N=162)	Total[a] (N=325)
Subjects without any protocol deviations	12 (23.1)	7 (14.3)	34 (30.6)	40 (35.4)	46 (28.2)	47 (29.0)	93 (28.6)
Subjects with at least one protocol deviation	40 (76.9)	42 (85.7)	77 (69.4)	73 (64.6)	117 (71.8)	115 (71.0)	232 (71.4)
Subjects without any major protocol deviations	28 (53.8)	30 (61.2)	71 (64.0)	73 (64.6)	99 (60.7)	103 (63.6)	202 (62.2)
Subjects with at least one major protocol deviation	24 (46.2)	19 (38.8)	40 (36.0)	40 (35.4)	64 (39.3)	59 (36.4)	123 (37.8)
Type of major protocol deviations							
Inclusion criteria	1 (1.9)	2 (4.1)	1 (0.9)	3 (2.7)	2 (1.2)	5 (3.1)	7 (2.2)
Exclusion criteria	1 (1.9)	2 (4.1)	2 (1.8)	2 (1.8)	3 (1.8)	4 (2.5)	7 (2.2)
Study treatment	9 (17.3)	3 (6.1)	29 (26.1)	15 (13.3)	38 (23.3)	18 (11.1)	56 (17.2)
Assessment safety	14 (26.9)	12 (24.5)	13 (11.7)	14 (12.4)	27 (16.6)	26 (16.0)	53 (16.3)
Assessment efficacy	5 (9.6)	5 (10.2)	2 (1.8)	3 (2.7)	7 (4.3)	8 (4.9)	15 (4.6)
Visit Window	0	0	0	1 (0.9)	0	1 (0.6)	1 (0.3)
Informed consent (ICF)	3 (5.8)	1 (2.0)	6 (5.4)	5 (4.4)	9 (5.5)	6 (3.7)	15 (4.6)
Other	1 (1.9)	2 (4.1)	1 (0.9)	0	2 (1.2)	2 (1.2)	4 (1.2)

[a] Total includes all subjects from both treatment groups in the Preliminary Part (I) and the Primary Part (II).

- **Baseline data**

Table 16: Demographics (ITT Population)

Characteristics	Preliminary Part (I)		Primary Part (II)		Part I + Part II		
	FS Grifols (N=52)	Surgicel (N=49)	FS Grifols (N=111)	Surgicel (N=113)	FS Grifols (N=163)	Surgicel (N=162)	Total[a] (N=325)
Sex - n (%)							
Male	26 (50.0)	22 (44.9)	59 (53.2)	63 (55.8)	85 (52.1)	85 (52.5)	170 (52.3)
Female	26 (50.0)	27 (55.1)	52 (46.8)	50 (44.2)	78 (47.9)	77 (47.5)	155 (47.7)
Age (years)							
Mean (SD)	56.58 (16.464)	55.49 (18.429)	59.87 (12.222)	57.71 (13.595)	58.82 (13.753)	57.04 (15.194)	57.93 (14.494)
Median	61.00	62.00	61.00	61.00	61.00	61.00	61.00
Min, Max	6.0, 83.0	1.0, 82.0	25.0, 82.0	19.0, 84.0	6.0, 83.0	1.0, 84.0	1.0, 84.0
Age Category (years) – n (%)							
≤11	2 (3.8)	1 (2.0)	0	0	2 (1.2)	1 (0.6)	3 (0.9)
<2 (28 days-23 months)	0	1 (2.0)	0	0	0	1 (0.6)	1 (0.3)
2-11	2 (3.8)	0	0	0	2 (1.2)	0	2 (0.6)
12-17	0	2 (4.1)	0	0	0	2 (1.2)	2 (0.6)
18-64	30 (57.7)	25 (51.0)	70 (63.1)	76 (67.3)	100 (61.3)	101 (62.3)	201 (61.8)
≥65	20 (38.5)	21 (42.9)	41 (36.9)	37 (32.7)	61 (37.4)	58 (35.8)	119 (36.6)
65-84	20 (38.5)	21 (42.9)	41 (36.9)	37 (32.7)	61 (37.4)	58 (35.8)	119 (36.6)
≥85	0	0	0	0	0	0	0
Ethnicity - n (%)							
Hispanic or Latino	1 (1.9)	2 (4.1)	5 (4.5)	7 (6.2)	6 (3.7)	9 (5.6)	15 (4.6)
Not Hispanic or Latino	51 (98.1)	47 (95.9)	106 (95.5)	105 (92.9)	157 (96.3)	152 (93.8)	309 (95.1)
Not specified	0	0	0	1 (0.9)	0	1 (0.6)	1 (0.3)
Race – n (%)							
White (Caucasian)	44 (84.6)	42 (85.7)	106 (95.5)	103 (91.2)	150 (92.0)	145 (89.5)	295 (90.8)
Black or African American	2 (3.8)	4 (8.2)	1 (0.9)	2 (1.8)	3 (1.8)	6 (3.7)	9 (2.8)
Asian	6 (11.5)	1 (2.0)	4 (3.6)	6 (5.3)	10 (6.1)	7 (4.3)	17 (5.2)
American Indian or Alaskan Native	0	0	0	1 (0.9)	0	1 (0.6)	1 (0.3)
Multi-racial (no primary race)	0	1 (2.0)	0	0	0	1 (0.6)	1 (0.3)
Other	0	1 (2.0)	0	0	0	1 (0.6)	1 (0.3)
Not Specified	0	0	0	1 (0.9)	0	1 (0.6)	1 (0.3)
Height (cm)							
Mean (SD)	167.2 (12.40)	167.4 (15.37)	169.6 (9.17)	170.2 (9.26)	168.8 (10.33)	169.4 (11.48)	169.1 (10.90)
Median	168.0	170.0	170.0	170.0	168.0	170.0	170.0
Min, Max	118, 189	83, 188	152, 190	147, 195	118, 190	83, 195	83, 195
Weight (kg)							
Mean (SD)	77.3 (21.94)	77.9 (19.07)	77.4 (14.80)	78.5 (17.08)	77.3 (17.33)	78.3 (17.65)	77.8 (17.47)
Median	73.5	79.0	77.0	77.0	75.0	78.0	77.0
Min, Max	25, 137	12, 120	46, 113	51, 135	25, 137	12, 135	12, 137

Characteristics	Preliminary Part (I)		Primary Part (II)		Part I + Part II		
	FS Grifols (N=52)	Surgicel (N=49)	FS Grifols (N=111)	Surgicel (N=113)	FS Grifols (N=163)	Surgicel (N=162)	Total[a] (N=325)
TBS size – n (%)							
Small (≤10 cm^2)	17 (32.7)	23 (46.9)	10 (9.0)	13 (11.5)	27 (16.6)	36 (22.2)	63 (19.4)
Medium (>10 and ≤100 cm^2)	32 (61.5)	24 (49.0)	93 (83.8)	94 (83.2)	125 (76.7)	118 (72.8)	243 (74.8)
Large (>100 cm^2)	3 (5.8)	2 (4.1)	8 (7.2)	6 (5.3)	11 (6.7)	8 (4.9)	19 (5.8)

[a] Total includes all subjects from both treatments in Preliminary Part (I) and Primary Part (II).

Medical History Findings

Findings in medical history were reported for 98.8% (161/163) of the subjects randomized to FS Grifols in Part I + Part II and in 98.1% (159/162) of the subjects randomized to Surgicel in Part I + Part II. Overall, the patterns of these findings were quite diverse but similar between the FS Grifols and Surgicel treatment groups. The most frequent findings that were reported in ≥ 15% of the subjects in the FS Grifols treatment group in Part I + Part II were hypertension (61.3%, 100/163 subjects), gastro-oesophageal reflux disease (19.0%, 31/163 subjects), drug hypersensitivity (19.0%, 31/163 subjects), and metastases to liver (17.2%, 28/163 subjects).

Similarly, the most frequent findings that were reported in ≥ 15% of the subjects in the Surgicel treatment group in Part I + Part II were hypertension (90/162 [55.6%] subjects), metastases to liver (21.6%, 35/162 subjects), and drug hypersensitivity (19.8%, 32/162 subjects).

Surgical History Findings

Findings in surgical history in the ITT population were reported for 42.9% (70/163) of the subjects randomized to FS Grifols in Part I + Part II and in 45.1% (73/162) of the subjects randomized to Surgicel in Part I + Part II (Post-text Table 14.1.3/1.2). Overall, the patterns of these findings were quite diverse but similar between the FS Grifols and Surgicel treatment groups. The most frequent surgical history findings that was reported in ≥ 5% of the subjects in the FS Grifols treatment group in Part I + Part II were colectomy (12/163 [7.4%] subjects), cholecystectomy (9/163 [5.5%] subjects), and resection of rectum (9/163 [5.5%] subjects).

Similarly, the most frequent findings that were reported in ≥ 5% of the subjects in the Surgicel treatment group in Part I + Part II were colectomy (14/162 [8.6%] subjects) and resection of rectum (12/162 [7.4%] subjects).

Bleeding Abnormality History Findings

Findings in bleeding abnormality history in the ITT population were reported for 0.6% (1/163) of the subjects randomized to FS Grifols (Factor V Leiden mutation) in Part I + Part II and in 0.6% (1/162) of the subjects randomized to Surgicel (haemorrhagic disorder) in Part I + Part II.

No subjects in either treatment group reported a finding in family bleeding abnormality history.

- **Numbers analysed**

Table 17: Disposition of Subjects (All Subjects Screened)

Subject Disposition	Preliminary Part (I)		Primary Part (II)		Part (I) + Part (II)		Total[a]
	FS Grifols n (%)	Surgicel n (%)	FS Grifols n (%)	Surgicel n (%)	FS Grifols n (%)	Surgicel n (%)	
Subjects screened	139		287		--		426
Subjects randomized (ITT Population)	52	49	111	113	163	162	325
Subjects Valid for PP Population	41 (78.8)	43 (87.8)	87 (78.4)	100 (88.5)	128 (78.5)	143 (88.3)	271 (83.4)
Subjects valid for Safety Population (actual treatment)	52	49	111	113	163	162	325
Subjects completed the study up to Week 6	47 (90.4)	45 (91.8)	100 (90.1)	108 (95.6)	147 (90.2)	153 (94.4)	300 (92.3)
Subjects discontinued prematurely before Week 6	5 (9.6)	4 (8.2)	11 (9.9)	5 (4.4)	16 (9.8)	9 (5.6)	25 (7.7)
Withdrawal of consent	1 (1.9)	2 (4.1)	2 (1.8)	4 (3.5)	3 (1.8)	6 (3.7)	9 (2.8)
Lost to follow-up	1 (1.9)	1 (2.0)	4 (3.6)	0	5 (3.1)	1 (0.6)	6 (1.8)
Death	3 (5.8)	1 (2.0)	4 (3.6)	1 (0.9)	7 (4.3)	2 (1.2)	9 (2.8)
Other	0	0	1 (0.9)	0	1 (0.6)	0	1 (0.3)
Subjects completed the study up to Virology Follow-up[b]	42 (80.8)	37 (75.5)	96 (86.5)	102 (90.3)	138 (84.7)	139 (85.8)	277 (85.2)
Subjects discontinued before Virology Follow-up[b]	8 (15.4)	9 (18.4)	15 (13.5)	11 (9.7)	23 (14.1)	20 (12.3)	43 (13.2)
Pediatric subjects (Virology Follow-up visit was not required)	2 (3.8)	3 (6.1)	0	0	2 (1.2)	3 (1.9)	5 (1.5)

[a] Total includes all subjects from both treatments in Preliminary Part (I) and Primary Part (II).

[b] Virology Follow-up is either Month 3 or Month 6 visit

Note: Percentages are based on the number of subjects in the FS Grifols or Surgicel Part I + Part II ITT Population as the denominator.

- **Outcomes and estimation**

Trial IG1102

Primary efficacy analysis

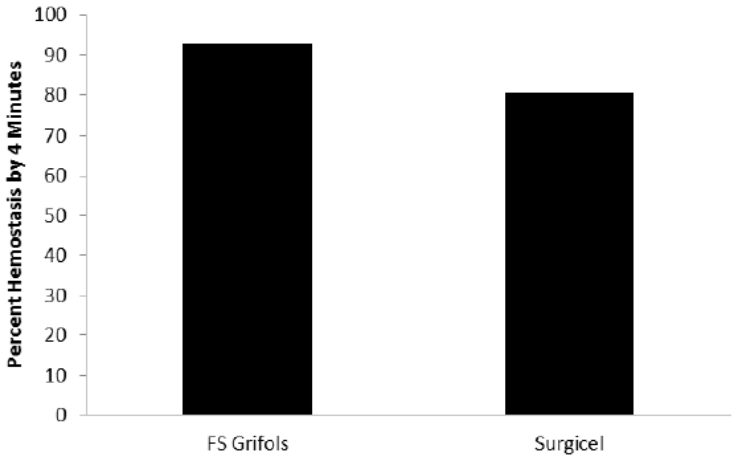

Figure 11-1 Analysis of Hemostasis by T_4 at Target Bleeding Site (ITT Population)

The primary efficacy analysis of haemostasis at the TBS by T4 based on nominal time points in the ITT population in the Primary Part (II) of the study is presented in Figure 11-1. The rate of haemostasis by T4 was 92.8% (103/111 subjects) in the FS Grifols treatment group and was 80.5% (91/113 subjects) in the Surgicel treatment group. Inferential analyses of the ratio and 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.152 (1.038, 1.279),

indicating that FS Grifols is non-inferior to Surgicel and that the primary efficacy objective was achieved in the ITT population. The rate of haemostasis by T4 was statistically significantly higher in the FS Grifols treatment group compared to the Surgicel treatment group (p-value = 0.010).

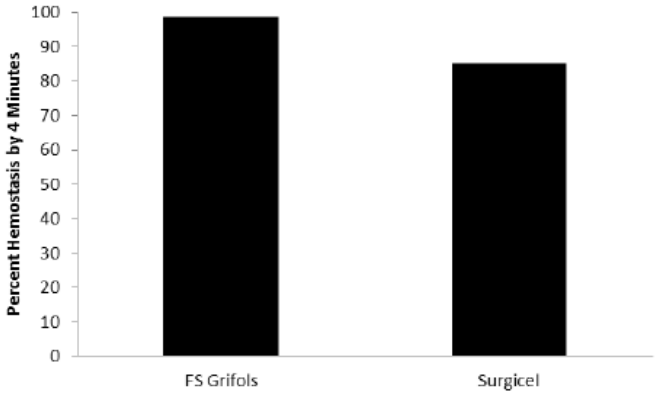

Figure 11-2 Analysis of Hemostasis by T_4 at Target Bleeding Site (PP Population)

Analysis of the primary efficacy endpoint of haemostasis at the TBS by T4 in the PP population in the Primary Part (II) of the study is presented in Figure 11-2. The rate of haemostasis by T4 was 98.9% (86/87 subjects) in the FS Grifols treatment group and was 85.0% (85/100 subjects) in the Surgicel treatment group. Similar to the ITT population, inferential analyses of the ratio and 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.163 (1.068, 1.267), indicating that FS Grifols is non-inferior to Surgicel and that the primary efficacy objective was achieved in the PP population. The rate of haemostasis by T4 was statistically significantly higher in the FS Grifols treatment group compared to the Surgicel treatment group (p-value <0.001).

Sensitivity Analysis

A sensitivity analysis of haemostasis at the TBS based on the exact (actual) assessment time at the first and last haemostatic assessment selected within the time window was performed. For the primary efficacy endpoint of haemostasis by T4, the results were the same for when the first and last haemostatic assessment was selected, and they were also identical to those of the primary efficacy analysis using the nominal assessment time.

The rate of haemostasis by T4 was 92.8% (103/111 subjects) in the FS Grifols treatment group and was 80.5% (91/113 subjects) in the Surgicel treatment group. Inferential analyses of the ratio and 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.152 (1.038, 1.279), indicating that FS Grifols is superior to Surgicel and supporting the primary efficacy endpoint. The rate of haemostasis by T4 was statistically and significantly higher in the FS Grifols treatment group compared to the Surgicel treatment group (p-value = 0.010).

In the Preliminary Part (I) of the study, the rate of haemostasis at the TBS by T4 in the ITT population was higher in the FS Grifols treatment group (42/52 [80.8%] subjects) compared to the Surgicel treatment group (27/49 [55.1%] subjects).

In the Preliminary Part (I) of the study, the rate of haemostasis by T4 in the PP population was higher in the FS Grifols treatment group (35/41 [85.4%] subjects) compared to the Surgicel treatment group (23/43 [53.5%] subjects).

Secondary efficacy analyses

Time to Haemostasis

Table 18: Analysis of Time to Hemostasis at Target Bleeding Site (ITT Population)

Statistics	Primary Part (II) FS Grifols N=111	Surgicel N=113	P-value[a]
Mean (SE)	2.8 (0.14)	3.8 (0.24)	<0.001
Q25	2.0	2.0	
Median (95% CI)	2.0 (2.00, 3.00)	3.0 (2.00, 3.00)	
Q75	3.0	4.0	

Note: TTH was measured in minutes

[a] P-value was calculated from Log-rank test.

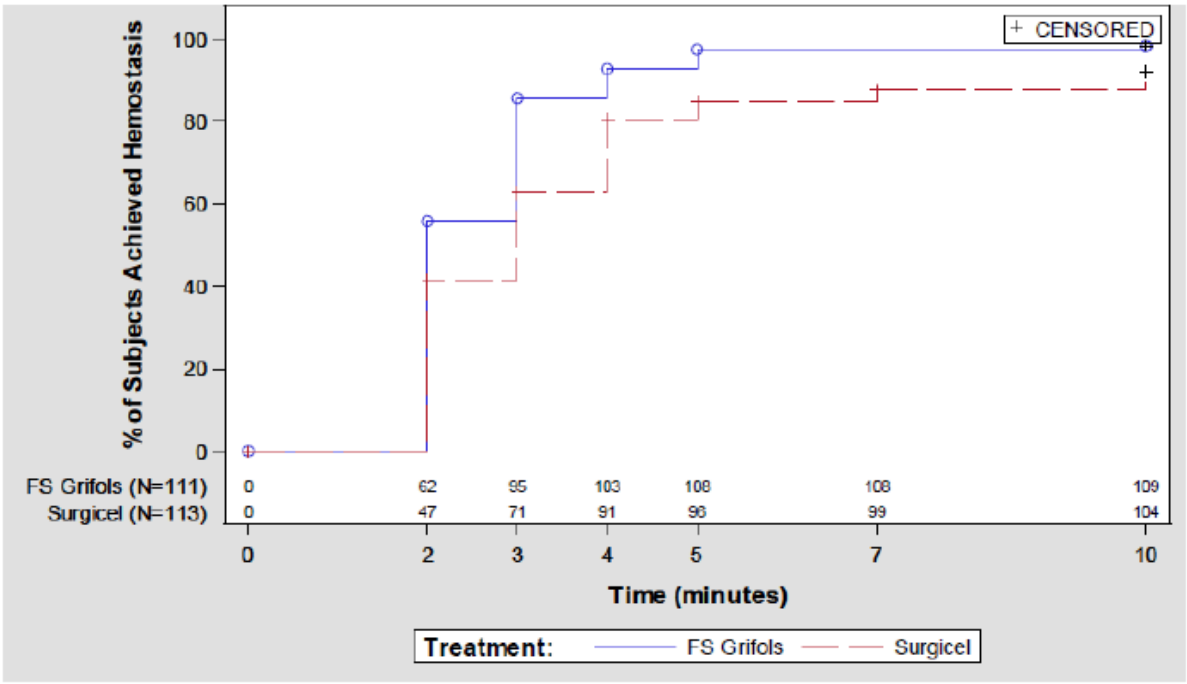

Figure 11-4 Time to Hemostasis at Target Bleeding Site (ITT Population)

Source: Post-text Figure 14.2.1.

Preliminary Part

Table 19: Analysis of Time to Hemostasis at Target Bleeding Site (TBS) Population: Intent to - Treat

	Preliminary Part (I)		Primary Part (II)		
	FS Grifols (N=52)	Surgicel (N=49)	FS Grifols (N=111)	Surgicel (N=113)	P-value [1]
Statistics					
Mean (SE)	3.1 (0.24)	5.6 (0.48)	2.8 (0.14)	3.8 (0.24)	<0.001
Q25	2.0	3.0	2.0	2.0	
Median (95% CI)	2.0 (NA, NA)	4.0 (3.00, 7.00)	2.0 (2.00, 3.00)	3.0 (2.00, 3.00)	
Q75	3.0	NA	3.0	4.0	

Cumulative Proportion of Subjects Achieving Haemostasis at the Target Bleeding Site by T2 T5, T7, and T10

Table 20: Analysis of Hemostasis by T2 T5, T7, and T10 at Target Bleeding Site (ITT Population)

	Primary Part (II)			
	FS Grifols N=111 n (%)	Surgicel N=113 n (%)	RR (95% CI)[a]	P-value[b]
Hemostasis by 2 minutes	62 (55.9)	47 (41.6)	1.343 (1.021, 1.766)	0.045
Hemostasis by 5 minutes	108 (97.3)	96 (85.0)	1.145 (1.053, 1.245)	0.002
Hemostasis by 7 minutes	108 (97.3)	99 (87.6)	1.111 (1.029, 1.198)	0.010
Hemostasis by 10 minutes	109 (98.2)	104 (92.0)	1.067 (1.005, 1.133)	0.059

[a] RR was the ratio of proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in Primary Part II (FS Grifols relative to Surgicel)

[b] P-value was calculated from Fisher Exact Test

Preliminary Part

Table 21: Analysis of Haemostasis by Each Time Point at Target Bleeding Site (TBS) Population: Intent-to-Treat

	Preliminary Part (I)	
	FS Grifols (N=52) n (%)	Surgicel (N=49) n (%)
Primary Efficacy Endpoint		
Hemostasis by 4 Minutes	42 (80.8)	27 (55.1)
Secondary Efficacy Endpoints		
Hemostasis by 2 Minutes	33 (63.5)	12 (24.5)
Hemostasis by 3 Minutes	40 (76.9)	20 (40.8)
Hemostasis by 5 Minutes	45 (86.5)	30 (61.2)
Hemostasis by 7 Minutes	47 (90.4)	33 (67.3)
Hemostasis by 10 Minutes	47 (90.4)	34 (69.4)

Treatment Failures

The analysis of treatment failure at the TBS is presented in Table 22. The estimated ratio of proportion of treatment failure in subjects receiving FS Grifols relative to Surgicel was 0.370 (0.172, 0.796). The rate of treatment failure was statistically and significantly lower (p-value = 0.010) in the FS Grifols treatment group (8/111 [7.2%] subjects) compared to the Surgicel treatment group (22/113 [19.5%] subjects). The most common cause of treatment failure in the FS Grifols and Surgicel treatment groups was persistent bleeding (7.2% and 18.6%, respectively).

In the FS Grifols treatment group, treatment failure due to persistent bleeding occurred in 1/8 (12.5%) subjects with a small TBS and in 7/8 (87.5%) subjects with a medium TBS.

In the Surgicel treatment group, treatment failure due to persistent bleeding occurred in 7/21 (33.3%) subjects with a small TBS and in 14/21 (66.7%) subjects with a medium TBS.

Table 22: Analysis of treatment failure at target bleeding site (ITT population)

	Primary Part (II)			
	FS Grifols N=111 n (%)	Surgicel N=113 n (%)	RR (95% CI)[a]	P-value[b]
Treatment failure	8 (7.2)	22 (19.5)	0.370 (0.172, 0.796)	0.010
Reason[c]				
Persistent bleeding	8 (7.2)	21 (18.6)		
Breakthrough bleeding	0	1 (0.9)		
Re-bleeding	0	4 (3.5)		
Use of alternative hemostatic treatment or maneuvers	1 (0.9)	9 (8.0)		
Re-applied treatment[d]	1 (0.9)	1 (0.9)		

[a] RR was the proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in Primary Part II (FS Grifols relative to Surgicel).

[b] P-value was calculated from Fisher Exact Test.

[c] The reasons were not mutually exclusive.

[d] Treatment could be reapplied beyond T_4 and until the completion of the surgical closure, but would be considered a treatment failure.

Preliminary Part

Table 23: Analysis of Treatment Failure at Target Bleeding Site (TBS) Population: Intent-to-Treat

	Preliminary Part (I)	
	FS Grifols (N=52) n (%)	Surgicel (N=49) n (%)
Treatment Failure	10 (19.2)	22 (44.9)
Reason [3]		
Persistent Bleeding	9 (17.3)	20 (40.8)
Breakthrough Bleeding	1 (1.9)	4 (8.2)
Re-bleeding	2 (3.8)	3 (6.1)
Use of Alternative Hemostatic Treatment or Maneuvers	3 (5.8)	14 (28.6)
Reapplied Treatment [4]	2 (3.8)	1 (2.0)

- **Ancillary analyses**

Trial IG1102

Subgroup Analyses

In the subgroup analyses of the primary efficacy endpoint, study centres, age group, and approximate size of the bleeding surface at the TBS, were used as stratifying variables in order to control for the effect of these covariates. The pooled estimate of the ratio of proportion of subjects meeting the primary efficacy endpoint and its 95% CI were calculated using a Cochran-Mantel-Haenszel (CMH) test stratified by these covariates, respectively.

Subgroup Analysis by Study Centre

Analysis of haemostasis at the TBS by T4 stratified by study centre in the Primary Part (II) of the study is presented in Table 24. All small study centres, defined as less than 3 subjects in either treatment group of the Primary Part II of the study, were pooled together for efficacy analyses. Inferential analyses of the ratio and 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.141 (1.036, 1.258), demonstrating that FS Grifols is superior to Surgicel. The rate of haemostasis by T4 was statistically and significantly higher (p-value = 0.007) in subjects receiving FS Grifols relative to Surgicel. Overall, in the Primary Part (II) of the study, the rates of haemostasis at the TBS by T4 were comparable to the overall primary efficacy analysis in most study centres.

Table 24: Analysis of Hemostasis by T_4 at Target Bleeding Site Stratified by Investigational Study Centres (ITT Population)

	Primary Part (II)			
Site	FS Grifols n/N (%)	Surgicel n/N (%)	RR (95% CI)[a]	P-Value[b]
Hemostasis by 4 minutes			1.141 (1.036, 1.258)	0.007
Pooled sites[c]	5/7 (71.4)	4/7 (57.1)		
201	2/3 (66.7)	2/3 (66.7)		
202	3/3 (100.0)	1/4 (25.0)		
213	2/3 (66.7)	2/4 (50.0)		
214	14/14 (100.0)	13/14 (92.9)		
218	3/3 (100.0)	1/4 (25.0)		
232	15/18 (83.3)	12/18 (66.7)		
600	10/11 (90.9)	12/12 (100.0)		
602	4/4 (100.0)	2/3 (66.7)		
620	14/14 (100.0)	14/14 (100.0)		
621	11/11 (100.0)	10/10 (100.0)		
622	20/20 (100.0)	18/20 (90.0)		

[a] Risk ratio (RR) was the estimated common ratio of the proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in Primary Part II (FS Grifols relative to Surgicel)

[b] P-value was calculated from CMH Test

[c] All small sites, defined as <3 subjects in either treatment group of the Primary Part (II), were pooled together for efficacy analyses. Sites 233, 206, 204, 212, 207, and 224 were pooled (Post-text Table 14.1.1/2)

Subgroup Analysis by Age Group

Analysis of haemostasis by T4 stratified by age group in the Primary Part (II) of the study is presented in Table 25. Inferential analyses of the ratio and 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.149 (1.036, 1.274), demonstrating that FS Grifols is superior to Surgicel. The rate of haemostasis by T4 was statistically and significantly higher (p-value = 0.008) in subjects receiving FS Grifols relative to Surgicel.

There were no paediatric subjects in either treatment group in the Primary Part (II) of the study. In adult subjects aged 18 to 64 years old, the rate of haemostasis at the TBS by T4 was higher in the FS Grifols treatment group (64/70 [91.4%] subjects) compared to the Surgicel treatment group (59/76 [77.6%] subjects) and was comparable to the overall primary efficacy analysis.

Likewise, in adult subjects aged ≥ 65 years old, the rate of haemostasis at the TBS by T4 was higher in the FS Grifols treatment group (39/41 [95.1%] subjects) compared to the Surgicel treatment group (32/37 [86.5%] subjects) and was comparable to the overall primary efficacy analysis.

Table 25: Analysis of Hemostasis by T_4 at Target Bleeding Site Stratified by Age Group (ITT Population)

	Primary Part (II)			
	FS Grifols n/N (%)	Surgicel n/N (%)	RR (95% CI)[a]	P-value[b]
Hemostasis by 4 minutes			1.149 (1.036, 1.274)	0.008
≤11 years	0	0		
12-17 years	0	0		
18-64 years	64/70 (91.4)	59/76 (77.6)		
≥65 years	39/41 (95.1)	32/37 (86.5)		

[a] Risk ratio (RR) was the estimated common ratio of the proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in Primary Part II (FS Grifols relative to Surgicel)

[b] P-value was calculated from CMH Test

Subgroup Analysis by Size of Bleeding Surface at Target Bleeding Site

Analysis of haemostasis by T4 stratified by the size of the bleeding surface at the TBS in the Primary Part (II) of the study is presented in Table 26. Inferential analyses of the ratio and 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.142 (1.032, 1.263), demonstrating that FS Grifols is superior to Surgicel. The rate of haemostasis by T4 was statistically and significantly higher (p-value = 0.010) in subjects receiving FS Grifols relative to Surgicel.

The rate of haemostasis at the TBS by T4 in subjects with a small (≤ 10 cm2) bleeding surface at the TBS was higher in the FS Grifols treatment group (9/10 [90.0%] subjects) compared to the Surgicel treatment group (6/13 [46.2%] subjects) (Table 26). The rate of haemostasis in the FS Grifols treatment group was comparable to the overall primary efficacy analyses.

In subjects with a medium (>10 cm2 and ≤ 100 cm2) bleeding surface at the TBS, the rate of haemostasis at the TBS by T4 was higher in the FS Grifols (86/93 [92.5%] subjects) and Surgicel (79/94 [84.0%] subjects) treatment groups and was comparable to the overall primary efficacy analyses.

The rate of haemostasis at the TBS by T4 in subjects with a large (>100 cm2) bleeding surface at the TBS was 8/8 (100.0%) subjects in the FS Grifols treatment group and 6/6 (100.0%) subjects in the Surgicel treatment group.

Table 26: Analysisi of Hemostasis by T_4 at Target Bleeding Site Stratified by Size of Bleeding Surface (ITT Population)

	Primary Part (II)			
	FS Grifols n/N (%)	Surgicel n/N (%)	RR (95% CI)[a]	P-value[b]
Hemostasis by 4 minutes			1.142 (1.032, 1.263)	0.010
Small	9/10 (90.0)	6/13 (46.2)		
Medium	86/93 (92.5)	79/94 (84.0)		
Large	8/8 (100.0)	6/6 (100.0)		

[a] Risk ratio (RR) was the estimated common ratio of the proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in Primary Part II (FS Grifols relative to Surgicel)

[b] P-value was calculated from CMH Test

Note: Small: ≤10 cm^2, Medium: >10 cm^2 and ≤100 cm^2, Large: >100 cm^2

Table 27: Summary of efficacy for trial IG1102

Title: A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis During Parenchymous Tissue Open Surgeries		
Study identifier	IG1102	
Design	This trial consists of 2 parts: a Preliminary Part (I) and a Primary Part (II). Preliminary Part (I): Subjects in the Preliminary Part (I) of the study were to be randomized in a 1:1 ratio into 1 of 2 treatment groups: FS Grifols or Surgicel. The main objective of this part of the clinical study was to ensure that local study teams familiarized themselves with the technique for FS Grifols application and with intra-operative procedures required by the protocol of the clinical study. For each study center participating in the study, the first 4 subjects were to be enrolled in the Preliminary Part (I). Primary Part (II): Subjects in the Primary Part (II) of the study were to be randomized in a 1:1 ratio into FS Grifols or Surgicel treatment groups. The two main objectives of this part were as follows: 1) Assessment of the safety of FS Grifols. 2) Assessment of the efficacy of FS Grifols.	
	Duration of main phase:	Intraoperatively: 10 minutes; Post-Operative assessments were performed on Days 1, 2, 3, 7, 14, Week 6 and Month 3. Viral safety follow-up at month 4 (earlier protocol versions: month 6)
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Non-inferiority	
	FS Grifols primary	N=111
	Surgicel primary	N=113

Endpoints and definitions	Primary endpoint	Haemostasis at T4	Proportion of subjects in the Primary Part (II) of the study achieving haemostasis (Yes/No) at the TBS by T4 without occurrence of re-bleeding and re-application of study treatment after T4 and until TClosure and without brisk bleeding and use of alternative haemostatic treatment after TStart and until TClosure.
	Secondary	TTH	Time to Haemostasis
	Secondary	T2 T3 T5 T7 T10	Cumulative Proportion of Subjects Achieving Haemostasis at the Target Bleeding Site by Each of the Following Time Points: T2, T3, T5, T7, and T10
	Secondary	Treatment Failure	Treatment Failures
Database lock	<date>		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	**Treatment group**	**FS Grifols preliminary**	**Surgicel preliminary**
	Number of subject	52	49
	Haemostasis at T4	80.8 % (n=42)	55.1% (n=27)
	Treatment group	**FS Grifols primary**	**Surgicel primary**
	Number of subject	111	113
	Haemostasis at T4	92.8% (103/111)	80.5% (91/113)
	TTH median	2.0	3.0
	95% CI	2.00, 3.00	2.00, 3.00
	Haemostasis by T2	55.9% (n=62)	41.6% (n=47)
	Haemostasis by T3	85.6% (n=95)	62.8% (n=71)
	Haemostasis by T5	97.3% (n=108)	85.0% (n=96)
	Haemostasis by T7	(97.3% (n=108)	87.6% (n=99)
	Haemostasis by T10	98.2% (n=109)	92.0% (n=104)
	Treatment Failure	7.2% (n=8)	19.5% (n=22)

Effect estimate per comparison	Primary endpoint Haemostasis at T4	FS Grifols primary vs. Surgicel	
		RR	1.152
		95% CI	1.038, 1.279
		P-value	0.010
	Secondary endpoint Treatment Failure	FS Grifols primary vs. Surgicel	
		RR	0.370
		95% CI	0.172, 0.796
		P-value	0.010

Study IG1103: A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis During Soft Tissue Open Surgeries

Methods

This clinical study consisted of 2 parts: a Preliminary Part (I) and a Primary Part (II).

Subjects in the **Preliminary Part (I)** were to be randomized in 1:1 ratio into 1 of 2 treatment groups: FS Grifols or Surgicel. The main objective of this part of the clinical study was to ensure that local study teams familiarized themselves with the technique for FS Grifols application and with intra-operative procedures required by the protocol of the clinical study. In addition, safety and efficacy data were collected from the subjects participating in the Preliminary Part (I) of the study. Efficacy data from subjects enrolled in the Preliminary Part (I) of the study were reviewed to verify the sample size assumptions for the Primary Part (II) of the study. For each study center participating in the study, the first 4 subjects were to be enrolled in the Preliminary Part (I).

Subjects in the **Primary Part (II)** were to be randomized in **1:1 ratio into FS Grifols or Surgicel treatment groups**. This part of the clinical study had 2 main objectives: (1) to assess the safety of FS Grifols and (2) to assess the efficacy of FS Grifols. For each study center, the Primary Part (II) of the study was to start only after enrollment of 4 subjects in the Preliminary Part (I).

In both parts of the clinical study, subjects undergoing an **elective** (non-emergency), **open** (non-laparoscopic) **retroperitoneal or pelvic surgical procedure**, wherein a target bleeding site (TBS) was identified on soft tissue and a topical haemostat was indicated, were initially eligible to participate. Following incorporation of changes made in Protocol Version 3.0 (dated 23 Aug 2013), enrollment of subjects undergoing certain soft tissue surgical types beyond the retroperitoneal or pelvic regions (ie, mastopexies and abdominoplasties) became permissible. A specific bleeding area/site was defined as the TBS when it was determined by the investigator (the surgeon) that control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) was ineffective or impractical and required an adjunct treatment to achieve haemostasis.

When the TBS was identified, the investigator was to rate the intensity of the bleeding at the TBS and the approximate size of the bleeding surface according to a 3-point scale (mild, moderate, severe for the

intensity of the bleeding and small, medium, large for the bleeding surface). In both parts of the study, only subjects with a TBS with bleeding of moderate intensity could be enrolled as detailed in Intra-operative inclusion criteria 6.

- **Study participants**

Inclusion Criteria

1. Signed the written ICF, or the subject's parent or legal guardian signed the ICF and Subject Authorization Form where applicable. Pediatric subjects, as defined by local regulations, were asked to sign an age-appropriate assent form.

2. Were male or female.

3. No lower or upper age limit.

4. Must have had haemoglobin (Hgb) ≥ 9.0 g/dL.

> - Following the incorporation of Protocol Versions 5.0 and 5.1 (both dated 16 Dec 2014), the Hgb levels criterion was decreased from ≥ 9.0 g/dL to ≥ 8.0 g/dL at baseline (within 24 hours prior to surgical procedure) to allow the enrollment of subjects with lower Hgb levels.

5. Required an elective (non-emergency), open (non-laparoscopic) retroperitoneal or pelvic surgical procedure involving soft (non-parenchymous) tissue:

> • Where TBS was identified on soft tissue during following urologic, gynecologic or general retroperitoneal or pelvic surgery procedures:
>
> a. Simple or radical nephrectomies.
>
> b. Total adrenalectomies.
>
> c. Radical prostatectomies.
>
> d. Pyeloplasties.
>
> e. Radical cystectomies.
>
> f. Simple or radical hysterectomies.
>
> g. Lymphadenectomies.
>
> h. Retroperitoneal tumour resections.
>
> - Following the incorporation of Protocol Version 3.0 (dated 23 Aug 2013), testing of FS Grifols in additional soft tissue surgical types beyond the retroperitoneal and pelvic regions was permitted, resulting in the inclusion of mastopexies and abdominoplasties. Lymphadenectomies were permitted in the retroperitoneal or pelvic region, only.

6. Intra-operative inclusion criteria:

A TBS could be identified according to the investigator's judgment (when there was generalized bleeding from the soft tissue that persisted after retroperitoneal soft tissue dissection, and it was determined by the investigator (the surgeon) that the primary control of arterial and venous bleeding by conventional surgical techniques was ineffective or impractical and required an adjunct treatment to achieve haemostasis, the

specific bleeding area/site was identified and defined as the TBS), and the approximate size of the TBS was rated by the investigator (the surgeon) using a 3-point scale:

- ◦ Small: TBS ≤ 10 cm2.
- ◦ Medium: 10 cm2 <TBS ≤ 100 cm2.
- ◦ Large: TBS >100 cm2.

• The TBS had a moderate bleeding according to the investigator's judgment.

- ◦ Following the incorporation of Protocol Version 2.0 (dated 16 Jul 2012), subjects with a mild bleeding TBS were excluded (ie, no subjects were enrolled in the study with a mild bleed).

• The intensity of the bleeding at the TBS was rated by the investigator using a predefined 3-point scale.

- ◦ Mild: oozing and capillary.
- ◦ Moderate: gradual and steady.
- ◦ Severe: brisk and forceful.

Exclusion Criteria

1. Required retroperitoneal or pelvic surgery due to trauma. Following the incorporation of Protocol Version 3.0 (dated 23 Aug 2013), subjects requiring thoracic and abdominal surgery due to trauma were also excluded.

2. Had an infection in the anatomic surgical area.

3. Had a history of severe (eg, anaphylactic) reactions to blood or to any blood-derived (human or animal) product.

4. Had previous known sensitivity to any FS Grifols component or any Surgicel component.

5. Had known (documented) previous exposure to thrombin-containing (bovine, human or recombinant) products. Following the incorporation of Protocol Version 3.0 (dated 23 Aug 2013), this exclusion was removed.

6. Were unlikely to adhere to the protocol requirements or to be cooperative during the study conduct.

7. Females who were pregnant or nursing a child. Following the incorporation of Protocol Version 3.0 (dated 23 Aug 2013), clarification was provided for this exclusion. Females who were pregnant or nursing a child at baseline (within 24 hours prior to surgical procedure) were excluded from the study.

8. Were receiving an organ transplant during the same surgical procedure.

9. Were currently participating or had participated in another clinical study in the context of which they had received investigational drug or device within 3 months from the Screening Visit or were scheduled to participate during the course of this study.

10. Had undergone a therapeutic surgical procedure within 30 days from the Screening Visit.

11. Were previously enrolled in clinical studies with FS Grifols.

12. Following the incorporation of Protocol Version 4.1 (dated 25 Mar 2014), subjects enrolled in Hungary could not have a known (documented) history of thrombophilia or IgA deficiency, as required by Hungary's national competent authority.

13. Intra-operative exclusion criteria:

- A TBS could not be identified according to the investigator's judgment.
- The TBS had mild or severe bleeding according to the investigator's judgment.
- Occurrence of major intra-operative complications that required resuscitation or deviation from the planned surgical procedure.
- Application of any topical haemostatic material on the cut soft tissue surface identified as the TBS prior to application of the study treatment.

- **Treatments**

Same as Trial IG1102 described above. Subjects were treated intra-operatively with FS Grifols or Surgicel.

Five units of applicator tips for dripping and 4 units of applicator tips for spraying were available for each subject undergoing soft tissue surgery.

For every subject undergoing soft tissue surgery, FS Grifols was administered by dripping or by spraying onto the TBS surface with the use of an applicator.

- **Objectives**

The purpose of this study was to demonstrate that FS Grifols was both safe and effective in achieving haemostasis during soft tissue open surgeries.

The efficacy objective of the study was to evaluate the haemostatic efficacy of FS Grifols in soft tissue open surgeries.

The safety objectives of the study included clinical safety, virus safety, and immunogenicity.

- **Outcomes/endpoints**

Same as trial IG1102 described above.

- **Sample size**

Same as trial IG1102 described above.

- **Randomisation**

Same as trial IG1102 described above.

- **Blinding (masking)**

Same as trial IG1102 described above.

- **Statistical methods**

Same as trial IG1102 described above.

Results

- **Participant flow**

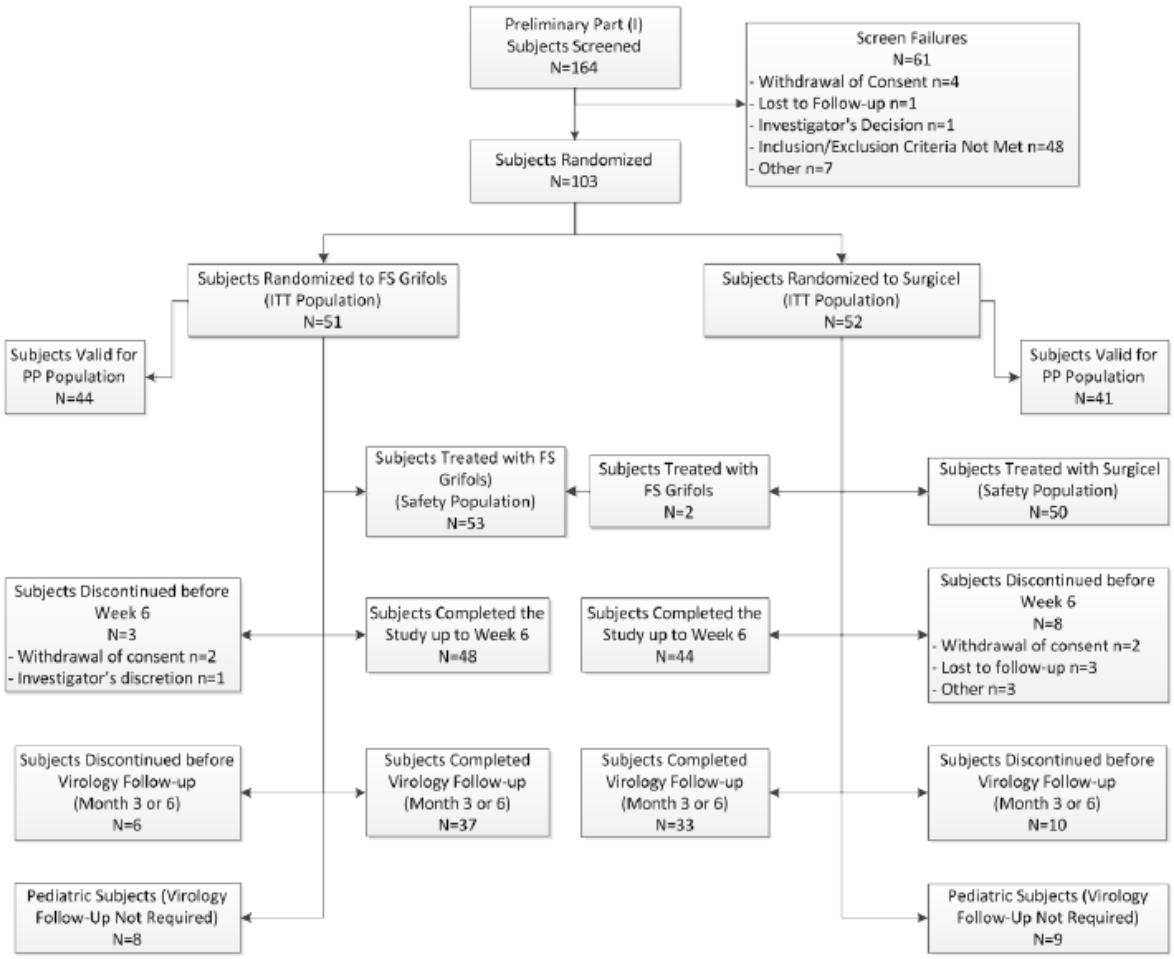

Figure 10-1 Disposition of Subjects during the Preliminary Part (I) of the Study

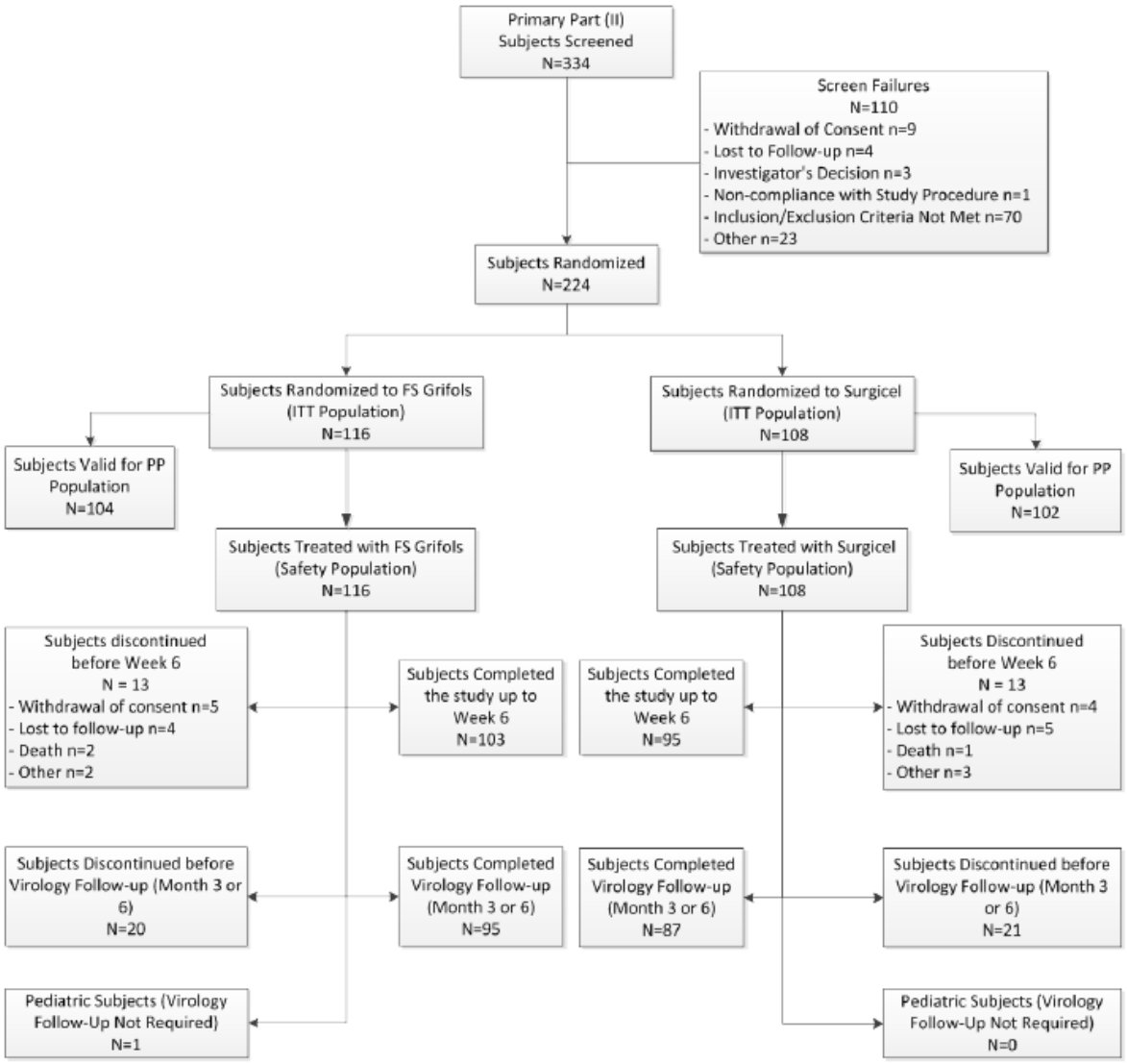

Figure 10-2 Disposition of Subjects during Primary Part (II)

- **Recruitment**

Study Period: approximately 2.5 years

(date of first enrolment) 19 Nov 2012

(date of last completed) 04 Jun 2015

- **Conduct of the study**

Protocol Amendments

7 protocol amendments were implemented during the conduct of this study, which mainly clarified in- or exclusion criteria or procedures to be done during the study.

Protocol Deviations

Table 28: Protocol Deviations (ITT Population)

Characteristics	Preliminary Part (I)		Primary Part (II)		Part (I) + Part (II)		Total[a] (N=327) n (%)
	FS Grifols (N=51) n (%)	Surgicel (N=52) n (%)	FS Grifols (N=116) n (%)	Surgicel (N=108) n (%)	FS Grifols (N=167) n (%)	Surgicel (N=160) n (%)	
Subjects without any protocol deviations	16 (31.4)	17 (32.7)	43 (37.1)	44 (40.7)	59 (35.3)	61 (38.1)	120 (36.7)
Subjects with at least one protocol deviation	35 (68.6)	35 (67.3)	73 (62.9)	64 (59.3)	108 (64.7)	99 (61.9)	207 (63.3)
Subjects without any major protocol deviations	41 (80.4)	35 (67.3)	92 (79.3)	89 (82.4)	133 (79.6)	124 (77.5)	257 (78.6)
Subjects with at least one major protocol deviation	10 (19.6)	17 (32.7)	24 (20.7)	19 (17.6)	34 (20.4)	36 (22.5)	70 (21.4)
Type of major protocol deviations							
Inclusion criteria	4 (7.8)	2 (3.8)	4 (3.4)	0	8 (4.8)	2 (1.3)	10 (3.1)
Exclusion criteria	0	0	1 (0.9)	0	1 (0.6)	0	1 (0.3)
Study treatment	3 (5.9)	4 (7.7)	12 (10.3)	10 (9.3)	15 (9.0)	14 (8.8)	29 (8.9)
Assessment safety	2 (3.9)	5 (9.6)	10 (8.6)	9 (8.3)	12 (7.2)	14 (8.8)	26 (8.0)
Assessment efficacy	3 (5.9)	6 (11.5)	1 (0.9)	0	4 (2.4)	6 (3.8)	10 (3.1)
Visit window	0	1 (1.9)	0	0	0	1 (0.6)	1 (0.3)
Informed consent	2 (3.9)	4 (7.7)	1 (0.9)	2 (1.9)	3 (1.8)	6 (3.8)	9 (2.8)

[a] Total includes all subjects from both treatments in the Preliminary Part (I) and the Primary Part (II) of the study.

- **Baseline data**

Table 29: Demographics (ITT Population)

Characteristics	Preliminary Part (I)		Primary Part (II)		Part (I) + Part (II)		Total[a] (N=327) n (%)
	FS Grifols (N=51) n (%)	Surgicel (N=52) n (%)	FS Grifols (N=116) n (%)	Surgicel (N=108) n (%)	FS Grifols (N=167) n (%)	Surgicel (N=160) n (%)	
Sex - n (%)							
Male	24 (47.1)	24 (46.2)	29 (25.0)	22 (20.4)	53 (31.7)	46 (28.8)	99 (30.3)
Female	27 (52.9)	28 (53.8)	87 (75.0)	86 (79.6)	114 (68.3)	114 (71.3)	228 (69.7)
Age (years)							
Mean (SD)	47.17 (25.635)	45.39 (25.024)	48.51 (14.369)	46.72 (14.330)	48.10 (18.476)	46.29 (18.424)	47.21 (18.444)
Median	48.00	47.00	46.00	45.00	46.00	45.50	46.00
Min, Max	0.3, 86.0	0.6, 85.0	15.0, 85.0	21.0, 84.0	0.3, 86.0	0.6, 85.0	0.3, 86.0
Age Category (years) – n (%)							
≤11	8 (15.7)	8 (15.4)	0	0	8 (4.8)	8 (5.0)	16 (4.9)
<2 (28 days-23 months)	5 (9.8)	6 (11.5)	0	0	5 (3.0)	6 (3.8)	11 (3.4)
2-11	3 (5.9)	2 (3.8)	0	0	3 (1.8)	2 (1.3)	5 (1.5)
12-17	0	1 (1.9)	1 (0.9)	0	1 (0.6)	1 (0.6)	2 (0.6)
18-64	27 (52.9)	28 (53.8)	98 (84.5)	90 (83.3)	125 (74.9)	118 (73.8)	243 (74.3)
≥65	16 (31.4)	15 (28.8)	17 (14.7)	18 (16.7)	33 (19.8)	33 (20.6)	66 (20.2)
65-84	13 (25.5)	14 (26.9)	16 (13.8)	18 (16.7)	29 (17.4)	32 (20.0)	61 (18.7)
≥85	3 (5.9)	1 (1.9)	1 (0.9)	0	4 (2.4)	1 (0.6)	5 (1.5)
Ethnicity - n (%)							
Hispanic or Latino	4 (7.8)	5 (9.6)	20 (17.2)	12 (11.1)	24 (14.4)	17 (10.6)	41 (12.5)
Not Hispanic or Latino	47 (92.2)	47 (90.4)	96 (82.8)	96 (88.9)	143 (85.6)	143 (89.4)	286 (87.5)
Race – n (%)							
White (Caucasian)	46 (90.2)	46 (88.5)	93 (80.2)	81 (75.0)	139 (83.2)	127 (79.4)	266 (81.3)
Black or African American	5 (9.8)	5 (9.6)	22 (19.0)	25 (23.1)	27 (16.2)	30 (18.8)	57 (17.4)
Asian	0	0	1 (0.9)	1 (0.9)	1 (0.6)	1 (0.6)	2 (0.6)
American Indian or Alaskan Native	0	0	0	1 (0.9)	0	1 (0.6)	1 (0.3)
Not Specified	0	1 (1.9)	0	0	0	1 (0.6)	1 (0.3)
Height (cm)							
Mean (SD)	156.2 (31.02)	155.8 (33.50)	167.0 (8.92)	167.1 (8.69)	163.7 (19.23)	163.4 (20.94)	163.6 (20.06)
Median	165.0	166.0	165.5	165.0	165.0	165.0	165.0
Min, Max	68, 188	70, 188	146, 191	150, 193	68, 191	70, 193	68, 193
Weight (kg)							
Mean (SD)	70.0 (28.90)	69.0 (28.41)	75.6 (16.26)	78.4 (17.76)	73.9 (21.01)	75.4 (22.15)	74.6 (21.56)
Median	75.0	75.0	71.0	74.5	73.0	75.0	74.0
Min, Max	6, 118	8, 111	48, 135	48, 156	6, 135	8, 156	6, 156

[a] Total includes all subjects from both treatments in the Preliminary Part (I) and the Primary Part (II) of the study.

Medical History Findings

Findings in medical history were reported for 164/167 (98.2%) subjects randomized to the FS Grifols treatment group in Part (I) + Part (II) and 156/160 (97.5%) subjects randomized to the Surgicel treatment. The pattern of these findings was quite diverse but similar between the FS Grifols and Surgicel treatment groups in Part (I) + Part (II). The most frequent findings that were reported in ≥ 10% of the subjects randomized to the FS Grifols treatment group were hypertension (54/167 [32.3%] subjects), lipodystrophy acquired (45/167 [26.9%] subjects), uterine leiomyoma (35/167 [21.0%] subjects), drug hypersensitivity (30/167 [18.0%] subjects), and gastroesophageal reflux disease (18/167 [10.8%] subjects). Similarly, the most frequent findings that were reported in ≥ 10% of the subjects randomized to the Surgicel treatment group were hypertension (50/160 [31.3%] subjects), lipodystrophy acquired (42/160 [26.3%] subjects), uterine leiomyoma (26/160 [16.3%] subjects), gastroesophageal reflux disease (23/160 [14.4%] subjects), drug hypersensitivity (22/160 [13.8%] subjects), and hyperlipidaemia (18/160 [11.3%] subjects).

Surgical History Findings

Findings in surgical history were reported for 52/167 (31.1%) subjects randomized to the FS Grifols treatment group and 48/160 (30.0%) subjects randomized to the Surgicel treatment group in the ITT population. The pattern of these findings was quite diverse but similar between the FS Grifols and Surgicel groups. The most frequent surgical history finding that was reported in ≥ 5% of the subjects was bladder neoplasm surgery (10/167 [6.0%] subjects) in the FS Grifols treatment group. The most frequent surgical history findings that were reported in ≥ 5% of the subjects randomized to the Surgicel treatment group were uterine dilation and curettage (8/160 [5.0%] subjects).

Bleeding Abnormality History Findings

Only 1 subject randomized to the FS Grifols treatment group had a bleeding abnormality history finding in this study. There were no family bleeding abnormality history findings in subjects randomized to the FS Grifols or Surgicel treatment groups in the study.

- **Numbers analysed**

Table 30: Disposition of Subjects (All Subjects Screened)

Table 10-2 Disposition of Subjects (All Subjects Screened)

Subject Disposition	Preliminary Part (I)		Primary Part (II)		Part (I) + Part (II)		Total[a]
	FS Grifols n (%)	Surgicel n (%)	FS Grifols n (%)	Surgicel n (%)	FS Grifols n (%)	Surgicel n (%)	
Subjects screened	164		334		--		498
Subjects randomized (ITT Population)	51	52	116	108	167	160	327
Subjects valid for PP Population[b]	44 (86.3)	41 (78.8)	104 (89.7)	102 (94.4)	148 (88.6)	143 (89.4)	291 (89.0)
Subjects valid for Safety Population (actual treatment)[b]	53	50	116	108	169	158	327
Subjects completed the study up to Week 6	48 (94.1)	44 (84.6)	103 (88.8)	95 (88.0)	151 (90.4)	139 (86.9)	290 (88.7)
Subjects discontinued prematurely before Week 6	3 (5.9)	8 (15.4)	13 (11.2)	13 (12.0)	16 (9.6)	21 (13.1)	37 (11.3)
Withdrawal of consent	2 (3.9)	2 (3.8)	5 (4.3)	4 (3.7)	7 (4.2)	6 (3.8)	13 (4.0)
Lost to follow-up	0	3 (5.8)	4 (3.4)	5 (4.6)	4 (2.4)	8 (5.0)	12 (3.7)
Death	0	0	2 (1.7)	1 (0.9)	2 (1.2)	1 (0.6)	3 (0.9)
Investigator's discretion	1 (2.0)	0	0	0	1 (0.6)	0	1 (0.3)
Other	0	3 (5.8)	2 (1.7)	3 (2.8)	2 (1.2)	6 (3.8)	8 (2.4)
Subjects completed the study up to Virology Follow-Up[c]	37 (72.5)	33 (63.5)	95 (81.9)	87 (80.6)	132 (79.0)	120 (75.0)	252 (77.1)
Subjects discontinued before Virology Follow-Up[c]	6 (11.8)	10 (19.2)	20 (17.2)	21 (19.4)	26 (15.6)	31 (19.4)	57 (17.4)
Pediatric subjects (Virology Follow-Up visit was not required)	8 (15.7)	9 (17.3)	1 (0.9)	0	9 (5.4)	9 (5.6)	18 (5.5)

Note: Percentages are based on the number of subjects randomized (ITT Population) as the denominator.

[a] Total includes all subjects from both treatments in the Preliminary Part (I) and the Primary Part (II) of the study.

[b] Subjects 4053001 and 4073001 were randomized to Surgicel but actually received FS Grifols in the Preliminary Part (I) of the study. The 2 subjects were excluded n and were included in the FS Grifols Safety Population.

[c] Virology Follow-Up is either Month 3 or Month 6 visit for any protocol version.

- **Outcomes and estimation**

Primary efficacy analysis

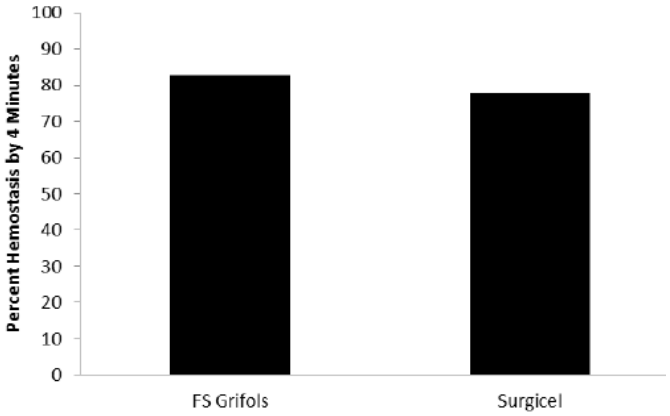

Figure 11-1 Analysis of Hemostasis by T_4 at Target Bleeding Site (ITT Population)

The primary efficacy analysis of haemostasis at the TBS by T4 based on nominal time points in the ITT population in the Primary Part (II) of the study is presented in Figure 11-1. The rate of haemostasis by T4 was 82.8% (96/116 subjects) in the FS Grifols treatment group and was 77.8% (84/108 subjects) in the Surgicel treatment group. Inferential analyses of the ratio and 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.064 (0.934, 1.213), indicating that FS Grifols is non-inferior to Surgicel and that the primary efficacy objective was achieved in the ITT population. The rate of haemostasis by T4 was higher, but not statistically superior in the FS Grifols treatment group compared to the Surgicel treatment group.

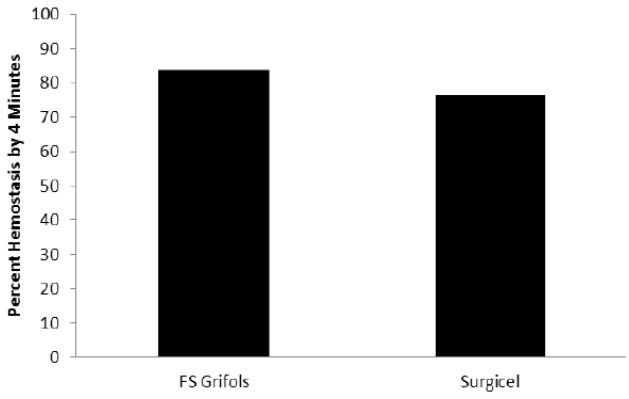

Figure 11-2 Analysis of Hemostasis by T_4 at Target Bleeding Site (PP Population)

Analysis of the primary efficacy endpoint of haemostasis at the TBS by T4 in the PP population in the Primary Part (II) of the study is presented in Figure 11-2. The rate of haemostasis by T4 was 83.7% (87/104 subjects) in the FS Grifols treatment group and was 76.5% (78/102 subjects) in the Surgicel treatment group. Similar to the ITT population, inferential analyses of the ratio and 95% CI of proportion of subjects

meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.094 (0.954, 1.255), indicating that FS Grifols is non-inferior to Surgicel and that the primary efficacy objective was achieved in the PP population. The rate of haemostasis by T4 was higher, but not statistically superior in the FS Grifols treatment group compared to the Surgicel treatment group.

Sensitivity Analysis

A sensitivity analysis of haemostasis at the TBS based on the exact (actual) assessment time at the first and last haemostatic assessment selected within the time window was performed. For the primary efficacy endpoint of haemostasis by T4, the results were the same for when the first and last haemostatic assessment was selected, and they were also identical to those of the primary efficacy analysis using the nominal assessment time.

The rate of haemostasis by T4 was 82.8% (96/116 subjects) in the FS Grifols treatment group and was 77.8% (84/108 subjects) in the Surgicel treatment group. Inferential analyses of the ratio and 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.064 (0.934, 1.213), demonstrating that FS Grifols is non-inferior to Surgicel and supporting the primary efficacy endpoint. The rate of haemostasis by T4 was higher, but not statistically superior in the FS Grifols treatment group compared to the Surgicel treatment group.

In the Preliminary Part (I) of the study, the rate of haemostasis at the TBS by T4 in the ITT population was higher in the FS Grifols treatment group (46/51 [90.2%] subjects) compared to the Surgicel treatment group (41/52 [78.8%] subjects).

In the Preliminary Part (I) of the study, the rate of haemostasis at the TBS by T4 in the PP population was higher in the FS Grifols treatment group (40/44 [90.9%] subjects) compared to the Surgicel treatment group (35/41 [85.4%] subjects).

Secondary efficacy analyses

Time to Haemostasis

Table 31: Analysis of Time to Hemostasis at Target Bleeding Site (ITT Population)

	Primary Part (II)		
Statistics	FS Grifols N=116	Surgicel N=108	P-value[a]
Mean (SE)	3.6 (0.25)	4.2 (0.29)	0.060
Q25	2.0	2.0	
Median (95% CI)	2.0 (2.00, 3.00)	3.0 (2.00, 3.00)	
Q75	3.0	4.0	

Note: TTH was measured in minutes

[a] P-value was calculated from Log-rank test.

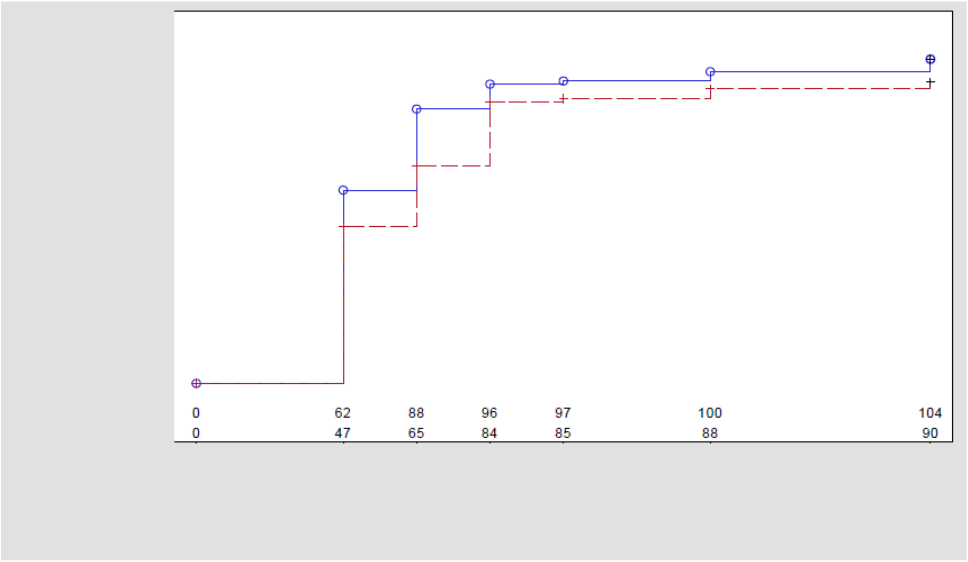

Figure 11-4 Time to Hemostasis at Target Bleeding Site (ITT Population)

Preliminary Part

Table 32:

Analysis of Time to Hemostasis at Target Bleeding Site (TBS)
Population: Intent-to-Treat

	Preliminary Part (I)		Primary Part (II)		
	FS Grifols (N=51)	Surgicel (N=52)	FS Grifols (N=116)	Surgicel (N=108)	P-value [1]
Statistics					
Mean (SE)	2.5 (0.14)	3.7 (0.38)	3.6 (0.25)	4.2 (0.29)	0.060
Q25	2.0	2.0	2.0	2.0	
Median (95% CI)	2.0 (NA, NA)	2.0 (2.00, 3.00)	2.0 (2.00, 3.00)	3.0 (2.00, 3.00)	
Q75	3.0	4.0	3.0	4.0	

Cumulative Proportion of Subjects Achieving Haemostasis at the Target Bleeding Site by T2 T5, T7, and T10

Table 33: Analysis of Hemostasis by T_2, T_5, T_7, and T10 at Target Bleeding Site (ITT Population)

	Primary Part (II)			
	FS Grifols N=116 n (%)	**Surgicel N=108 n (%)**	**RR (95% CI)[a]**	**P-value[b]**
Hemostasis by 2 minutes	62 (53.4)	47 (43.5)	1.228 (0.934, 1.615)	0.144
Hemostasis by 5 minutes	97 (83.6)	85 (78.7)	1.062 (0.936, 1.206)	0.394
Hemostasis by 7 minutes	100 (86.2)	88 (81.5)	1.058 (0.942, 1.188)	0.367
Hemostasis by 10 minutes	104 (89.7)	90 (83.3)	1.076 (0.969, 1.194)	0.176

[a] RR was the ratio of proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in Primary Part (II) (FS Grifols relative to Surgicel)

[b] P-value was calculated from Fisher Exact Test

Preliminary Part

Table 34: Analysis of Haemostasis by Each Time Point at Target Bleeding Site (TBS) Population: Intent-to-Treat

	Preliminary Part (I)	
	FS Grifols (N=51) n (%)	Surgicel (N=52) n (%)
Primary Efficacy Endpoint		
Hemostasis by 4 Minutes	46 (90.2)	41 (78.8)
Secondary Efficacy Endpoints		
Hemostasis by 2 Minutes	37 (72.5)	29 (55.8)
Hemostasis by 3 Minutes	43 (84.3)	38 (73.1)
Hemostasis by 5 Minutes	47 (92.2)	43 (82.7)
Hemostasis by 7 Minutes	47 (92.2)	45 (86.5)
Hemostasis by 10 Minutes	47 (92.2)	46 (88.5)

Treatment Failures

Table 35: Analysis of Treatment Failure at Target Bleeding Site (ITT Population)

	Primary Part (II)			
	FS Grifols N=116 n (%)	Surgicel N=108 n (%)	RR (95% CI)[a]	P-value[b]
Treatment failure	20 (17.2)	24 (22.2)	0.776 (0.456, 1.321)	0.401
Reason[c]				
Persistent bleeding	16 (13.8)	23 (21.3)		
Breakthrough bleeding	3 (2.6)	3 (2.8)		
Re-bleeding	5 (4.3)	3 (2.8)		
Use of alternative hemostatic treatment or maneuvers	9 (7.8)	18 (16.7)		
Re-applied treatment[d]	2 (1.7)	0		

[a] RR was the proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in Primary Part (II) (FS Grifols relative to Surgicel).

[b] P-value was calculated from Fisher Exact Test.

[c] The reasons were not mutually exclusive.

[d] Treatment could be reapplied beyond T_4 and until the completion of the surgical closure, but would be considered a treatment failure.

Preliminary Part

Table 36: Analysis of Treatment Failure at Target Bleeding Site (TBS) Population: Intent-to-Treat

	Preliminary Part (I)	
	FS Grifols (N=51) n (%)	Surgicel (N=52) n (%)
Treatment Failure	5 (9.8)	11 (21.2)
Reason [3]		
Persistent Bleeding	3 (5.9)	10 (19.2)
Breakthrough Bleeding	2 (3.9)	1 (1.9)
Re-bleeding	3 (5.9)	2 (3.8)
Use of Alternative Hemostatic Treatment or Maneuvers	4 (7.8)	3 (5.8)
Reapplied Treatment [4]	0	2 (3.8)

- **Ancillary analyses**

Subgroup Analyses

In the subgroup analyses of the primary efficacy endpoint, study centres, age group, approximate size of the bleeding surface at the TBS, and surgery type were used as stratifying variables in order to control for the effect of these covariates.

Subgroup Analysis by Study Centre

Analysis of haemostasis at the TBS by T4 stratified by study centre in the Primary Part (II) of the study is presented in Table 37. All small study centres, defined as less than 3 subjects in either treatment group of the Primary Part (II) of the study, were pooled together for efficacy analyses. Inferential analyses of the ratio and 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.079 (0.963, 1.209), demonstrating that FS Grifols is non-inferior to Surgicel.

Overall, in the Primary Part (II) of the study, the rates of haemostasis at the TBS by T4 were comparable to the overall primary efficacy analysis in most study centres. However, in study centre 320, the rates of haemostasis in the FS Grifols and Surgicel treatment groups were 11/19 (57.9%) subjects and 2/17 (11.8%) subjects, respectively.

Table 37: Analysis of Hemostasis by T4 at Target Bleeding Site Stratified by Investigational Study Centers (ITT Population)

	Primary Part (II)			
Site	FS Grifols n/N (%)	Surgicel n/N (%)	RR (95% CI)[a]	P-Value[b]
Hemostasis by 4 minutes			1.079 (0.963, 1.209)	0.170
Pooled sites[c]	7/10 (70.0)	4/6 (66.7)		
300	2/4 (50.0)	2/3 (66.7)		
304	2/4 (50.0)	4/5 (80.0)		
320	11/19 (57.9)	2/17 (11.8)		
321	13/13 (100.0)	12/12 (100.0)		
322	15/17 (88.2)	17/19 (89.5)		
323	4/4 (100.0)	1/3 (33.3)		
402	1/3 (33.3)	2/3 (66.7)		
405	3/3 (100.0)	3/3 (100.0)		
701	5/5 (100.0)	5/5 (100.0)		
702	7/7 (100.0)	6/6 (100.0)		
720	9/9 (100.0)	10/10 (100.0)		
721	8/9 (88.9)	8/8 (100.0)		
722	9/9 (100.0)	8/8 (100.0)		

[a] RR was the estimated common ratio of the proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in Primary Part (II) (FS Grifols relative to Surgicel)

[b] P-value was calculated from Cochran-Mantel-Haenszel Test

[c] All small sites, defined as <3 subjects in either treatment group of the Primary Part (II), were pooled together for efficacy analyses. Sites 307, 407, 325, 700, and 724 were pooled (Post-text Table 14.1.1/2)

Subgroup Analysis by Age Group

Analysis of haemostasis at the TBS by T4 stratified by age group in the Primary Part (II) of the study is presented in Table 38. Inferential analyses of the ratio and 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.064 (0.931, 1.215), demonstrating that FS Grifols is non-inferior to Surgicel.

There were no paediatric subjects aged ≤ 11 years old in either treatment group in the Primary Part (II) of the study. In the FS Grifols treatment group, 1/1 (100.0%) subject between the age of 12 to 17 years old achieved haemostasis; no subjects aged 12 to 17 years old received Surgicel treatment.

In adult subjects aged 18 to 64 years old, the rate of haemostasis at the TBS by T4 was higher in the FS Grifols treatment group (82/98 [83.7%] subjects) compared to the Surgicel treatment group (67/90 [74.4%] subjects) and was comparable to the overall primary efficacy analysis. The rate of haemostasis at the TBS by T4 in adult subjects ≥ 65 years old was lower in the FS Grifols treatment group (13/17 [76.5%] subjects) compared to the Surgicel treatment group (17/18 [94.4%] subjects).

Table 38: Analysis of Hemostasis by T_4 at Target Bleeding Site Stratified by Age Group (ITT Population)

	Primary Part (II)			
	FS Grifols n/N (%)	Surgicel n/N (%)	RR (95% CI)[a]	P-value[b]
Hemostasis by 4 minutes			1.064 (0.931, 1.215)	0.354
≤11 years	0	0		
12-17 years	1/1 (100.0)	0		
18-64 years	82/98 (83.7)	67/90 (74.4)		
≥65 years	13/17 (76.5)	17/18 (94.4)		

[a] RR was the estimated common ratio of the proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in Primary Part (II) (FS Grifols relative to Surgicel)

[b] P-value was calculated from Cochran-Mantel-Haenszel Test

Subgroup Analysis by Size of Bleeding Surface at Target Bleeding Site

Analysis of haemostasis at the TBS by T4 stratified by the size of the bleeding surface in the Primary Part (II) of the study is presented in Table 39. Inferential analyses of the ratio and 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.062 (0.932, 1.210), demonstrating that FS Grifols is non-inferior to Surgicel.

The rate of haemostasis at the TBS by T4 in subjects with a small (≤ 10 cm2) bleeding surface at the TBS was higher in the FS Grifols treatment group (46/54 [85.2%] subjects) compared to the Surgicel treatment group (38/51 [74.5%] subjects) and was comparable to the overall primary efficacy analyses.

In subjects with a medium (>10 cm2 and ≤ 100 cm2) bleeding surface at the TBS, the rate of haemostasis at the TBS by T4 was nearly identical in the FS Grifols (48/60 [80.0%] subjects) and Surgicel (45/56 [80.4%] subjects) treatment groups and was comparable to the overall primary efficacy analyses.

The rate of haemostasis at the TBS by T4 in subjects with a large (>100 cm2) bleeding surface at the TBS was identical in the FS Grifols (2/2 [100.0%] subjects) and Surgicel (1/1 [100.0%] subjects) treatment groups.

Table 39: Analysis of Hemostasis by T_4 at Target Bleeding Site Stratified by Size of Bleeding Surface (ITT Population)

	Primary Part (II)			
	FS Grifols n/N (%)	Surgicel n/N (%)	RR (95% CI)[a]	P-value[b]
Hemostasis by 4 minutes			1.062 (0.932, 1.210)	0.366
Small	46/54 (85.2)	38/51 (74.5)		
Medium	48/60 (80.0)	45/56 (80.4)		
Large	2/2 (100.0)	1/1 (100.0)		

Note: Small: ≤10 cm^2, Medium: >10 cm^2 and ≤100 cm^2, Large: >100 cm^2

[a] RR was the estimated common ratio of the proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in Primary Part (II) (FS Grifols relative to Surgicel)

[b] P-value was calculated from Cochran-Mantel-Haenszel Test

Subgroup Analysis by Surgery Type

Analysis of haemostasis at the TBS by T4 stratified by the type of soft tissue surgery in the Primary Part (II) of the study is presented in Table 40. Surgery types with <3 subjects in either treatment group in Primary Part (II) were pooled together. Inferential analyses of the ratio and 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.078 (0.952, 1.220), demonstrating that FS Grifols is non-inferior to Surgicel.

In subjects receiving abdominoplasties, haemostasis at the TBS by T4 occurred at a higher rate in the FS Grifols treatment group (30/40 [75.0%] subjects) compared to the Surgicel treatment group (18/37 [48.6%] subjects). The rates of haemostasis compared to the overall primary efficacy analysis were consistent in the FS Grifols treatment group, but was much lower in the Surgicel treatment group.

The rate of haemostasis at the TBS by T4 in subjects receiving radical cystectomies occurred at a lower rate in the FS Grifols treatment group (11/14 [78.6%] subjects) compared to the Surgicel treatment group (7/8 [87.5%] subjects). The rates of haemostasis compared to the overall primary efficacy analysis were consistent in both treatment groups.

In subjects receiving simple or radical hysterectomies and simple or radical nephrectomies, haemostasis at the TBS by T4 occurred at similar rates in the FS Grifols (37/39 [94.9%] and 9/10 [90.0%] subjects, respectively) and Surgicel (38/39 [97.4%] and 13/14 [92.9%] subjects, respectively) treatment groups. The rates of haemostasis were higher than the overall primary efficacy analyses in both treatment groups.

In subjects receiving radical prostatectomies, haemostasis at the TBS by T4 occurred at similar rates in the FS Grifols (6/8 [75.0%] subjects) and Surgicel (5/7 [71.4%] subjects) treatment groups and was consistent with the overall primary efficacy analyses.

In subjects receiving other pooled surgeries (lymphadenectomies, mastopexies, pyeloplasties, retroperitoneal tumor resections, and non-protocol defined surgeries), the rate of haemostasis at the TBS by T4 in the FS Grifols treatment group was 3/5 (60.0%) subjects. In the Surgicel treatment group, 3/3 (100.0%) subjects achieved haemostasis by T4.

Table 40: Analysis of Hemostasis by T_4 at Target Bleeding Site Stratified by Surgery Type (ITT Population)

	Primary Part (II)			
	FS Grifols n/N (%)	Surgicel n/N (%)	RR (95% CI)[a]	P-value[b]
Hemostasis by 4 minutes			1.078 (0.952, 1.220)	0.232
Abdominoplasties	30/40 (75.0)	18/37 (48.6)		
Radical cystectomies	11/14 (78.6)	7/8 (87.5)		
Radical prostatectomies	6/8 (75.0)	5/7 (71.4)		
Simple or radical hysterectomies	37/39 (94.9)	38/39 (97.4)		
Simple or radical nephrectomies	9/10 (90.0)	13/14 (92.9)		
Other surgeries pooled[c]	3/5 (60.0)	3/3 (100.0)		

[a] RR was the estimated common ratio of the proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in Primary Part (II) (FS Grifols relative to Surgicel)

[b] P-value was calculated from Cochran-Mantel-Haenszel Test

[c] Surgery types with <3 subjects in either treatment group in Primary Part (II) were pooled together (surgeries included lymphadenectomies, mastopexies, pyeloplasties, retroperitoneal tumor resections, and non-protocol defined surgeries)

Table 41: Summary of efficacy for trial IG1103

Title: A Prospective, A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis During Soft Tissue Open Surgeries		
Study identifier	IG1103	
Design	This trial consists of 2 parts: a Preliminary Part (I) and a Primary Part (II). Preliminary Part (I): Subjects in the Preliminary Part (I) of the study were to be randomized in a 1:1 ratio into 1 of 2 treatment groups: FS Grifols or Surgicel. The main objective of this part of the clinical study was to ensure that local study teams familiarized themselves with the technique for FS Grifols application and with intra-operative procedures required by the protocol of the clinical study. For each study center participating in the study, the first 4 subjects were to be enrolled in the Preliminary Part (I). Primary Part (II): Subjects in the Primary Part (II) of the study were to be randomized in a 1:1 ratio into FS Grifols or Surgicel treatment groups. The two main objectives of this part were as follows: 1) Assessment of the safety of FS Grifols. 2) Assessment of the efficacy of FS Grifols.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Intraoperatively: 10 minutes; Post-Operative assessments were performed on Days 1, 2, 3, 7, 14 and Week 6. Viral safety follow-up at month 3 (earlier protocol versions: month 6) not applicable not applicable
Hypothesis	Non-inferiority	
	FS Grifols primary	N=116
	Surgicel primary	N=108

Endpoints and definitions	Primary endpoint	Haemostasis at T4	Proportion of subjects in the Primary Part (II) of the study achieving haemostasis (Yes/No) at the TBS by T4 without occurrence of re-bleeding and re-application of study treatment after T4 and until TClosure and without brisk bleeding and use of alternative haemostatic treatment after TStart and until TClosure.
	Secondary	TTH	Time to Haemostasis
	Secondary	T2 T3 T5 T7 T10	Cumulative Proportion of Subjects Achieving Haemostasis at the Target Bleeding Site by Each of the Following Time Points: T2, T3, T5, T7, and T10
	Secondary	Treatment Failure	Treatment Failures

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	**Treatment group**	**FS Grifols preliminary**	**Surgicel preliminary**
	Number of subject	51	52
	Haemostasis at T4	90.2 % (n= 46)	78.8% (n=41)
	Treatment group	**FS Grifols primary**	**Surgicel primary**
	Number of subject	116	108
	Haemostasis at T4	82.8% (n=96)	77.8% (n=84)
	TTH median	2.0	3.0
	95% CI	2.00, 3.00	2.00, 3.00
	Haemostasis by T2	53.4% (n=62)	43.5% (n=47)
	Haemostasis by T3	75.9% (n=88)	60.2% (n=65)
	Haemostasis by T5	83.6% (n=97)	78.7% (n=85)
	Haemostasis by T7	86.2% (n=100)	81.5% (n=88)
	Haemostasis by T10	89.7% (n=104)	83.3% (n=90)
	Treatment Failure	17.2% (n=20)	22.2% (n=24)

Effect estimate per comparison	Primary endpoint Haemostasis at T4	FS Grifols primary vs. Surgicel	
		RR	1.064
		95% CI	0.934, 1.213
		P-value	0.401
	Secondary endpoint Treatment Failure	FS Grifols primary vs. Surgicel	
		RR	0.776
		95% CI	0.456, 1.321
		P-value	0.401

Statistical methods (studies IG1101, IG1102, IG1103)

The statistical analyses in studies IG1101, IG1102, IG1103 were planned and performed in a very similar manner. The same primary and secondary endpoints were tested and the same statistical analysis methodology was applied. This concerns the Fisher test respectively 95% confidence intervals for the binary haemostatic response variable (primary and secondary endpoints) and the log-rank test and Kaplan-Meier plots for time-to haemostasis.

2.5.2. Main studies

Analysis performed across trials (pooled analyses and meta-analysis)

A summary of the primary efficacy analysis of haemostasis at the TBS by T4 (ITT Population) in the Primary Part (II) of the clinical studies is presented in Table 42.

Table 42: Analysis of Hemostasis at the Target Bleeding Site by T_4 in the Primary Part (II) (ITT Population)

	Primary Part (II)			
Study	FS Grifols n/N (%)	Control[a] n/N (%)	RR (95% CI)	P-value
Integrated (IG1102 + IG1103)	199/227 (87.7)	175/221 (79.2)	1.109 (1.021, 1.205)[b]	0.014[d]
IG1101	83/109 (76.1)	13/57 (22.8)	3.339 (2.047, 5.445)[c]	<0.001[e]

[a] Control treatment = Surgicel (integrated studies [IG1102 and IG1103]) or MC (IG1101).

[b] RR was the estimated common ratio of the proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in the Primary Part (II) (FS Grifols relative to Surgicel).

[c] RR was the ratio of proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in the Primary Part (II) (FS Grifols relative to MC).

[d] P-value was calculated from CMH Test stratified by study/surgery type.

[e] P-value was calculated from Fisher Exact Test.

A summary of the primary efficacy analysis of haemostasis at the TBS by T4 in the PP Population in the Primary Part (II) of the clinical studies is presented in Table 43.

Table 43: Analysis of haemostasis at the target bleeding site by T4 in the primary part (II) (PP population

Study	Primary Part (II)			
	FS Grifols n/N (%)	Control[a] n/N (%)	RR (95% CI)	P-value
Integrated (IG1102 + IG1103)	173/191 (90.6)	163/202 (80.7)	1.129 (1.042, 1.223)[b]	0.003[d]
IG1101	75/97 (77.3)	12/52 (23.1)	3.351 (2.016, 5.567)[c]	<0.001[e]

[a] Control treatment = Surgicel (integrated studies [IG1102 and IG1103]) or MC (IG1101).

[b] RR was the estimated common ratio of the proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in the Primary Part (II) (FS Grifols relative to Surgicel).

[c] RR was the ratio of proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in the Primary Part (II) (FS Grifols relative to MC).

[d] P-value was calculated from CMH Test stratified by study/surgery type.

[e] P-value was calculated from Fisher Exact Test.

In the integrated primary efficacy analysis of clinical studies IG1102 and IG1103, there was a statistically significant difference in the comparison of the rates of haemostasis at the TBS by T4 between the FS Grifols (87.7% [199/227 subjects]) and Surgicel (79.2% [175/221 subjects]) treatment groups (p-value = 0.014). These results were confirmed by analysis of PP population. There was a statistically significant difference in the comparison of the rates of haemostasis at the TBS by T4 between the FS Grifols (90.6% [173/191 subjects]) and Surgicel (80.7% [163/202 subjects]) treatment groups (p-value = 0.003). These data indicate that FS Grifols is superior to Surgicel and that the primary efficacy objective was achieved in ITT and PP Population.

Clinical studies in special populations

Table 44: Proportion of Subjects Achieving Haemostasis at the Target Bleeding Site by T_4 for Categorized Elderly Age Groups (ITT Population)

Study Part	Age 65-74 n/N (%)	Age 75-84 n/N (%)	Age 85+ n/N (%)
IG1101[a]			
Preliminary Part (I)			
FS Grifols	11/19 (57.9)	3/8 (37.5)	0
Control[b]	--	--	--
Primary Part (II)			
FS Grifols	25/35 (71.4)	13/16 (81.3)	0
Control[b]	5/20 (25.0)	0/5	0
IG1102			
Preliminary Part (I)			

FS Grifols	13/17 (76.5)	3/3 (100.0)	0
Control[b]	9/18 (50.0)	3/3 (100.0)	0
Primary Part (II)			
FS Grifols	31/31 (100.0)	8/10 (80.0)	0
Control[b]	23/27 (85.2)	9/10 (90.0)	0
IG1103			
Preliminary Part (I)			
FS Grifols	8/8 (100.0)	5/5 (100.0)	2/3 (66.7)
Control[b]	8/9 (88.9)	4/5 (80.0)	1/1 (100.0)
Primary Part (II)			
FS Grifols	9/11 (81.8)	4/5 (80.0)	0/1
Control[b]	14/15 (93.3)	3/3 (100.0)	0
Integrated (IG1102 + IG1103)			
Preliminary Part (I)			
FS Grifols	21/25 (84.0)	8/8 (100)	2/3 (66.7)
Control[b]	17/27 (63.0)	7/8 (87.5)	1/1 (100.0)
Primary Part (II)			
FS Grifols	40/42 (95.2)	12/15 (80.0)	0/1
Control[b]	37/42 (88.1)	12/13 (92.3)	0

Supportive study

NA

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant has submitted the results of three completed phase III studies in peripheral vascular surgery (IG1101), parenchymal organ surgery (IG1102) and soft tissue surgery (IG1103) which represent the usual spectrum of the clinical investigation for fibrin sealants. All three submitted trials are single blind with the patient blinded towards assigned treatment and the investigator (surgeon) not. All trials consist of a preliminary phase intended for familiarisation with study procedures, and a primary phase which forms the basis of the primary efficacy analysis.

In the preliminary phase, the first two patients of each study centre were treated with VeraSeal in vascular surgery and the first four patients of each centre were randomized 1:1 to VeraSeal or Surgicel for parenchymous organ and soft tissue surgery. In the primary phase of each trial, patients were randomized 2:1 to VeraSeal or manual compression in vascular surgery or 1:1 to VeraSeal or Surgicel in parenchymous organ and soft tissue surgery.

A sufficient number of subjects were exposed to VeraSeal in the primary part of each study, 109, 111 and 116 patients in IG1101, IG1102 and IG1103, respectively. In addition, 59, 52 and 51 subjects in the preliminary parts of IG1101, IG1102 and IG1103, respectively, provided efficacy data for VeraSeal.

The chosen comparator arms, manual compression for vascular surgery and treatment with Surgicel, an oxidised cellulose polymer in clinical use for decades both in the EU and the US, are considered appropriate and acceptable.

The selected primary efficacy endpoint, the proportion of subjects achieving haemostasis at 4 minutes, is considered relevant for each type of surgery. The secondary endpoints (Time to haemostasis; Cumulative proportion of subjects achieving haemostasis at 2,3,5,7 and 10 minutes; Treatment failures) are appropriate, however, they represent mainly different aspects of the primary endpoint. There is an apparent lack of other, clinically relevant endpoints which could have provided a more complete picture of the efficacy of FS Grifols. Transfusion requirements, postoperative rebleeding at TBS, reoperation at TBS, postoperative blood loss, graft thrombosis or occlusion, length of hospital stay would have been secondary endpoints of interest.

Subgroup analyses supplement the primary analysis and substantiate the robustness of the findings in different settings, i.e. according to study centres, age group, type of surgery and size of the bleeding surface at the TBS (IG1102 and IG1103). Sensitivity analyses of the primary endpoint using the actual assessment time confirm the findings of the primary analysis for each trial.

The statistical analysis has altogether been well preplanned and performed. Nevertheless two methodological issues deserved a further look: randomization has been done with the minimal block size possible (block size 3 for IG1101, block size 2 for IG1102 and IG1103). In these investigator unblinded trials it needs to be demonstrated that this has not resulted in a biased patient selection. Furthermore, the statistical analyses did not use the time point of randomisation as starting point, but used the start of the treatment application. Sensitivity analyses addressing these two issues were requested and confirmed that the initial conclusions remained valid.

There were several changes to the protocols prior to or after randomization in all presented studies. The changes before randomization amongst others concerned age/weight of paediatric population then children withdrawal, withdrawal of patients with mild bleeding and visit at month 6 of the study. There were also modifications in the statistical part (SAP) of the study IG1101 and concerned sample size calculations. The changes are considered to be non-substantial and to most likely not impact the study results.

Efficacy data and additional analyses

The provided efficacy data show that VeraSeal is superior to manual compression for the control of moderate bleeding in peripheral vascular surgery. The rate of haemostasis by T4 in the ITT population in trial **IG1101** was 76.1% (83/109 subjects) in the FS Grifols treatment group and 22.8% (13/57 subjects) in the MC treatment group. This difference is statistically significant in favour of VeraSeal (p-value <0.001). In the PP population, this result is mirrored with the rate of haemostasis by T4 being 77.3% (75/97 subjects) in the FS Grifols treatment group and 23.1% (12/52 subjects) in the MC treatment group. The rate of treatment failure

in the ITT population was 26/109 [23.9%] subjects in FS Grifols treatment group compared to 44/57 [77.2%] subjects in the MC treatment group (p-value <0.001).

For the treatment of moderate bleeding from a raw cut liver surface in study **IG1102**, the rate of haemostasis by T4 was 92.8% (103/111 subjects) in the VeraSeal treatment group and 80.5% (91/113 subjects) in the Surgicel treatment group in the ITT population. The rate of haemostasis by T4 was significantly higher in the FS Grifols treatment group (p-value = 0.010), indicating that non-inferiority to treatment with Surgicel was achieved. Additionally, the lower limit of the 95% CI above 1 indicates that FS Grifols is superior to Surgicel [RR 1.152 (1.038, 1.279)]. In the PP population, the rate of haemostasis by T4 was 98.9% (86/87 subjects) in the FS Grifols treatment group and 85.0% (85/100 subjects) in the Surgicel treatment group. The rate of treatment failure was 8/111 [7.2%] subjects in the FS Grifols treatment group compared to 22/113 [19.5%] in the Surgicel treatment group (p-value = 0.010).

And finally, in the treatment of moderate generalized bleeding after retroperitoneal soft tissue dissection (trial **IG1103**), the rate of haemostasis by T4 was 82.8% (96/116 subjects) in the FS Grifols treatment group and 77.8% (84/108 subjects) in the Surgicel treatment group of the ITT population. A RR and 95% CI of 1.064 (0.934, 1.213) indicates that FS Grifols is non-inferior to Surgicel. The rate of haemostasis by T4 was higher, but not statistically superior in the FS Grifols treatment group compared to the Surgicel treatment group. In the PP population, the rate of haemostasis by T4 was 83.7% (87/104 subjects) in the FS Grifols treatment group and 76.5% (78/102 subjects) in the Surgicel treatment group. The rate of treatment failure was 20/116 [17.2%] subjects in the FS Grifols treatment group compared to 24/108 [22.2%] subjects in the Surgicel treatment group.

Sensitivity and subgroup analyses support the results of the primary efficacy evaluation of all three trials.

2.5.4. Conclusions on the clinical efficacy

The efficacy of VeraSeal in achieving haemostasis has been demonstrated in three phase III studies, covering the usual clinical development areas of a fibrin sealant (soft tissue surgery, parenchymal organ surgery and peripheral vascular surgery). FS Grifols was compared to manual compression in vascular surgery and to Surgicel in parenchymous and soft tissue surgery. The primary efficacy objective of superiority to manual compression in vascular surgery and non-inferiority to Surgicel in parenchymous and soft tissue surgery was achieved. A number of subgroup analyses and sensitivity analyses substantiate the results of the primary efficacy evaluations. The beneficial effect of VeraSeal inducing haemostasis could be replicated in three different surgical settings. Clinical trials IG1102 and IG1103 in parenchymal organ and soft tissue surgery provide the basis for granting the indication ‘supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis’. Clinical trial IG1101 in peripheral vascular surgery, which is commonly used as a reproducible model for general vascular surgery, provides the basis for granting the indication ‘suture support for haemostasis in vascular surgery’.

Thus, a marketing authorisation can be recommended for VeraSeal frome a clinical efficacy perspective.

2.6. Clinical safety

The available safety data on the Fibrin Sealant Grifols (FS Grifols) are derived from an Integrated Summary/Analysis of Safety which includes 3 studies, and summaries of the results presented in the individual final clinical study reports from:

- **Study IG1101**: A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis during *Peripheral Vascular Surgery*
- **Study IG1102**: A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis During *Parenchymous Tissue Open Surgeries*
- **Study IG1103**: A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis during *Soft Tissue Open Surgeries*

The target populations in the 3 clinical trials summarized in this ISS included subjects undergoing vascular, parenchymous, or soft tissue surgeries, either male or female, and without an upper or lower age limit.

All 3 phase 3 clinical trials were conducted using the same general trial design with each trial consisting of a *Preliminary Part (I)* (uncontrolled in Study IG1101; comparator controlled in Studies IG1102 and IG1103) followed by a *Primary Part (II)* (comparator controlled) phase and with similar subject monitoring and follow-up periods. The individual subject data from all 3 phase 3 trials were combined for the analyses of e.g. treatment exposure, adverse events (AEs), adverse drug reactions (ADRs), AEs by subgroups (age groups, adult versus paediatric, and gender).

Patient exposure

Among the 3 clinical trials, 877 subjects were assigned or randomized to a specific study treatment. Among those, 498 subjects were assigned or randomized to receive FS Grifols (intent-to-treat [ITT] Population), 322 subjects were randomized to receive Surgicel (ITT Population), and 57 subjects were randomized to receive MC.

Due to 2 subjects who were randomized to Surgicel but actually received FS Grifols in error in Preliminary Part (I) of Study IG1103, the Safety Population included 500 subjects treated with FS Grifols. Thus the control group consisted of 320 subjects treated with Surgicel (in the IG1102 trial of parenchymous surgeries and the IG1103 trial of soft tissue surgeries) and 57 subjects treated with manual compression (in the IG1101 trial of vascular surgeries).

The following table shows the subjects receiving FS Grifols by clinical trial:

Table 45: Subjects Exppsed to FS Grifols by Study (All Subjects Assigned or Randomized)

Subject Disposition	IG1101 n (%)	IG1102 n (%)	IG1103 n (%)	Total n (%)
Subjects randomized (ITT Population)	168 (33.7%)	163 (32.7%)	167 (33.5%)	498 (100%)
Subjects valid for Safety Population (actual treatment)	168 (33.6%)	163 (32.6%)	169[a] (33.8%)	500 (100%)

Note: Percentage values are calculated using the Total column as the denominator.

[a] Two subjects were randomized to Surgicel in IG1103 but actually received FS Grifols in the Preliminary Part (I) of the trial.

Subjects in the FS Grifols treatment group undergoing vascular surgery were to receive up to a maximum of 6 mL FS Grifols compared with subjects undergoing parenchymous or soft tissue surgeries who were to receive up to a maximum of 12 mL FS Grifols. Subjects in the Surgicel treatment group undergoing parenchymous or soft tissue surgeries were to receive up to the allotted 4 Surgicel sheets.

The mean volume of FS Grifols exposure was 6.78 mL, with a median volume of 6.00 mL and a range of 0.3 to 18.0 mL (minimum to maximum). The mean volume of FS Grifols applied in study IG1101 was 4.23 mL, with a median of 4.20 mL and a range of 0.3 to 12.0 mL (minimum to maximum). The mean volume of FS Grifols applied in studies IG1102 and IG1103 combined was 8.07 mL, with a median of 6.0 mL and a range of 0.3 to 18.0 mL (minimum to maximum). The mean number of Surgicel treatment sheets applied was 1.59 sheets, and the median number was 1.00 sheet, and the minimum and the maximum numbers of the sheets used were 1 to 4, respectively.

Adverse events

The safety and tolerability of FS Grifols were assessed by analyzing e.g. adverse events (AEs), adverse drug reactions (ADRs) or laboratory values (including virus safety assessments and immunogenicity).

The following table provides a summary of treatment-emergent adverse events (TEAEs) including adverse drug reactions (ADRs) in the integrated dataset:

Table 46: Summary of Treatment Emergent Adverse Events by Treatment Group in All 3 Studies (Safety Population)

	Pooled Safety FS Grifols N=500 n (%)	Pooled Safety Surgicel N=320 n (%)	MC N=57 n (%)
Subjects with any TEAE	419 (83.8)	278 (86.9)	44 (77.2)
Total number of TEAEs	1763	1263	104
Subjects with any ADR	64 (12.8)	27 (8.4)	3 (5.3)
Total number of ADRs	128	65	5
Subjects with any ADR attributable to application technique	1 (0.2)	0	0
Total number of ADRs attributable to application technique	2	0	0
Subjects with any SAE	81 (16.2)	41 (12.8)	11 (19.3)
Total number of SAEs	167	65	14
Subjects with any TEAE with outcome of death	13 (2.6)	4 (1.3)	0
Subjects with any serious ADR	9 (1.8)	0	1 (1.8)
Total number of serious ADRs	15	0	1
Subjects with any AE leading to withdrawal	0	0	0
Total number of AEs leading to withdrawal	0	0	0

Source: Table 5.3/1.2 of ISS in Module 5.3.5.3

Treatment-emergent AEs (TEAEs) were defined as AE which occurred on or after the start of the study treatment up to and including the date of the week 6 visit whereas non-TEAEs was defined as an AE occurring prior to study treatment.

As can be seen in the table above, overall the incidences with TEAEs among the 3 studies can be deemed comparable among the FS Grifols (83.8%) and Surgicel (86.9%) treatment group with a slightly lower incidence in the MC Group (77.2%).

Common Adverse Events

The following table provides a summary of TEAEs reported for at least 5% of subjects within a treatment group is provided by preferred term for all 3 clinical trials:

Table 47: Treatment-Emergent Adverse Events Reported in ≥% of Subjects by Preferred Term within a Treatment Group in All 3 Studies (Safety Population)

Preferred Term	FS Grifols N=500 n (%)	Surgicel N=320 n (%)	Manual Compression N=57 n (%)
Procedural pain	209 (41.8)	147 (45.9)	21 (36.8)
Nausea	67 (13.4)	56 (17.5)	2 (3.5)
Pyrexia	50 (10.0)	35 (10.9)	6 (10.5)
Anaemia	45 (9.0)	40 (12.5)	2 (3.5)
Constipation	46 (9.2)	34 (10.6)	4 (7.0)
Hypotension	36 (7.2)	15 (4.7)	3 (5.3)
Hypertension	35 (7.0)	24 (7.5)	1 (1.8)
Oedema peripheral	30 (6.0)	14 (4.4)	1 (1.8)
Vomiting	29 (5.8)	26 (8.1)	3 (5.3)
Incision site pain	28 (5.6)	18 (5.6)	1 (1.8)
Procedural nausea	24 (4.8)	32 (10.0)	0
Tachycardia	23 (4.6)	31 (9.7)	1 (1.8)
Pruritus	23 (4.6)	22 (6.9)	0
Body temperature increased	11 (2.2)	2 (0.6)	4 (7.0)
Hyperglycaemia	9 (1.8)	18 (5.6)	0
Hypophosphataemia	9 (1.8)	16 (5.0)	0
Vascular graft thrombosis	2 (0.4)	0	3 (5.3)

Note: For each preferred term, subjects are counted only once.

Source: Post-text Table 5.3/1.19 of ISS in Module 5.3.5.3

Among the treatment groups, the nature of the TEAE´s were comparable, also in terms of the incidences. The most frequently reported TEAE in at least 5% of subjects in the FS Grifols treatment group were Procedural pain (41.8%), nausea (13.4%), and pyrexia (10%) which are typical and common in open surgeries.

Treatment-Emergent Adverse Events by Severity

60/500 (12.0%) subjects experienced a TEAE with a severity of severe, 163/500 (32.6%) subjects experienced a TEAE with a severity of moderate, and 196/500 (39.2%) subjects experienced a TEAE with a severity of mild in the FS Grifols group. in the Surgicel treatment group, 21/320 (6.6%) subjects experienced a TEAE with a severity of severe, 140/320 (43.8%) subjects experienced a TEAE with a severity of moderate, and 117/320 (36.6%) subjects experienced a TEAE with a severity of mild. In the MC treatment group, 8/57 (14.0%) subjects experienced a TEAE with a severity of severe, 11/57 (19.3%) subjects experienced a TEAE with a severity of moderate, and 25/57 (43.9%) subjects experienced a TEAE with a severity of mild.

Overall, the frequencies can be deemed comparable among all 3 treatment groups although there were proportionally slightly more severe events in the FC Grifols Group, slightly fewer moderate events in the MC group and slightly more mild events in the MC group.

On day 121 of the procedure, a thorough discussion has been provided covering the very slight numerical imbalances observed with regards to TEAEs, total SAEs or deaths between the FS Grifols and the Surgicel treatment group which could theoretically be based on a potential failure in the randomization scheme. The applicant has sufficiently clarified these uncertainties and no safety issues in this context are apparent. The AEs reported are considered to be consistent with the study population, the nature of the surgery and the underlying medical condition. Furthermore, no notable differences were observed, but only very slight tendencies which are most likely based on random chance.

Adverse Drug Reactions (Adverse Reaction by relationship assessed by the investigator as definitely related, probably related, possibly related, or unlikely related).

In the FS Grifols and Surgicel treatment group the majority of individual ADRs occurred in ≤ 2 subjects. Exceptions for the FS Grifols group were:

FS Grifols	*Surgicel*
procedural pain (10/500 [2.0%]	procedural pain (6/320 [1.9%]
nausea (6/500 [1.2%]	pyrexia (5/320 [1.6%]
pruritus (5/500 [1.0%]	anemia (5/320 [1.6%]
pyrexia (3/500 [0.6%]	
B19V test positive (3/500 [0.6%]	

Among subjects in the Surgicel treatment group, no subjects experienced a TEAE that was considered definitely or probably related.

In the FS Grifols treatment group 1/500 (0.2%) experienced an ADR that was considered definitely related to the study treatment (Procedural pain 1//128 (0.8%)). Most of the ADRs occurred in the FS Grifols treatment group were considered unlikely related to the study treatment (111 of 128 (86.7%). Among the ADRs considered possibly related to study treatment were: procedural pain, pruritus, pyrexia, B19V test positive (3 ADRs), prothrombin time prolonged (2 ADRs), vascular graft complication, hyperthermia, cellulitis, contusion, peritonitis, abdominal wound dehiscence, and somnolence.

In the Surgicel treatment group most of the ADEs were considered unlikely related to the study treatment (53 of 65 (81.5%). Among the ADRs considered possibly related to study treatment were: were procedural pain (2 ADRs), pyrexia (3 ADRs), anemia (2 ADRs), prothrombin time prolonged, vaginal cellulitis, pancreatitis, and white blood cell count increased.

In the MC treatment group, all of the individual ADRs (preferred terms) occurred in single subjects, and all were considered unlikely related to study treatment.

The majority of ADRs in all treatment groups were either mild to moderate in severity (94% FS Grifols; 97% Surgicel, 100% MC). 7/500 (1.4%) subjects experienced a severe ADR compared to 2/320 (0.6%) in the surgical treatment group and 0/57 (0%) in the MC treatment group. No severe ADR was experienced by more than one subject for any preferred term within a treatment group.

Overall, the ADRs reported are considered to be consistent with the study population and the nature of the surgery. Furthermore, no notable differences of incidences between the treatment groups were noted and the majority of ADR were considered unlikely related to the study treatment (FS Grifols (111 of 128 (86.7%); Surgicel (53 of 65 (81.5%); all in the MC treatment group).

Intra-Operative Treatment-Emergent Adverse Events (TEAEs that started during surgery until the completion of the surgical closure), **Surgical Treatment-Emergent Adverse Events** (events that happened from the end of the surgery until 24 hours after the end of surgery or until recovery from anesthesia, whichever was later) and **Nonsurgical Treatment-Emergent Adverse Events** (events that started more than 24 hours after the end of surgery or after recovery from anesthesia, whichever was later)

The most frequent types of intra-operatively TEAEs were typical of open surgeries under general anesthesia or were related to the underlying medical conditions of the study population. Among the treatment groups, the incidences can be considered comparable.

When looking at the most frequent types of surgical TEAEs, these were typical of open surgeries under general anaesthesia or were related to the underlying medical conditions of the study population. Among the treatment groups, the incidences can be considered comparable as well.

With regards to the nonsurgical TEAE no unexpected AE occurred. The AE noted were typical for subjects that underwent surgical procedures and could also be related to the underlying medical condition.

Serious adverse event / deaths / other significant events

Deaths

In the pooled analysis set 17/820 (2.1%) subjects died: Thirteen of 500 (2.6%) subjects in the FS Grifols treatment group, 4/320 (1.3%) subjects from the Surgicel treatment group, and no subjects from the MC treatment group died.

Most TEAEs with a fatal outcome started several days to weeks after surgery. Exceptions were:

☐ Subject in the *FS Grifols treatment group*, who experienced hypotension on Day 1 and respiratory failure and hepatic failure on Day 4

☐ Subject in the *Surgicel treatment group*, who experienced haemorrhage, venous injury, disseminated intravascular coagulation and cardiac arrest on Day 1

☐ Subject in the *FS Grifols treatment group*, who experienced respiratory failure and vena cava thrombosis on Days 3 and 4, respectively

☐ Subject in the *FS Grifols treatment group*, who experienced multi-organ failure on Day 3

When looking at the narratives provided, the fatal outcomes which occurred short after the surgery (3 cases in the FS Grifols treatment group, 1 case in the surgical treatment group) are most likely associated to the underlying medical condition, the comorbidities and the advanced age of the subjects undergoing serious interventions such as hepatectomy or lobectomy.

All TEAEs with a fatal outcome were considered not related to study treatment.

Serious Adverse Events

Among the treatment groups, the SAE occurred can be considered typical for open surgeries. Most of the SAEs which occurred in the FS Grifols treatment group (72/81 subjects) were considered unrelated to study treatment. In 9 subjects (9/81 subjects), 6 subjects had SAEs that were considered unlikely related (postoperative wound infection, wound infection, abdominal abscess, deep vein thromboses, pulmonary embolism, postprocedural bile leak liver abscess) and 3 subjects had SAEs that were considered possibly related (cellulitis, parvovirus B19 (B19V) test positive, abdominal wound dehiscence, and peritonitis) to the study treatment. With regards to abdominal wound dehiscence and peritonitis which occurred in one subject (SAE in subject), the Applicant has discussed this case more thoroughly as requested in the D120 LoQ. It is considered very unlikely in this specific case that the study treatment or application technique are related to the widespread adhesions, wound dehsicence or peritonitis. This is especially true, when considering the underlying diagnosis, the comorbidities and the subjects' major surgeries in this context.

In the Surgicel treatment group (41/320 subjects), all SAEs were considered unrelated to the study treatment. In the Manual Compression treatment group (11/57 subjects) all SAE were considered unrelated except for 1 subject (sepsis, considered unlikely related).

Overall, the SAE presented so far did not give any grounds for concerns since they can be considered typical for open surgeries. Furthermore, the applicant has sufficiently provided detailed data and a respective discussion on day 121 of the procedure covering the uncertainties raised with regards to re-bleeding events and hypersensitivity reactions. No notable differences between the treatment groups are apparent and the remaining uncertainties could be resolved. Furthermore, no evidence of a lack of efficacy of the study treatment in relation to re-bleeding events was apparent, as sufficiently outlined by the applicant.

In addition, the applicant has elaborated further on local complications or findings potentially linked to the study treatment. From the table and discussion provided, the applicant´s conclusion that no local complications related to the study treatment have occurred in the studies conducted can be followed.

More data on thrombotic events associated with the study medication were provided including any SAE observed throughout the studies potentially associated to an increased thrombogenicity. From the data set provided, no increased risk for thrombogenicity could be identified. Furthermore, no statistically significant difference between the treatments groups in the studies conducted could be observed.

Laboratory findings

With regards to the Complete Blood Count no notable differences among the treatment groups with regards to changes from baseline values could be observed. It has to be noted as well that shifts in e.g. Haematocrit, red blood cells, haemoglobin etc. are typical for long and open surgeries (or for the preparation of these procedures).

Between the FS Grifols treatment group and the comparator treatment group, no significant differences were noted with regards to Clinical Chemistry values.

When looking at changes from baseline regarding aPTT ratio and prothrombin INR, changes in the FS Grifols and the comparator group were noticed. However these changes are deemed rather small and may be linked to the surgery itself or the preparation of the procedure.

Overall, the changes in haematology and coagulation parameters observed can be expected for subjects undergoing surgical procedures or may be related to the underlying medical condition and did not give any reasons for concern.

With regards to the virology results, no concerns arise. The data provided suggest no treatment-emergent viral infection.

Safety in special populations

Paediatric Subjects

Only a small number of paediatric patients were evaluated in the 3 clinical trials with only 23 paediatric subjects in the treatment groups: Eleven paediatric subjects ranging 3 to 16 years old were enrolled in the FS Grifols treatment group, 12 paediatric subjects were enrolled in the Surgicel treatment group and none in the MC treatment group. Therefore caution is required when interpretation these outcomes due to the small sample size.

Overall the TEAEs reported in the paediatric subjects were comparable between the FS Grifols treatment group and the surgical treatment group with procedural pain being the most frequently reported AE. However no clear pattern can be identified due to the small sample size and the large imbalance in numbers between adults and paediatric subjects.

Elderly Subjects

288 subjects were in the ≥ 65 years of age subgroup with 172/288 (59,7%) receiving FS Grifols. The overall TEAE incidence was 143/172 (83.1%) in the FS Grifols treatment group which can be considered comparable to the control group (77/91 (84.6%) in the Surgicel treatment group and 20/25 (89%) in the MC treatment group. Overall, the incidences of the most frequently reported TEAEs were comparable among the treatment groups, with a few exemptions such as nausea, peripheral oedema, incision site pain, hypokalaemia, ileus or atelectasis which occurred less likely in the MC treatment group. However, the small number in the MC treatment group (n=25) should be kept in mind when interpreting these results.

Compared to the adults subgroup 18 to 64 years of age (n=566) with an overall TEAE incidence of 266/317 (83.9%) in the FS Grifols treatment group, 189/217 (87.1%) in the Surgicel treatment group and 24 /32 (75.0%) in the MC treatment group, the incidences of TEAE can be deemed comparable. It is noted that Hypertension occurred more frequently in the in the elderly Surgicel subgroup (13/91 [14.3%] subjects) compared with the 18 to 64 years of age Surgicel subgroup (9/217 [4.1%] subjects).

Immunological events

Subjects were tested for immunogenicity (AB against antibodies against human coagulation factor V, human thrombin, and human fibrinogen at baseline, postoperative Day 14 (± 2 days), and postoperative Week 6 (± 4 days) visits) if 1 or more of their post exposure samples had inexplicable prolonged coagulation times (INR ≥ 2.0 or aPTT ratio ≥ 1.5). Only two specimens were found to be positive for AB to human thrombin (subject in the FS Grifols treatment group) in the 29 subjects tested, which however were already present at baseline. In the absence of any other AB titres determined, it can therefore be concluded that no immunogenicity from the treatment with FS Grifols, Surgicel or MC occurred.

However, the validity/usefulness of the assay could not be assessed properly since the relevant documents were missing in the dossier. The applicant has submitted the SOP and validation of the assays for antibody testing, which were found satisfactory.

Safety related to drug-drug interactions and other interactions

No formal drug interaction assessments were performed.

Discontinuation due to adverse events

No subjects discontinued the study due to an AE in any treatment groups in all 3 studies IG1101, IG1102, and IG1103.

2.6.1. Discussion on clinical safety

The available safety data on the Fibrin Sealant Grifols (FS Grifols) are derived from an Integrated

Summary/Analysis of Safety which includes 3 studies, and summaries of the results presented in the individual final clinical study reports from Study IG1101 (Peripheral vascular surgery), Study IG1102 (Parenchymous Tissue Open Surgeries) and Study IG1103 (Soft Tissue Open Surgeries). All 3 phase 3 clinical trials were conducted using the same general trial design. Among the 3 clinical trials, 877 subjects were assigned or randomized to a specific study treatment (FS Grifols, Surgicel, Manual Compression).

The Safety Population included 500 subjects treated with FS Grifols including 168 subjects undergoing vascular surgery, 163 subjects undergoing parenchymous surgery, and 169 undergoing soft tissue surgery. The comparator treatment group consisted of 320 subjects treated with Surgicel and 57 subjects treated with MC. Overall, an adequate number of subjects have been included to evaluate the safety profile of FS Grifols.

The volume of FS Grifols administered was up to 6 mL in study IG1101 (vascular surgery) and up to 12 mL in studies IG1102 and IG1103 (parenchymous surgery and soft tissue surgery, respectively). The mean volume of FS Grifols applied among all 3 studies was 6.78 mL, with a median of 6.0 mL and a range of 0.3 to 18.0 mL (minimum to maximum). Overall the exposure to FS Grifols among the 3 studies can be considered adequate. The maximal individual volume of 12 ml of FS Grifols was the dose established in the Protocol.

The most frequently reported TEAEs were representative for major surgical procedures of long duration. The most frequently reported TEAE in at least 5% of subjects in the FS Grifols treatment group were Procedural pain (41.8%), nausea (13.4%), pruritus (1%) and pyrexia (10%). No substantial differences in TEAE incidences were noted between treatment groups. The most common TEAEs for the comparator group were for the Surgicel treatment group: Procedural pain (45.9%), nausea (17.5%), anemia (12.5%), pyrexia (10.9%), constipation (10.6%), and procedural nausea (10.0%) and for the Manual Compression treatment group Procedural pain (36.8%) and pyrexia (10.5%).

The majority of TEAEs in all treatment groups were either mild or moderate in severity.

In 64/500 (12.8%) of with any ADR reported in the FS Grifols group, only 1 subject had 1 event (procedural pain) that was considered definitely related to study treatment. Among the ADRs considered possibly related to study treatment were: procedural pain, pruritus, pyrexia, B19V test positive (3 ADRs), prothrombin time prolonged (2 ADRs), vascular graft complication, hyperthermia, cellulitis, contusion, peritonitis, abdominal wound dehiscence, and somnolence.

Most of the SAEs occurred in the FS Grifols treatment group (72/81 subjects) were considered unrelated to study treatment. In 9 subjects (9/81) 6 subjects had SAEs that were considered unlikely related and 3 subjects had SAEs that were considered possibly related to the study treatment. In the Surgicel treatment group, all SAEs were considered unrelated to the study treatment. In the Manual Compression treatment group all SAE were considered unrelated except for 1 subject.

From the data set provided, no increased risk for thrombogenicity could be identified. Furthermore, no statistical significant difference between the treatments groups in the studies conducted could be observed in this context. Nevertheless, since thromboembolic complications may occur if the preparation is unintentionally applied intravascularly, this has been reflected in Section 4.4 of the SmPC and added as a potential risk in the RMP.

No local complications related to the study treatment have occurred in the studies conducted. In the all 3 studies conducted, no fatal outcome was considered related to the study treatment. Life-threatening air or gas embolism has occurred with the use of spray devices employing a pressure regulator to administer fibrin sealant products. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface. Hence, a warning in section 4.4 of the SmPC has been added to highlight this risk and instructions to minimise this risk has been added to

section 6.6 of the SmPC.

The risk appears to be higher when fibrin sealants are sprayed with air, as compared to CO_2 and, therefore, cannot be excluded with VeraSeal. To minimize this risk, the spray device should be operated according to the instructions provided in section 6.6. of the SmPC.

Most TEAEs with a fatal outcome started several days to weeks after surgery, with only a few exceptions (3 cases in the FS Grifols treatment group, 1 case in the surgical treatment group). When looking at the narratives provided, the fatal outcomes which occurred short after the surgery are most likely associated to the underlying medical condition, the comorbidities and the advanced age of the subjects undergoing serious interventions such as haepatectomy or lobectomy.

Changes in haematology and coagulation parameters observed can be expected for subjects undergoing surgical procedures or postoperative situation and did not give any reasons for concern. No concerns arise from the virology results.

With regards to special population, caution is required when interpretation the outcomes due to the small sample size in the paediatric population. However, it is noted, that with this MAA no indication for use in children is sought. This is also reflected in section 4.1 of the SmPC "*Supportive treatment in **adults** where standard surgical techniques are insufficient*"

The incidences in the elderly population were comparable between the treatment groups and also to the 18 – 65 age subgroup.

Only two specimens were found to be positive for AB to human thrombin in the 29 subjects tested, which however were already present at baseline. In the absence of any other AB titres determined, it can therefore be concluded that no immunogenicity from the treatment with FS Grifols, Surgicel or MC occurred.

No subjects discontinued the study due to an AE in any treatment groups in all 3 studies IG1101, IG1102, and IG1103.

As fibrin sealants are to be applied via dripping or spraying, an application at sites with severe or brisk arterial bleeding will most likely not achieve the desired effect of haemostasis, since standard surgical techniques like ligature are indicated to control the situation. This is also reflected by 'severe or brisk arterial bleeding' representing an intropeative exclusion criterion in all three clinical trials.

Adequate application of fibrin sealant cannot be guaranteed at sites were the bleeding cannot be sufficiently visually targeted or easily applied via spraying or dripping, e.g. in the course of endoscopic procedures. These aspects are covered via contraindications in section 4.3 of the SmPC and the respective section of the PIL in order to ensure an appropriate and safe use of FS Grifiols.

With regard to drug interactions, the wording in section 4.5 of the SmPC reflects the data provided and is in accordance with the currently approved Core SmPC for Fibrin sealants as follows: "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". As with any protein product, allergic type hypersensitivity reactions are possible; hence this has been adequately reflected in section 4.4 of the SmPC.

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

The observed adverse event profile did not give rise to concern. No unexpected safety signals other than those typical for major surgeries could be observed. In conclusion, the safety database is considered to be sufficient to support a MA for VeraSeal. The SmPC provides adequate recommendations and warnings for the safe use of VeraSeal.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Re-bleeding due to lack of efficacy
Important potential risks	Hypersensitivity/allergic reactions, including severe anaphylaxis Antibodies against components of fibrin sealant Thromboembolic events Transmission of infectious agents Tissue adhesion Air/Gas Embolism Medication Error
Missing information	Use in women who are pregnant or lactating Use in tissue glueing Use in neurosurgery Use in application through a flexible endoscope for treatment of bleeding Use for gastrointestinal anastomoses

Pharmacovigilance plan

Routine pharmacovigilance activities are considered sufficient to identify and/or further characterise the above safety concerns and to measure the effectiveness of the requested risk minimisation measures. The results of the evaluation of the effectiveness of the additional risk minimisation measures will be reported in the relevant PSURs.

Risk minimisation measures

Summary of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Re-bleeding due to lack of efficacy	Wording in section 4.4 of the SmPC	None proposed
Hypersensitivity/allergic reactions, including severe anaphylaxis	Wording in sections 4.3, 4.4 and 4.8 of the SmPC	None proposed
Antibodies against components of fibrin sealant	Wording in section 4.8 of the SmPC	None proposed
Thromboembolic event	Wording in sections 4.3, 4.4 and 4.8 of the SmPC	None proposed
Transmission of infectious agents	Wording in sections 4.4 and 4.8 of the SmPC	None proposed
Tissue adhesion	Wording in section 4.4 of the SmPC	None proposed
Air or gas embolism	Wording in sections 4.2, 4.4 and 6.6 of the SmPC	Implementation of educational materials - Educational pack: guidance on application and description of the risk - Warning card on the pressure regulator
Medication error	Wording in sections 4.2 and 4.4 of the SmPC	None proposed
Use in women who are pregnant or lactating	Wording in section 4.6 of the SmPC	None proposed
Use in tissue glueing	Wording in section 4.4 of the SmPC	None proposed
Use in neurosurgery	Wording in section 4.4 of the SmPC	None proposed
Use in application through a flexible endoscope for treatment bleeding	Wording in section 4.4 of the SmPC	None proposed
Use for gastrointestinal anastomoses	Wording in section 4.4 of the SmPC	None proposed

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD).

2.9. Product information

2.9.1. User consultation

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

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, VeraSeal (human fibrinogen / human thrombin) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

When surgical haemostasis using sutures, ligature or cautery is inadequate or impractical, topical haemostatic agents are routinely employed to achieve haemostasis during surgical procedures. Two different approaches are implemented, i.e. physical agents, which promote haemostasis using a passive substrate and which are licensed as devices, and biologically active agents, which enhance coagulation at the bleeding site and are licensed as medicinal products.

The objective of the use of such topical agents is to stop surgical wound bleeding, therefore time to haemostasis, proportion of subjects achieving haemostasis at a certain time point and treatment failure are commonly used efficacy endpoints.

3.1.2. Available therapies and unmet medical need

A number of devices are in widespread clinical use, e.g. collagen patches, gelatine sponges or powder, regenerated oxidised cellulose. At the same time, several fibrin sealants are licensed in the EU either nationally, like Tisseel, or via the centralised procedure, like Evicel.

3.1.3. Main clinical studies

The applicant has submitted the results of three phase III studies in peripheral vascular surgery (IG1101), parenchymal organ surgery (IG1102) and soft tissue surgery (IG1103) which represent the usual spectrum of the clinical investigation for fibrin sealants. Patients had to undergo elective surgical procedures and a suitable target bleeding site needed to be identified intraoperatively. All three submitted trials are single blind with the patient blinded towards assigned treatment and the investigator (surgeon) not. All trials consist of a preliminary phase intended for familiarisation with study procedures, and a primary phase which forms the basis of the primary efficacy analysis.

In the primary phase of each trial, patients were randomized 2:1 to VeraSeal or manual compression in vascular surgery or 1:1 to VeraSeal or Surgicel in parenchymous organ and soft tissue surgery.

A sufficient number of subjects were exposed to VeraSeal in the primary part of each study, 109, 111 and 116 patients in IG1101, IG1102 and IG1103, respectively. In addition, 59, 52 and 51 subjects in the preliminary parts of IG1101, IG1102 and IG1103, respectively, provided efficacy data for FS Grifols.

The chosen comparator arms, manual compression for vascular surgery and treatment with Surgicel, an oxidised cellulose polymer in clinical use for decades both in the EU and the US, are considered appropriate and acceptable.

The selected primary efficacy endpoint, the proportion of subjects achieving haemostasis at 4 minutes, is considered relevant for each type of surgery. The secondary endpoints (Time to haemostasis; Cumulative proportion of subjects achieving haemostasis at 2,3,5,7 and 10 minutes; Treatment failures) are appropriate.

3.2. Favourable effects

The provided efficacy data show that VeraSeal is superior to manual compression for the control of moderate bleeding in peripheral vascular surgery. The rate of haemostasis by T4 in the ITT population in trial **IG1101** was 76.1% (83/109 subjects) in the FS Grifols treatment group and 22.8% (13/57 subjects) in the MC treatment group. This difference is statistically significant in favour of VeraSeal (p-value <0.001). In the PP population, this result is mirrored with the rate of haemostasis by T4 being 77.3% (75/97 subjects) in the FS Grifols treatment group and 23.1% (12/52 subjects) in the MC treatment group. The rate of treatment failure in the ITT population was 26/109 [23.9%] subjects in FS Grifols treatment group compared to 44/57 [77.2%] subjects in the MC treatment group (p-value <0.001).

For the treatment of moderate bleeding from a raw cut liver surface in study **IG1102**, the rate of haemostasis by T4 was 92.8% (103/111 subjects) in the VeraSeal treatment group and 80.5% (91/113 subjects) in the Surgicel treatment group in the ITT population. The rate of haemostasis by T4 was significantly higher in the FS Grifols treatment group (p-value = 0.010), indicating that non-inferiority to treatment with Surgicel was achieved. Additionally, the lower limit of the 95% CI above 1 indicates that FS Grifols is superior to Surgicel [RR 1.152 (1.038, 1.279)]. In the PP population, the rate of haemostasis by T4 was 98.9% (86/87 subjects) in the FS Grifols treatment group and 85.0% (85/100 subjects) in the Surgicel treatment group. The rate of treatment failure was 8/111 [7.2%] subjects in the FS Grifols treatment group compared to 22/113 [19.5%] in the Surgicel treatment group (p-value = 0.010).

In the treatment of moderate generalised bleeding after retroperitoneal soft tissue dissection (trial **IG1103**), the rate of haemostasis by T4 was 82.8% (96/116 subjects) in the FS Grifols treatment group and 77.8% (84/108 subjects) in the Surgicel treatment group of the ITT population. A RR and 95% CI of 1.064 (0.934,

1.213) indicates that FS Grifols is non-inferior to Surgicel. The rate of haemostasis by T4 was higher, but not statistically superior in the FS Grifols treatment group compared to the Surgicel treatment group. In the PP population, the rate of haemostasis by T4 was 83.7% (87/104 subjects) in the FS Grifols treatment group and 76.5% (78/102 subjects) in the Surgicel treatment group. The rate of treatment failure was 20/116 [17.2%] subjects in the FS Grifols treatment group compared to 24/108 [22.2%] subjects in the Surgicel treatment group.

Sensitivity and subgroup analyses support the results of the primary efficacy evaluation of all three trials.

3.3. Uncertainties and limitations about favourable effects

The selection of other, clinically relevant endpoints could have provided a more complete picture of the efficacy of FS Grifols. Transfusion requirements, postoperative rebleeding at TBS, reoperation at TBS, postoperative blood loss, graft thrombosis or occlusion, length of hospital stay would have been secondary endpoints of interest. Nevertheless, it is acknowledged that the efficacy of VeraSeal has been demonstrated as shown above. In addition, as with all plasma derived products, transmission of infectious entities cannot be completely excluded. For VeraSeal, the implementation of double nanofiltration lessens this concern and leads to a final product with a high safety standard.

3.4. Unfavourable effects

Regarding the clinical safety database, an adequate number of subjects have been included into the clinical trial programme to evaluate the safety profile FS Grifols. FS Grifols was well tolerated in 500 subjects in 3 completed studies (IG1101, IG1201 and IG1103) undergoing peripheral vascular surgery, parenchymous tissue open surgeries and soft tissue open surgeries.

A total of 1763 AE were reported in 419/500 (83.8%) subjects which were mostly either mild or moderate in severity. Of 64/500 (12.8%) subjects with any adverse drug reaction reported in the VeraSeal group, only 1 subject had 1 event (procedural pain) that was considered definitely related to study treatment. The most common ADRs were procedural pain (10/500 (2.0%)), nausea (6/500 (1.2%)), pruritus (5/100 (1.0%)) and pyrexia and B19V test positive (3/500 (0.6%)). Most of the adverse drug reactions were considered unlikely related to the study treatment (111 of 128 (86.7%)) and no subject has discontinued due to one of these events. Overall, the ADRs reported are considered to be consistent with the study population, the underlying medical condition (co-morbidities) and the nature of the surgery.

3.5. Uncertainties and limitations about unfavourable effects

When looking at the subjects with any TEAE, the Surgicel treatment group had fewer severe TEAE 21/320 (6.6%) compared to the VeraSeal treatment group 60/500 (12.0%).

Re-bleeding events which also could be potentially linked to lack of efficacy, hypersensitivity reactions or an increased thrombogenicity in the course of the study treatment represent important and potentially life threatening conditions. These possible AEs of special interest however are covered via the Risk management plan as important identified risks and important potential risks.

In the submitted studies only a limited sample size of paediatric subjects has been included. Therefore, no conclusive data regarding efficacy or safety are available in the paediatric population. However, no paediatric indication is sought in the course of this MAA and a deferral was granted by the PDCO within the agreed PIP.

3.6. Effects Table

Table 48:.Effects Table for VeraSeal for supportive treatment where standard surgical techniques are insufficient

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
T4	Haemostasis at 4 minutes	Proportion of subjects	**VeraSeal**	IG1102: **Manual compression** IG1102 + IG1103: **Surgicel**	Randomization has been done with the minimal block size possible; Statistical analyses did not use the time point of randomisation as starting point, but the start of the treatment application. Submitted sensitivity analyses confirmed that initial results remain valid.	
IG1101			76.1% (83/109)	22.8% (13/57)		
IG1102			92.8% (103/111)	80.5% (91/113)		
IG1103			82.8% (96/116)	77.8% (84/113)		
TTH	Time to haemostasis	Median (95% CI)				
IG1101			4.0 NA, NA	NA (⩾10.0) (10.00, NA)		
IG1102			2.0 (2.00, 3.00)	3.0 (2.00, 3.00)		
IG1103			2.0 (2.00, 3.00)	3.0 (2.00, 3.00)		
Unfavourable Effects						
AEs of special interest						
ISS (integrtd Summary of Safety)	TEAE	Proportion of subjects	Veraseal IG1102 + IG1103 + IG1101 12.0% (60/500)	Surgicel IG1102 + IG1103 6.6 % (21/320)		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
	hypersensitivity reactions	Proportion of subjects	Veraseal 2.0% (10/500)	Surgicel 0.6% (2/320) Manual Compression (MC) 0% (0/57)		
	TESAEs consisting of re-bleeding events (may potentially be linked to lack of efficacy)	Proportion of subjects	Veraseal 2.6% (13/500)	Surgicel 1.9% (6/320) MC 0% (0/57)		
	Possible TESAEs of local complications	Proportion of subjects	Veraseal 5.0% (25/500)	Surgicel 4.1% (13/320) MC 5.3% (3/57)		
	thrombotic TESAEs	Proportion of subjects	Veraseal 3.4% (17/500)	Surgicel 1.9% (6/320) MC 5.3% (3/57)		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The observed favourable effects, i.e. achievement of haemostasis in a timely manner, translate into further benefit for patients as regards blood loss, time in the operating theatre and probably even length of hospital stay. As already discussed earlier, these measures would have also served as informative secondary endpoints in the phase III trials. Unfortunately, they were not implemented and thus it can only be speculated about the effect of VeraSeal use on clinical outcomes. However, the availability of a reliable method to stop otherwise difficult to handle surgical bleedings is considered a tangible benefit on the patient but also the hospital and public health level.

Safety concerns may arise due to AB against coagulation factor V, human thrombin, and human fibrinogen, which may compromise efficacy and in consequence the safety profile. With VeraSeal treatment, no subject developed antibodies to coagulation factor V, human thrombin or human fibrinogen. In addition, as with all plasma derived products, transmission of infectious entities cannot be completely excluded. For VeraSeal, the implementation of double nanofiltration lessens this concern and leads to a final product with a high safety standard.

3.7.2. Balance of benefits and risks

From an efficacy point of view, the observed beneficial effects with regard to local haemostasis could be replicated in all three clinical trials in a sufficiently large number of patients (n= 500) and covering three different surgical scenarios (peripheral vascular surgery, parenchymous and soft tissue surgery), which adequately support the indications sought by the Applicant. The selected efficacy endpoints do not cover all clinically relevant areas, but the available data provide sufficient reassurance with regard to the haemostatic properties of VeraSeal when applied either via dripping or spraying.

The observed AE profile did not give rise to concern. No unexpected safety signals other than those typical for major surgeries or the underlying medical condition (co-morbidities) could be observed.

The benefit-risk balance can therefore be regarded as positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of VeraSeal is positive.

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 VeraSeal is favourable in the following indication:

Supportive treatment in adults where standard surgical techniques are insufficient:
- for improvement of haemostasis.
- as suture support: in vascular surgery

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and

any subsequent updates published on the European medicines web-portal.

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Additional risk minimisation measures

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

The educational material is aimed at ensuring that all users of Veraseal via spray application are properly informed about the risk of air or gas embolism occurring with inappropriate administration technique with use of the spray device.

The MAH shall ensure that in each Member State where Veraseal is marketed, all healthcare professionals who are expected to use Veraseal have access to/are provided with the following educational package:

- Educational material for healthcare professionals
- Warning card (sticky tag) on the pressure regulator.

The educational material shall contain the following key elements:

- Description of the risk of life-threatening gas embolism if the product is sprayed incorrectly;
- Reinforced recommendation regarding the use of CO2 pressuring and the correct pressure and distance from tissue;
- Requirement to dry the wound using standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices) prior to using the product;
- Requirement to closely monitor blood pressure, pulse rate, oxygen saturation and end tidal CO2 when spraying the product, for the occurrence of gas embolism;
- Reminder of which pressure regulator(s) should be used, in line with manufacturer recommendations and the SmPC instructions for use.

The MAH shall ensure that a warning card/sticky tag is applied on the pressure regulator in use in each surgery unit. The warning card shall include the following key elements:

- Information on the maximum allowed pressure, and minimal distance to adhere to;
- Reminder that pressurised CO2 is recommended for use as spray gas for the spray application of Veraseal to avoid the risk of potentially life-threatening air or gas embolism.

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

Not applicable.

Paediatric Data

No significant studies in the agreed paediatric investigation plan P/0289/2014 have been completed, in accordance with Article 45(3) of Regulation (EC) No 1901/2006, after the entry into force of that Regulation.