22 October 2015
EMA/674875/2015
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Veraseal

International non-proprietary name: human fibrinogen / human thrombin

Procedure No. EMEA/H/C/003914/0000

## Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

# Table of contents

## List of abbreviations

| | |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| CBC | complete blood count |
| CMH | Cochran-Mantel-Haenszel |
| CRF | case report form |
| CSR | clinical study report |
| DSMB | Data Safety Monitoring Board |
| EC | Ethics Committee |
| FS | fibrin sealant |
| FS Grifols | Fibrin Sealant Grifols |
| HTC | hemostatic time category |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| Ig | immunoglobulin |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| ITT | intent-to-treat |
| MC | manual compression |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NAT | nucleic acid testing |
| $NHTC_{>10}$ | non-hemostatic 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 |
| SAE | serious adverse event |
| SAF | subject authorization form |
| SAP | statistical analysis plan |
| SWFI | sterile water for injection |
| $T_0$ | time of randomization |
| T3, T4, T5, T7, and T10 | hemostatic 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 |
| TTH | time to hemostasis |
| ULN | upper limit of normal |
| WBC | White Blood Cell |

## Disclaimer

VeraSeal and FS Grifols are used interchangeably in the AR.

# 1. Recommendation

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the CHMP considers that the application for VeraSeal for supportive treatment where standard surgical techniques are insufficient, for improvement of haemostasis in vascular surgery and as a suture support in vascular surgery is not approvable since findings from a GCP inspection of the study sites raised serious questions about the data from the main study submitted in support of the application.

## Questions to be posed to additional experts

N/A

## Inspection issues

### GMP inspections

N/A

### GCP inspections

A routine GCP inspection of study IG402 at 4 sites (2 clinical investigator sites, the sponsor site and the site where the TMF is located) has been requested. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure and were received on 7 September 2015.

The findings observed at the three sites inspected have a relevant impact on the quality and integrity of the data. The ethical conduct of the trial was not affected. Several GCP breaches where identified at all sites inspected including the sponsor and the affiliate and all of them along with the CRO critical performance contributed to the fact that data are not considered trustworthy. The investigational sites are considered non GCP compliant and the sponsor processes, procedures and practices departed in numerous occasions of GCP.

*Documentation and reporting of efficacy data.*

Some data included in the CSR could not be verified during the source data verification process as they were not in any of the source documents used at sites. This has an impact on data consistency and of course and on data integrity.

*Documentation and reporting of Safety Data.*

At the sites discrepancies on surgical and non-surgical events were observed and a deficient management of safety documentation. At sponsor and its affiliate the deficiencies were more around the absence of tracking of cases, limited review of safety information included in the CSR and its consistency with data at sites which is a monitor's CRO responsibility but ultimately a sponsor responsibility.

In conclusion, the efficacy and safety data submitted for the inspection are considered by the inspection team not acceptable for the evaluation by the CHMP in relation to the application for marketing authorisation presented to the Agency.

The CHMP accepts and supports this conclusion, as the interpretation of measures and procedures required by the protocol as optional by the investigational sites and the sponsor and the sheer amount of documented protocol deviations were reasons for concern already at D80. Doubt regarding the study's internal consistency and external validity as well as suitability as a one

pivotal trial were constantly expressed and those concerns have been confirmed by the inspection outcome.

### New active Substance status

Based on the review of the data the CHMP considers that the active substance human fibrinogen, human thrombin contained in the medicinal product VeraSeal is not to be qualified as a new active substance in itself. A number of comparable fibrin sealants, licensed by either decentralised or centralized procedures, are available on the market.

# 2. Executive summary

## *2.1. Problem statement*

The human fibrin adhesion system initiates the last phase of the physiological blood coagulation system leading to the formation of a semi-rigid fibrin clot: fibrinogen, the main structural protein in the blood responsible for forming clots, is proteolytically cleaved and converted into fibrin monomers by thrombin. The fibrin monomers 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. The presence of calcium ions (Ca++) is 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). Intended benefit of the FS application is to support local hemostasis, to “glue” surface of injured tissues in order to obtain adaptation or sealing of surfaces, to support sutures, or to improve repair or healing.

## *2.2. About the product*

VeraSeal is a frozen, 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 which are held together by a syringe holder designed by Grifols. Each syringe contains equal amounts of frozen Fibrinogen and Thrombin).

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.

After non-clinical studies were performed, a clinical development plan has been designed to assess the safety and the efficacy of FS Grifols in the surgical setting as adjunct to local haemostasis.

## *2.3. The development programme/compliance with CHMP guidance/scientific advice*

Applicable Guidelines:

Guideline on the Clinical Investigation of Plasma Derived Fibrin Sealant/ Haemostatic Products (CPMP/BPWG/1089/00); Points to Consider on Application with 1.Meta-Analyses; 2.One-Pivotal Study' (CPMP/EWP/2330/99).

The requirements of both guidelines have not been fulfilled regarding the submitted phase II/III trial. However, as there are 3 phase III trials in surgery ongoing, it can be assumed that GL requirements will be fulfilled by the full dossier, when it is ultimately available.

No national or EMA scientific advice was received by the company.

## *2.4. General comments on compliance with GMP, GLP, GCP*

**GMP**

A valid GMP certificate has been provided for all manufacturing and testing site. The manufacturing plant in which human Fibrinogen (component 1) as well as human Thrombin (component 2) are manufactured is subject to inspections at suitable intervals and conforms to GMP requirements.

**GLP**

All nonclinical toxicity studies were conducted consistent with ICH Nonclinical Testing Guidelines but not in compliance with the Good Laboratory Practice (GLP) Regulations.

Final reports of all single dose toxicology studies in both animal species used (mouse and rat) indicate no GLP compliance.

A certificate on the GLP status of the toxicity studies, issued by the collaborating centre or the Quality Assurance Unit, should be provided by the applicant (nonclinical OC 2).

**GCP**

The applicant confirms that the submitted study IG402 was conducted in accordance with GCP and ICH guidelines, ethical principles of the Declaration of Helsinki, and local regulations.

VeraSeal has been selected for a routine GCP inspection, involving two investigator sites in Spain, the sponsor in Spain and the site in the United States where the TMF is located. The preliminary inspection report indicated a high number of critical findings and GCP non-compliance. The final integrated inspection report was received on 7 September 2015, stating that the quality and the integrity of the data are not robust enough to accept them for supporting the marketing authorisation application submitted to the EMA for approval.

## *2.5. Type of application and other comments on the submitted dossier*

- Legal basis

Optional scope according to Article 3(2) of Regulation (EC) No 726/2004, Annex 3(2)(b) (Significant innovation or interest of patients at EU level); Article 8(3) application, (i.e dossier with administrative, quality, pre-clinical and clinical data)

- Accelerated procedure

  N/A

- Conditional approval

  N/A

- Exceptional circumstances

N/A

- Biosimilar application

  N/A

- 1 year data exclusivity

  N/A

- Significance of paediatric studies

A PIP decision dated Oct 24, 2014 granting a deferral until March 2021 was submitted by the applicant.

# 3. Scientific overview and discussion

## *3.1. Quality aspects*

Comment on quality dossier (Module 3):

With regard to Module 3 the dossier was presented in an insufficient and not well organized manner, i.e.

- CTD template organization was not followed consequently – the main part of Module 3 was presented in section 3.2.P., whereas section 3.2.S. included only few parts. The applicant´s argumentation that the manufacturing process of VeraSeal is a continuous one and therefore not divided into drug substance and drug product (as there is no distinct intermediate drug substance defined). This approach is generally accepted, but it should be reminded that the presentation of the respective dossier should reflect this continuous process and therefore all data provided shall be put together.
- Many parts of the dossier could not be found easily as they were included into sections where they are not expected (assuming that the CTD format is properly followed).
- Some reports could not be found in the dossier under the quoted document number, but under a different one. No explanation for the false quotations was given and the finding of the respective reports was quite time consuming.

Overall, the whole presentation of Module 3 reveals lack of a continuous organisation.

### 3.1.1. Introduction

VeraSeal is a solution for sealant, containing two active substances: Human fibrinogen and Human thrombin.

Human plasma-derived fibrin sealant Grifols 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 provided.

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.

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

### 3.1.2. Active Substance

**Human Fibrinogen (component 1)** *(complies with Monograph 0903 "Fibrin Sealant Kit", Ph. Eur.)*

**Human Thrombin (component 2)** *(complies with Monograph 0903 "Fibrin Sealant Kit", Ph. Eur.)*

## Manufacture, characterisation and process controls

#### Manufacture

Both components of VeraSeal are manufactured based on Cohn´s fractionation. Due to continuous manufacturing process of both components of FS Grifols from fractionation to the final component, there is no distinct intermediate active substance stage. Therefore, active substances sections are not included beside the information on control of raw materials used in the manufacture of fibrinogen and thrombin component. Information on the entire fractionation process is presented and included in the Finished Product section.

#### Characterization

Biochemical characterization was extensively performed on a total of three industrial lots using different test methods. Testing was done on the active substances in order to give evidence on identification, potency, protein content, etc. as well as on degradation products such as polymers. Content of excipients used for manufacture and the amount of process-related impurities, e.g. solvent detergent reagents were also defined.

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 confocal microscopy
- Macroscopic study of clot polymerization and fibrinolysis

The characterization studies seem to be appropriately performed and give sufficient information on the fibrin sealant components. Questions regarding test methods in the course of the characterization studies were clarified by the applicant.

#### Process controls

Details on process controls are found in the Finished Product section.

## 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 are justified. The proposed storage periods are justified based on the respective data of stability investigations.

**Human Fibrinogen (Component 1)**

A stability study was conducted on three lots of fibrinogen intermediates in order to verify the stability profile.
The samples were stored at a temperature-controlled chamber or freezer by simulating the storage conditions during production process in transparent polyethylene bags.
The results obtained showed no signs of instability.
Therefore the claimed storage periods for the intermediate products seem appropriate.

**Human Thrombin (component 2)**

3 lots of each process intermediate were studied. Two steps were studied.
Three lots of the first intermediate were stored simulating industrial conditions and two lots of the second intermediate were also stored simulating the industrial process storage conditions.

## 3.1.3. Finished Medicinal Product

## Description of the product and Pharmaceutical Development

### Description of the product

The active substances, fibrinogen (component 1) and thrombin (component 2) of VeraSeal are derived from human plasma.

The choice of excipients is justified and their functions explained. Both components are filled in syringes. The container closure system complies with Ph. Eur. requirements.

## Pharmaceutical development

**Human Fibrinogen (Component 1)**

Detailed descriptions on the individual process steps and their development were given. S/D treatment was successfully implemented for inactivation of enveloped viruses, followed by the removal of S/D reagents and fibrinogen purification from accompanying proteins.

Special focus was laid on viral safety of the product, therefore double nanofiltration was implemented: in a first step nanofiltration with 35nm pore size was evaluated in order to eliminate viruses larger than 35nm. At a later stage in development a 20nm filtration was additionally implemented and subsequently follows 35nm filtration in order to reduce small viruses, preferably those which are highly resistant to other inactivation/removal processes, i.e. non-enveloped viruses.

For product concentration to the desired protein concentration another step was implemented, followed by final adjustment of the drug product.

**Human Thrombin (component 2)**

Thrombin is obtained from the fractionation of pooled plasma. Intermediate product is obtained by alcohol fractionation based on the Cohn method. A chemical treatment for viral inactivation with organic solvent and detergent is performed. Thrombin is then purified from S/D reagents. Several optimizations on that process step were done during the whole development phase. Then a double nanofiltration through two 15 nm pore size filters connected in series is performed. Implementing double nanofiltration was considered to offer greater robustness to this step.

Final sterile filtration is performed before the aseptic filling of the syringes.

#### Human Fibrinogen (Component 1) and Human Thrombin (component 2)

Batch consistency: Reproducibility and batch consistency for both components at a final scale was performed in the Fibrin Sealant facilities with several process runs, resulting in representative lots for each product presentation.

Microbiological attributes: Both components of VeraSeal undergo a purification process including viral safety steps (S/D treatment, double nanofiltration) and are sterile filtered before aseptic filling into syringes. The syringes are sterilized. The applicant has a system in place (GMP for sterile medicinal products) to control microbiological contamination throughout the manufacturing process of VeraSeal.

At this stage of the procedure insufficient information was provided on the development section. The applicant justified these questions sufficiently but one question for the Thrombin component was not sufficiently answered. Therefore, the question about formulation development and excipients is still open.

## Manufacture of the product and process controls

### Manufacturing process

#### Human Fibrinogen (Component 1)

Human fibrinogen is obtained from human plasma fractionation according to a procedure based on Cohn's method. The intermediate undergoes solvent/detergent treatment. Fibrinogen is purified and nanofiltered through 35 nm and 20 nm pore size. Subsequently, the bulk undergoes sterile filtration before the syringes are aseptically filled.

#### Human Thrombin (component 2)

Thrombin of FS Grifols is obtained from fresh plasma fractionation, according to the Instituto Grifols' production method.

After obtaining the intermediate, a chemical treatment for virus inactivation using organic solvent and detergent is carried out. Next, purification of thrombin is performed. Then a double nanofiltration through two 15 nm pore size filters connected in series is carried out. Final sterile filtration and aseptic filling in syringes is performed.

Several questions are raised regarding the manufacturing process due to the limited information provided on the individual process steps. Questions about filters – repeated use, reprocessing and removal of the aggregate forms in the manufacturing process for the Fibrin component are not solved yet. Additionally, a question about – validation of one step of the Thrombin component is not answered sufficiently by the applicant.

### Process controls

The applicant has established in-process controls and defined acceptance criteria at critical steps of the manufacturing process of both components to assure that the process is controlled.

## Product specification

VeraSeal complies with the Ph. Eur. monograph “Fibrin sealant kit” 0903.

Appropriate finished product specifications are set for the product and are sufficiently justified.

## Stability of the product

The conditions used in the stability studies are according to relevant ICH stability guidelines. Long-term stability study with conformance lots are still on-going.

### Human Fibrinogen (Component 1) and Human Thrombin (component 2)

Data of two long term stability studies have been submitted. The data received from both studies so far are in accordance with the specifications.
Further a stability study under stress conditions was as well performed. The data of this stress study show that VeraSeal is stable even under stress conditions over a defined period of time.
The data provided so far show adequate stability and are acceptable. However, additional stability data throughout the marketing authorization procedure are still required for the Fibrin component.

In-use stability (stability after thawing) of VeraSeal was investigated at three different temperatures for up to several hours. For the thawed product only data at the beginning of shelf life are available at the moment. Appropriate data at the end of the proposed shelf life have not been submitted, although the study should have been already completed. No evidence of the stability behaviour at the end of the shelf life was given.
The claimed in-use stability is acceptable based on the data provided.

### Human Albumin 20% Grifols – excipient of component 2

A summary report of stability results of the human albumin 20% Grifols was provided. Stability data were submitted by the applicant.

## Adventitious agents

### Human Fibrinogen (Component 1)

### Viral safety

The Fibrinogen manufacturing process includes two dedicated virus inactivation/removal steps, S/D treatment and double nanofiltration (35nm and 20nm filtration). Additionally other steps were evaluated for their contributory effect for removal of non-enveloped viruses which are known as highly resistant to several inactivation/removal processes.

S/D treatment: Effective (> $4\log_{10}$) virus inactivation for all viruses tested within 120 minutes (at the most) with 90% S/D reagent and also PRV was inactivated below the limit of detection in the robustness investigations.

Double nanofiltration: The fibrinogen manufacturing process includes sequential double nanofiltration by Planova 35N followed Planova 20N filters as specific virus removal step. For viruses larger than 35nm (e.g. HIV, PRV, BVDV, WNV) the double nanofiltration shows satisfying reduction factors (> $4\log_{10}$) and also for the small non-enveloped viruses HAV and PPV effective

reduction rates (> $4\log_{10}$) were found. For the large viruses the 20nm filtration step is considered as additional safety step.

Additional steps: The results show effective reduction of HAV (> $5\log_{10}$) and just $2\log_{10}$ for PPV. Based on the data provided, it could be demonstrated, that these additional steps can be considered contributory to viral safety of fibrinogen.

**TSE safety**

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. Additional steps contribute to the elimination of TSE agents, therefore they would eliminate the physico-chemical forms of the protein.
The results obtained in the experiments show that the process during Fibrinogen production partially removes the TSE-causing agent used as a model of the variant Creutzfeldt-Jakob disease causing agent, irrespective of the type of spike and that the additional steps can be considered as contributory step for TSE safety of fibrinogen.
Nanofiltration 20nm: A laboratory-scale study investigated the capacity of the nanofiltration step of the Grifols Fibrinogen production process to remove Transmissible Spongiform Encephalopathy (TSE)-causing agents experimentally spiked in the process intermediate prior to the nanofiltration step.
The results reveal that the nanofiltration step is effectively capable to remove TSE agents and can therefore be considered as relevant prion reduction step in the manufacturing process of fibrinogen.

**Human Thrombin (component 2)**

**Viral safety**

The Thrombin manufacturing process includes two dedicated virus inactivation/removal steps, Solvent / Detergent treatment and double nanofiltration. Additionally two process steps were assessed for virus removal.

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

**Adventitious agents for human Albumin 20% Grifols (excipient of component 2)**

Relevant virus inactivation steps and further manufacturing steps were investigated. In summary, the virus validation studies performed are considered sufficient and adequate.

**TSE safety of Human 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 by the applicant was experimentally tested in laboratory scale studies.

These laboratory-scale studies investigated the capacity of the different steps and of the double nanofiltration step through 15 nm pore-size of the Grifols Thrombin production process.

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

**TSE safety for human Albumin Grifols (excipient)**

The applicant presented a summary report where the potential prion-removal capacity of the manufacturing process of Grifols 20% human albumin was estimated.

Based on the risk assessment the risk of a contamination with the addition of human albumin 20% Grifols as a stabilizer of thrombin (component 2) is very low.

## Discussion on chemical, pharmaceutical and biological aspects

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

The submitted validation studies (viral safety and TSE agents) and overall information provided are sufficient to demonstrate acceptable adventitious agents control.

**Active substance**

Human Fibrinogen + Thrombin (component 1 + component 2):

The chemical-pharmaceutical documentation and Expert Report in relation to VeraSeal / Fibrinogen Component are of sufficient quality in view of the present European regulatory requirements.

The control tests and specifications for the active substances are adequately drawn up.

Based on the results from the stability studies presented no significant changes in any parameters were observed. The proposed holding times are justified.

**Finished product**

Human Fibrinogen (component 1):

The development of the product has been described, the choice of excipients is justified and their functions sufficiently explained.

Several product specific parameters and process variables were investigated and the data provided demonstrate fulfilment of all predefined acceptance criteria.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for the finished product are adequately drawn up.

Long-term stability study with conformance lots is still ongoing.

Human Thrombin (component 2):

The development of the product has been described, the choice of excipients is justified and their functions explained.

Process Validation was sufficiently performed for the different manufacturing steps of thrombin.

The product specifications cover appropriate parameters for the intended dosage form.

The batch analysis results show that the finished product meets the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for the finished product are adequately drawn up.

Long-term stability study with conformance lots is still ongoing.

In summary, prior to granting marketing authorisation a number of concerns as outlined in the LoOI should be adequately addressed by the Applicant.

### Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, the CHMP considers that the marketing authorisation application for VeraSeal could be approvable from the quality point of view provided that the Applicant gives satisfactory responses to the List of Outstanding Issues (LoOI).

## *3.2. Non clinical aspects*

### 3.2.1. Pharmacology

Characterisation of the pharmacological potential of the product is appropriate. The company conducted primary pharmacodynamic studies in-vitro and in two different animal species in vivo in its indication as adjuvant to hemostasis in surgery. 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 (Tisseel®, Evicel® and Crosseal®).

No secondary pharmacodynamic studies and no studies on pharmacodynamic drug interactions were performed since FS Grifols' components (Fibrinogen and Thrombin) are normal constituents of human plasma, which is agreed.

Specific non-clinical conventional safety pharmacology studies of FS Grifols were not conducted, which is, due to the nature of the product, considered appropriate.

**Overall**, the presented preclinical studies reveal evidence that FS Grifols will exert hemostatic effects as desired.

### 3.2.2. Pharmacokinetics

No pharmacokinetic studies have been performed by the applicant, which is, due to the nature of the product and the only topical application, considered acceptable. The product acts locally and does not distribute, appreciably to distal tissue or organs. The fibrin clot generated by FSG is metabolized according to the fibrinolytic and phagocytic process that metabolizes endogenous fibrin.

### 3.2.3. Toxicology

Six single dose toxicity studies with the fibrinogen component of the Fibrin Sealant (FS) Grifols VeraSeal were conducted in mice and rats. 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 in the mouse and the rat, respectively. The main single dose toxicity studies were designed to evaluate hematology, clinical chemistry, necropsy, and histopathology

data after a single administration, with further evaluations conducted 2 weeks later to assess delayed toxicity and/or recovery.

The two main studies only vary in using different lots of fibrinogen. One main study in each animal species was performed with product nano-filtered by DV 50nm and DV 20nm. In the second main study animals were administered by intravenous route with fibrinogen nano-filtered with Planova 35nm and Planova 20nm.

No toxicity studies have been performed with thrombin, the second component of the FS Grifols. . Lack of the acute toxicity studies for thrombin was justified because of the following facts:

- Thrombin is thrombogenic protein and it cannot be administered intravenously
- Thrombin is natural precursor is circulating in human plasma
- Excess thrombin (if any) is inactivated by protease inhibitors that are present in blood

Possible toxic effects were evaluated during the FSG safety studies in cardiac and vascular surgery on pigs and in vascular surgeries in rabbits.

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.

The LD50 of FS Grifols fibrinogen component was adequately evaluated. No mortality occurred.

An editorial mistake has to be recognized. In the Nonclinical overview of the Dossier (2.4.01. page 10) provided by the applicant, it is stated that four Wistar rats (two male, two female) were given the product by intravenous bolus. In the final report of the preliminary rat study (015/02), the specified number of animals used is repeatedly mixed up (5 males and 5 females on page 12 / 2 animals per sex on page 14 / as well on page 14 just several lines below: one group made up of 5 males and 5 females…).

Due to the tables indicating the results of the preliminary rat study, it can be assumed, that 2 animals/sex have been used. However, the correct animal numbers should be indicated in all future citations of this study.

The omission of the genotoxicity studies of FSG as a whole and of fibrinogen and thrombin is considered acceptable. Studies on carcinogenicity and reproductive and developmental toxicity have not been performed. The omission of such studies is justified.

No other toxicity studies were done. The immunotoxicity of xenogenic proteins (human fibrinogen, human thrombin) for tested animals was observed during the primary pharmacodynamics studies.

### 3.2.4. Ecotoxicity/environmental risk assessment

Exemption from the need for an environmental risk assessment was claimed by the applicant with reference to the Guideline on Environmental Risk Assessment of Medicinal Products for Human use CHMP/SWP/4447/00.

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.

### 3.2.5. Discussion on non-clinical aspects

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 and showed that FSG is effective in haemostasis and tissue sealing in different animal models. There was lack of thrombotic complications within scope of intended use of FSG.

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. The LD50 of FS Grifols fibrinogen component was adequately evaluated. No mortality occurred.

In addition, results of preclinical and clinical studies support the local tolerance of FSG.

Taken together, the submitted preclinical data support the human use of VeraSeal.

### 3.2.6. Conclusion on non-clinical aspects

The preclinical 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.

From the nonclinical perspective, the application for VeraSeal is approvable.

## *3.3. Clinical aspects*

- **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 |
|---|---|---|---|---|---|---|---|---|---|
| **IG402** | 5/ Canada, 8/UK, 6/ES | | | | | Efficacy: duration of the surgical intervention; Safety: 6 mo follow up | | Required one of a list of predefined elective, open peripheral vascular surgical | time to hemostasis (TTH), measured in minutes from the start of treatment application at the |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | procedures | target bleeding site (TBS) during 10 min observational period |
| Preliminary Part | | First 2 subjects at each site; Open label | 2 FS Grifols (3 mL) kits | Familiarisation with FS Grifols and study procedures ; safety | 72/72 | | **17** (23,6%) /**55** (76.4%); Age: 70 | | |
| Primary Part | | single blind | 2 FS Grifols (3 mL) kits; Manual compression | Efficacy and safety | 111/110 FS Grifols 57/57 MC | | FS: **15** (13.6%)/ **95** (86.4%); MC: **18**, (31.6%)/ **39**, (68.4%) Age: FS: 69 MC: 67 | | |

### 3.3.1. Pharmacokinetics

### 3.3.2. Pharmacodynamics

### 3.3.3. Discussion on clinical pharmacology

### 3.3.4. Conclusions on clinical pharmacology

Since FS Grifols is intended for epilesional use only and intravascular administration is contraindicated, no pharmacokinetic studies have been performed in man. In addition, the product's action is based upon the well known physiological process of the final steps of the coagulation cascade and no specific pharmacodynamic studies were deemed needed.

The fibrin clot generated by FS Grifols is metabolized according to fibrinolytic and phagocytic processes that metabolize endogenous fibrin. Clinical pharmacological studies were not performed.

This is accepted.

### 3.3.5. Clinical efficacy

### Dose-response studies and main clinical studies

The dossier encompasses only a single phase II/III study, IG402, in vascular surgery.

Searching the EU Clinical Trials Register, the following ongoing phase III studies can be identified:

**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 Hemostasis during **Peripheral Vascular Surgery**

**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 Hemostasis During **Parenchymous Tissue Open Surgeries**

**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 Hemostasis During **Soft Tissue Open Surgeries**

For all three trials, 2014-06-16 is given as the start date. All three trials are also briefly described in the RMP.

Considering the submitted phase II/III study IG402 in context with the three ongoing phase III trials identified in the EU clinical trials register, the CHMP is lead to the conclusion that the company closely follows the advice given in the CHMP guideline on the clinical development of fibrin sealants, despite not having received scientific advice for this clinical development programme. Acceptable models for different surgical bleeding situations have been chosen by the company, ie. soft tissue surgery and parenchymal organ surgery. An additional trial in vascular surgery is replicating the clinical investigation from phase II, which is fully endorsed.

However, it is not fully understood why this clearly premature dossier with only a single available finished study, the design and conduct of which can in no way satisfy the demanding requirements for a single pivotal trial, is submitted for review concerning a marketing authorisation at the time being.

**Trial IG402**

**Design:** Single-blind randomized phase II/III study consisting of 2 phases. In the Preliminary phase, the first two subjects per centre were treated with FS Grifols in an open label manner to ensure that the local study teams familiarized themselves with the technique of FS Grifols application and with the intra-operative procedures required by the protocol.

In the Primary phase, subjects were randomized 2:1 to VeraSeal or manual compression. This part of the study was single blind, as the investigator could not be blinded due to the differences in the treatment arms.

**Population:** Male or female patients at least 18 years old in UK and Spain and at least 3 years old in the Canadian centres undergoing one of a list of 20 predefined peripheral vascular surgeries involving either an arterial patch angioplasty or an arterial anastomosis utilizing polytetrafluoroethylene (PTFE) or Dacron grafts.

**Treatments:** All of the preliminary part participants (N=72) were treated with FS Grifols.
The subjects from the part II of the study were treated intra-operatively with FS Grifols or manual compression after randomization (2:1).

The study protocol presents the dosage and method of application of FS Grifols as follows:

“FS Grifols is for local use only. It is not to be applied intravascularly. It should be used topically and applied on the surface of bleeding tissue only. Before the application of FS Grifols, the target surface area was to be as dry as possible, as can be achieved by gently sponging the target area with sterile gauze or sponge immediately before the application of FS Grifols. FS Grifols was only to be applied with the supplied administration device. It was to be dripped onto the desired area to produce a thin, even layer over the application area. The tip of the applicator was to be kept as close as possible to the desired tissue without touching the tissue.” And “The initial quantity of FS Grifols applied was to be sufficient to entirely cover the intended application area with a thin, even layer. If the hemostatic effect was incomplete after the initial application of FS Grifols, or the TBS re-bled within a 10-minute observational period, an additional amount of FS Grifols could be applied at the TBS, if necessary, until all prepared FS Grifols had been used (up to two kits of FS Grifols). “

For subjects randomized to MC, after randomization and clamp removal, direct MC was applied immediately to the TBS using gauze or laparotomy pads.

**Endpoints:** For surgical procedures in both the Preliminary Part (I) and the Primary Part (II), a 10-minute observational period followed the start of study treatment application (TStart) at the TBS, and hemostasis was assessed at predetermined time points.

The **primary efficacy endpoint** of the study is **time to hemostasis (TTH)**, measured in minutes from the start of treatment application (TStart) at the TBS to the achievement of hemostasis at that site or to the end of the 10-minute observational period if hemostasis has not yet been achieved.

The precise TTH was not observed in this study. However, if hemostasis had not been achieved at a given assessment time point, but had been achieved at the next assessment time point, then 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 1 of 5 hemostatic time categories (HTCs) or the non-HTC as follows:

1. HTC≤3: ≤3 minutes from TStart to hemostasis.

2. HTC>3 to ≤4: >3 minutes to ≤4 minutes from TStart to hemostasis.

3. HTC>4 to ≤5: >4 minutes to ≤5 minutes from TStart to hemostasis.

4. HTC>5 to ≤7: >5 minutes to ≤7 minutes from TStart to hemostasis.

5. HTC>7 to ≤10: >7 minutes to ≤10 minutes from TStart to hemostasis.

The following cases were considered to be **treatment failures**:

1. Persistent bleeding at the TBS beyond the 10-minute observational period.

2. Severe (brisk and forceful) bleeding according to the Investigator's judgment at the TBS during the 10-minute observational period.

**Secondary efficacy endpoints**

The secondary efficacy endpoints were as follows:

1. Cumulative proportion of subjects achieving hemostasis at the TBS at each of the 5 HTCs

2. Prevalence of treatment failure

Time to haemostasis is a commonly used primary efficacy endpoint for vascular surgery trials and therefore acceptable. The secondary endpoints are appropriate, however, they represent only a slightly different evaluation 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 than the TTH during the 10 minute observational period at the TBS. Transfusion requirements, postoperative rebleeding at TBS, reoperation at TBS, postoperative blood loss, graft thrombosis or occlusion, length of hospital stay come to mind.

**Statistical design and analysis aspects**

The Applicant informed that flexible block sizes (of size 3 or size 6) had been used. This strategy is very favourable in the presence of single-blinding, as this is a valid means to reduce the potential to anticipate the next treatment. Around one third of the trial population (50 patients) had already been randomized when relevant changes on the primary endpoint were introduced in the Statistical Analysis Plan (SAP). This is problematic in the single blind trial. However, after request the results

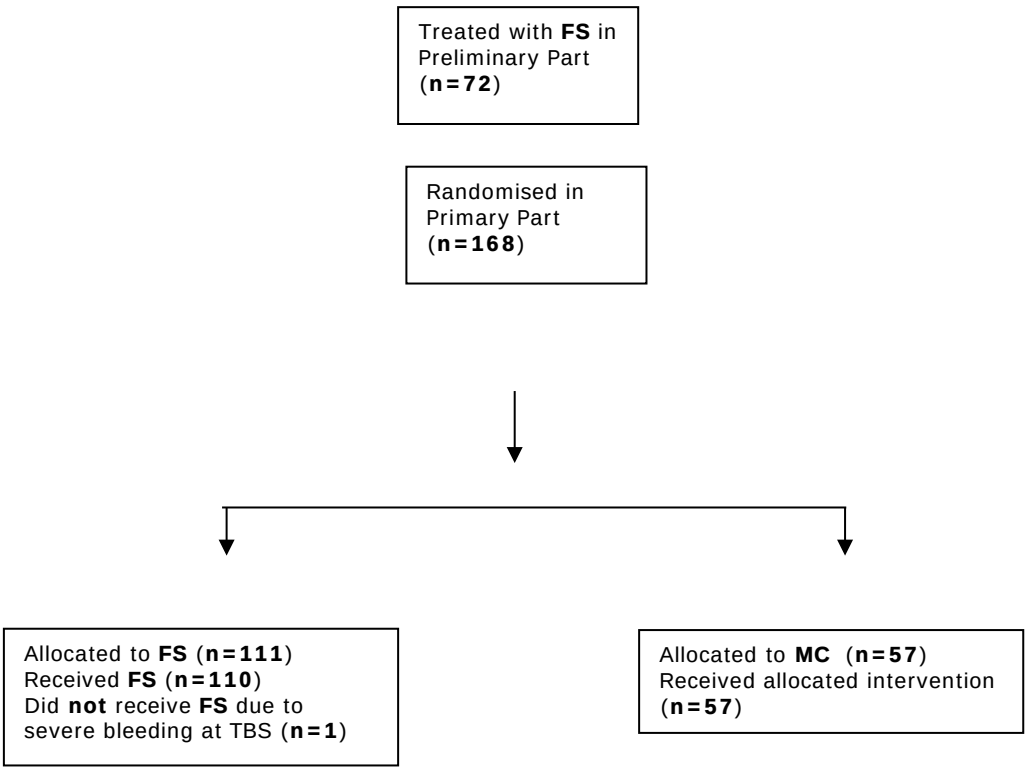
for the primary analysis from the Clinical Study Protocol, predefined prior to first patient randomization, was provided and this analysis allowed a conclusion on efficacy consistent with the one discussed previously.

Strong statistical evidence is needed for this single-pivotal trial to achieve the compelling evidence as outlined in the respective EMA Points to Consider. The trial had however been planned at the usual 5%, two-sided level. While on request it was shown that the relevant statistical tests performed could achieve a level of $p<0.00125$ (i.e. the equivalent criterion for the one-pivotal trial setting), the sole p-value of a test statistic is however only one aspect. The Clinical Study Protocol and the SAP had specified a proportional odds model for analysis of TTH. Following a pre-test however, the primary endpoint analysis had been changed (based on a procedure set during the course of the trial) and a CMH test was applied. This represents a data dependent decision and was of concern regarding inflation of the type I error. Similarly, control for the factor 'graft type' was initially not foreseen, but such was included in the statistical analysis. On request the predefined proportional odds model has been provided, and as discussed this showed that the conclusions were not impacted by these changes in the primary analysis.

The sample size was low, and no subgroup analysis at all had been performed. On request, some subgroup analyses (by gender, age, bleeding intensity, graft type) were performed. However, these are necessarily of even smaller sample size, thus uncertainty remains regarding the treatment effect in these subgroups, resulting in limited persuasiveness of these analyses. In addition the statistical test performed is not considered sensitive to address consistency over subgroups. Together with clinical concerns, including the insensitive measurement of the primary endpoint and resulting uncertainty on the effect size as well as lack of secondary endpoints it is questioned, that the stringent evidence for 'exceptionally compelling', 'internal and external validity' and 'internal consistency' of the data as outlined in the EMA 'Points to Consider on Application with 1.Meta-Analyses; 2.One-Pivotal Study' (CPMP/EWP/2330/99) is achieved with this single trial.

**Participant flow**

A total of 240 subjects underwent vascular surgery in the Preliminary (I) or Primary (II) part of the study. Of these, 72 were treated with FS Grifols in the Preliminary Part (I) of the study, 111 were randomized to receive FS Grifols in the Primary Part (II) of the study, and 57 were randomized to MC treatment in the Primary Part (II) of the study.




The following tables summarize types of vascular surgery procedures performed:

**Table 9. Summary of Vascular Surgical Procedures (ITT)**

| | FS Grifols Preliminary Part (I) (N=72) | FS Grifols Primary Part (II) (N=110) | MC Primary Part (II) (N=57) |
|---|---|---|---|
| Type of Vascular Surgery | | | |
| Carotid endarterectomy requiring patch angioplasty | 11 ( 15.3) | 23 ( 20.9) | 11 ( 19.3) |
| Femoral-femoral bypass grafting | 9 ( 12.5) | 20 ( 18.2) | 8 ( 14.0) |
| Abdominal aortic aneurysm resection and graft replacement | 16 ( 22.2) | 18 ( 16.4) | 11 ( 19.3) |
| Aorto-bi-femoral bypass grafting | 8 ( 11.1) | 15 ( 13.6) | 6 ( 10.5) |
| Femoral-popliteal bypass grafting | 10 ( 13.9) | 8 ( 7.3) | 9 ( 15.8) |
| Aorto-bi-iliac bypass grafting | 2 ( 2.8) | 4 ( 3.6) | 2 ( 3.5) |
| Ilio femoral bypass | 2 ( 2.8) | 4 ( 3.6) | 2 ( 3.5) |
| Femoral endarterectomy with patch angioplasty | 2 ( 2.8) | 4 ( 3.6) | 0 ( 0.0) |
| Aorto-uni-femoral bypass grafting | 2 ( 2.8) | 3 ( 2.7) | 1 ( 1.8) |
| Axillo-femoral bypass grafting | 2 ( 2.8) | 3 ( 2.7) | 1 ( 1.8) |
| Aorto-mesenteric bypass grafting | 1 ( 1.4) | 1 ( 0.9) | 0 ( 0.0) |
| Aorto-uni-iliac bypass grafting | 0 ( 0.0) | 1 ( 0.9) | 1 ( 1.8) |
| Aortic endarterectomy | 0 ( 0.0) | 1 ( 0.9) | 0 ( 0.0) |
| Axillo-bifemoral | 0 ( 0.0) | 1 ( 0.9) | 0 ( 0.0) |
| Carotid-subclavian bypass grafting | 0 ( 0.0) | 1 ( 0.9) | 0 ( 0.0) |
| Ilio popliteal bypass | 0 ( 0.0) | 1 ( 0.9) | 0 ( 0.0) |
| Left femoral endarterectomy | 0 ( 0.0) | 1 ( 0.9) | 0 ( 0.0) |
| R) femoral endarterectomy | 0 ( 0.0) | 1 ( 0.9) | 0 ( 0.0) |
| Femoral aneurysm resection and graft replacement | 2 ( 2.8) | 0 ( 0.0) | 2 ( 3.5) |
| Femoral endarterectomy | 2 ( 2.8) | 0 ( 0.0) | 0 ( 0.0) |
| Femoral trombendarterectomy plus profundoplasty | 1 ( 1.4) | 0 ( 0.0) | 0 ( 0.0) |
| Iliac aneurysm resection and graft replacement | 1 ( 1.4) | 0 ( 0.0) | 0 ( 0.0) |
| Right common iliac to sma | 1 ( 1.4) | 0 ( 0.0) | 0 ( 0.0) |

| | | | |
|---|---|---|---|
| Popliteal artery aneurysm revascularization (bypass grafting) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 1.8) |
| Right iliac to femoral artery bypass graft | 0 ( 0.0) | 0 ( 0.0) | 1 ( 1.8) |
| Missing | 0 ( 0.0) | 0 ( 0.0) | 1 ( 1.8) |
| Type of Graft/Patch Material[3] | | | |
| Dacron | 56 ( 77.8) | 64 ( 58.2) | 29 ( 50.9) |
| PTFE | 14 ( 19.4) | 46 ( 41.8) | 27 ( 47.4) |
| Bovine | 1 ( 1.4) | 0 ( 0.0) | 0 ( 0.0) |
| Vein | 1 ( 1.4) | 0 ( 0.0) | 0 ( 0.0) |
| Missing | 0 ( 0.0) | 0 ( 0.0) | 1 ( 1.8) |
| Applicator Tip | | | |
| Fibrijet Gauge 26 | 71 ( 98.6) | 97 ( 88.2) | 0 ( 0.0) |
| Fibrijet Gauge 20 | 1 ( 1.4) | 13 ( 11.8) | 0 ( 0.0) |
| TBS identified at | | | |
| Distal anastomosis | 25 ( 34.7) | 45 ( 40.9) | 27 ( 47.4) |
| Proximal anastomosis | 33 ( 45.8) | 38 ( 34.5) | 18 ( 31.6) |
| Other | 14 ( 19.4) | 27 ( 24.5) | 12 ( 21.1) |
| TBS bleeding intensity | | | |
| Moderate | 35 ( 48.6) | 100 ( 90.9) | 52 ( 91.2) |

**Recruitment**

Studied Period: Date of First Enrollment: 20 October 2008; Date of Last Completed: 5 May 2014

The protocol states that: Overall study duration is expected to total 17 months, including 5 months for study set-up and Ethics Committee (EC)/Institutional Review Board (IRB)/Research Ethics Board (REB) approval, and 6 months for recruitment. There is a 6-month observational period for viral safety and immunogenicity follow-up assessments.

It is not clear why this not overly large study took 6 years to finish. The long timeframe could introduce bias into the study as the fields of vascular surgery and anaesthesia continually evolve and the standard treatment modalities are subject to change (e.g. suture materials, suture techniques, improved management of anticoagulation during and after surgical procedures, novel anticoagulants, perioperative medication with statins and antiplatelet drugs, improved fluid and blood products management etc.) thus casting doubt on the internal consistency and external validity of this trial.

The applicant was asked to elaborate why the study duration is distinctly longer than expected (65 vs. 17 months) and if changed treatment standards are expected to have an impact on the outcomes of the trial. The grounds cited by the applicant (regulatory difficulties with clinical trial approval, suboptimal selection of treatment centres, slow enrollment) are acknowlegdeg. However, the claim that treatment modalities remained unchanged over the 6 year study duration has to be further substantiated by the company.

**Protocol deviations**

There is a multitude of protocol violations (filling 460 pages of report), classified mostly as minor, as for nearly every patient one or more lab tests have not been done or visits were outside of the specified timeframes.

The sheer amount of protocol deviations is astounding and leads to the conclusion that even though the assessment during the 10 minutes efficacy observation period has been done diligently, the rest of the patient evaluation was done rather halfheartedly. The applicant was asked to comment on the amount of protocol violations and how this may impact on the reliability of the conclusions. The Applicant is of the opinion that these minor protocol deviations do not impact on the validity of the study outcomes. However, it is not easily comprehensible why study sites were employed that lacked the facilities for undertaking study procedures required by the protocol. If procedures apart from determining the primary efficacy endpoint were superflous, they didn't need to be defined in the protocol in the first place and were not to be complacently skipped if they didn't appear convenient for individual sites.

In addition, what is more worrying is that the inability of study sites to perform basic laboratory evaluations like liver, kidney or coagulation panels leads inevitably to the inclusion of patients who would have met exclusion criteria as defined in the protocol (e.g. pre-operative INR ≥2.0; pre-operative aPTT ratio ≥ 1.5; pre-operative serum creatinine > 2 × ULN; pre-operative AST or ALT > 2.5 × the ULN).

**Treatment centres**

19 treatment centres recruited subjects. centre 28 in Surrey, UK, did not enrol any patients, but screened one subject who turned out to be an intraoperative screening failure.

Five of the 18 centres are classified as small sites (having enrolled < 3 patients in one or both treatment arms in the primary part). 6 sites have participated in the preliminary part of the trial, but did not enrol any patients in the primary part. The applicant was asked to discuss if this phenomenon reflects on the usability of the FS Grifols kit.

The company cited as reasons for the lacking enrolment of subjects inadequate or insufficient human resources being dedicated to the study, administrative reasons within the site such as internal issues between the investigative staff and the centre's management, unavailability of suitable patients for enrollment and lack of genuine interest in study participation and enrollment of subjects (reflected as absence or poor pre-screening/screening activity for prolonged periods).

The arguments of the applicant are acknowledged but considered to reflect poor selection of treatment centres for this study.

## Summary of main efficacy results

All efficacy analyses were performed using Primary Part (II) subjects to compare the efficacy of FS Grifols and MC. Subjects who were randomized to MC but received FS Grifols at the TBS in error or received FS Grifols at a non-TBS were categorized under the MC group in the ITT population for efficacy analyses.

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 XXX. Summary of efficacy for trial IG402**

| **Title: A Prospective, Single-blind, Randomized, Phase II/III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Hemostasis During Peripheral Vascular Surgery** | |
|---|---|
| Study identifier | IG402 |

| | | | |
|---|---|---|---|
| Design | This trial consists of 2 parts: a Preliminary Part (I) and a Primary Part (II).<br>Preliminary Part (I): All subjects enrolled in the Preliminary Part (I) were treated with FS Grifols. This part of the trial had 2 main objectives:<br>1) 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. To meet this objective, the first 2 subjects at each<br>site were enrolled and treated with FS Grifols.<br>2) To assess the clinical safety of FS Grifols. Treatment of 20 subjects with FS Grifols was considered sufficient for an initial assessment of clinical safety.<br>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 2 main objectives of this part were as follows:<br>1) Assessment of the safety of FS Grifols.<br>2) Assessment of the efficacy of FS Grifols. | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 10 min<br>not applicable<br>not applicable |
| Hypothesis | Superiority | | |
| Treatments groups | FS Grifols preliminary | | N=72 |
| | FS Grifols primary | | N=110 |
| | Manual compression | | N=57 |
| Endpoints and definitions | Primary endpoint | <label> | The primary efficacy endpoint of the study is time to hemostasis (TTH), measured in minutes from the start of treatment application (TStart) at the TBS to the achievement of hemostasis at that site or to the end of the 10-minute observational period if hemostasis has not yet been achieved.<br>TTH, although not observed directly, was ascertained as falling into 1 of 5 hemostatic time categories (HTCs) or the non-HTC as follows:<br>1. HTC $\leqslant$ 3: $\leqslant$ 3 minutes from TStart to hemostasis.<br>2. HTC>3 to $\leqslant$4: >3 minutes to $\leqslant$4 minutes from TStart to hemostasis.<br>3. HTC>4 to $\leqslant$5: >4 minutes to $\leqslant$5 minutes from TStart to hemostasis.<br>4. HTC>5 to $\leqslant$7: >5 minutes to $\leqslant$7 minutes from TStart to hemostasis.<br>5. HTC>7 to $\leqslant$10: >7 minutes to $\leqslant$10 minutes from TStart to hemostasis<br>A non-hemostatic time category, NHTC>10, was defined as persistent bleeding at the TBS<br>beyond the 10-minute observational period (i.e., >10 minutes from TStart). |
| | Secondary endpoint | | Cumulative proportion of subjects achieving hemostasis at the TBS at each of the 5 HTCs |
| | Secondary endpoint | | Prevalence of treatment failures |
| Database lock | | | |

**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 subjects | 72 | 110 | 57 |
| | TTH≤3 | 41 (56.9) | 51 (46.4) | 15 (26.3) |
| | TTH>3 but ≤4 | 11 (15.3) | 18 (16.4) | 3 (5.3) |
| | TTH>4 but ≤5 | 5 (6.9) | 13 (11.8) | 10 (17.5) |
| | TTH>5 but ≤7 | 3 (4.2) | 5 (4.5) | 4 (7.0) |
| | TTH>7 but ≤10 | 5 (6.9) | 10 (9.1) | 9 (15.8) |
| | Treatment failure | 7 (9.7) | 13 (11.8) | 16 (28.1) |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | First haemostatic category of the Primary endpoint: TTH≤ 3* | Comparison groups | FS Grifols primary vs. MC |
| | | test statistic | **46.4% vs. 26.3%** |
| | | variability statistic | Not done |
| | | P-value | CMH row mean score p<0.001 |
| | Secondary endpoint: Treatment failure | Comparison groups | FS Grifols primary vs. MC |
| | | test statistic | **11.8 % vs. 28.1 %** |
| | | variability statistic | Not done |
| | | P-value | Fisher's Exact test p<0.016 |

The slightly more favourable results in the preliminary part could be explained by the severity of bleeding at the TBS, which was mild for 51.4% and moderate for 48.6% of subjects, while in the primary part TBS bleeding intensity was moderate for most of the subjects in each of the FS Grifols (90.9%) and MC (91.2%) groups.

*p-value relates to the CMH statistic for the primary endpoint representing the ordinal scale of TTH, point estimates represent the proportion of patients with haemostatic success within the first 3 minutes.

### Clinical studies in special populations

| | **Age 65-74** (Older subjects number /total number) | **Age 75-84** (Older subjects number /total number) | **Age 85+** (Older subjects number /total number) |
|---|---|---|---|
| **IG402** | 101/239 | 52/239 | 7/239 |

### Analysis performed across trials (pooled analyses AND meta-analysis)

N/A

### Supportive study(ies)

N/A

## 3.3.6. Discussion on clinical efficacy

***Design and conduct of clinical studies***

The applicant has submitted one finished study in vascular surgery, while three additional clinical trials (in peripheral vascular surgery, parenchymal organ surgery and soft tissue surgery) which represent the usual spectrum of the clinical investigation for fibrin sealants, were started in June 2014 and are ongoing. The submitted trial IG402 is a single blind phase II/III study in peripheral vascular surgery with a preliminary phase, in which all patients were treated with VeraSeal, and a primary phase, in which patients were randomized 2:1 to VeraSeal or manual compression.

Study IG402 suffers from a number of weaknesses:

It was clearly planned as an exploratory phase II/III study and not as a single pivotal phase III trial, thus there are a number of methodological shortcomings.

For a single pivotal trial considerably stronger statistical evidence than the usual two-sided type I error of 5% is needed. This aspect could be met by $p<0.00125$ as achieved by the relevant statistical analyses, however the sole p-value of a test statistic is only one aspect of type I error control within a trial. The applicant had changed the statistical test following a pre-test, and during the course of the single blinded trial. These late specifications and remaining ambiguity in the test statistic introduced further multiplicity and potential for inflation (inclusion of a stratification factor for ‘graft type’, collapsing of categories, pooling of sites). Altogether these statistical deficiencies did not contribute to establishing compelling evidence. However, these concerns on the type I error could be resolved by providing a range of requested analyses, which altogether were capable to demonstrate that the conclusions from these additional analyses remained the same and thus the type I error was not inflated. In addition to these statistical aspects, further concerns regarding the study duration, non-availability of subgroup analyses and possible selection bias undermined the convincing power of the trial. The concern on selection bias could be resolved, supported by sensitivity analysis and the fact that a flexible block size was used. Some additional analyses by year of randomization have been added, however some more sensitive analyses are needed to finally rule out that the overall analysis results are not driven by a specific time-period during the trial. In addition while some subgroup analyses have now been provided, these are not considered to be very informative, but still additional analyses are requested to provide more informative results on the treatment effect estimates and confidence intervals.

In addition, the number of patients receiving VeraSeal, compared to development programmes of similar medicinal products is limited. Only 72 patients were exposed to the IMP during the non-randomized preliminary phase of the trial and 110 patients were randomized to VeraSeal during the primary phase of IG402, with 57 patients receiving manual compression.

The efficacy evaluation encompasses a 10 minutes observation of haemostatic efficacy after the administration of fibrin sealant or applying manual compression. This 10 minute observation window is not supported by clinically relevant secondary endpoints that would be expected in a pivotal trial, like rebleeding, reoperation, transfusion requirements, length of hospital stay, graft occlusion etc.

Initially, no subgroup analyses were foreseen for trial IG402, which is not in accordance with the GL on Points to Consider on Application with One Pivotal Trial (CPMP/EWP/2330/99). Such analyses would have been especially relevant for this application as IG402 is the sole source of clinical data for FS Grifols at the time being. The Applicant has now submitted post hoc subgroup analyses regarding gender, age >/<65, type of bleeding at TBS and type of graft. Although the selected subgroups can be considered as relevant, the performed subgroup analyses have limited convincing power. Methodologically, the CMH test is not sensitive and informative to address consistency of treatment effects, and therefore additional analyses using the POM are requested. Nevertheless, the limited value of the subgroup analyses is also based on their small sample sizes, leaving room for large uncertainty, questioning the generalizability to a larger patient population.

The duration of this small study is excessively long, the expected duration stated in the protocol was 17 months, while the actual time to finish the trial was 6 years (Oct 2008 - May 2014). The long timeframe could introduce bias into the study as the fields of vascular surgery and anaesthesia continually evolve and the standard treatment modalities are subject to change, e.g. suture materials, suture techniques, improved management of anticoagulation during and after surgical procedures, novel anticoagulants, perioperative medication with statins and antiplatelet drugs, improved fluid and blood products management etc. All of these factors are not reassuring regarding the study's internal consistency (including constancy of the treatment effect over time) and external validity. Regarding the comparability of the clinical situation, the applicant has merely stated that treatment modalities in vascular surgery and perioperative management have not changed without presenting any supporting data or literature. Although 19 treatment centres were active, only 18 were able to recruit subjects. Five of the 18 centres are classified as small sites (having enrolled < 3 patients in one or both treatment arms in the primary part). 6 further sites have participated in the preliminary part of the trial, but did not enrol any patients in the primary part. The Applicant has cited inadequate or insufficient human resources being dedicated to the study, administrative reasons within the site such as internal issues between the investigative staff and the centre's management, unavailability of suitable patients for enrollment and lack of genuine interest in study participation and enrollment of subjects (reflected as absence or poor pre-screening/screening activity for prolonged periods). This is considered to reflect poor selection of treatment centres for this study.

***Efficacy data and additional analyses***

The population eligible for entry into the study was well balanced at baseline in treatment groups. All subjects in the ITT population were White, with the exception of 1 Asian subject. The majority of subjects in the study were male, but a greater proportion of subjects in the MC group (31.6%) than in the FS Grifols pooled group (17.6%) were female. Mean and median ages in the MC group (67.0 years) were near the FS Grifols ages group - mean (68.4 years) and median (70.0 years).

In the Part I, the most common surgical procedure was abdominal aortic aneurysm resection and graft replacement -16/72 subjects (22.2%). In the Part II of the study, the most common surgical procedure was carotid endarterectomy – 23/110 subjects (20.9%) in FS Grifols group and 11/57 subjects (19.3%) in MC group. The proportions of subjects treated with FS Grifols overall were similar to those treated with MC for most types of vascular surgery.

The provided efficacy data show that VeraSeal is more effective than manual compression for the control of mild or moderate bleeding during a 10 minute observation period at the target bleeding site. 46.4 % vs. 26.3 % of patients in the ITT population could reach haemostasis below three minutes. This difference is statistically significant in favor of VeraSeal based on the CMH row mean score ($p < 0.001$). In the PP population, this result is mirrorred with 46.5 % vs. 27.1 % of patients achieving heamostasis in < 3 minutes.

11.8 % vs. 28.1% of ITT patients experienced treatment failure at 10 minutes and had to be treated with further haemostatic interventions. In the PP population, 12.8 % vs. 33.3 % of patients were considered treatment failures.

Apart from the ITT and PP analyses of the TTH and treatment failures, there were no further subgroup or sensitivity analyses prespecified and there are no further efficacy endpoints available.

## 3.3.7. Conclusions on clinical efficacy

It is acknowledged that vascular surgery is a challenging indication for a fibrin sealant and that VeraSeal has shown an improved haemostatic effect in comparison to manual compression in the 10 minute efficacy observational period in the overall population. However, the imprecise primary endpoint with haemostatic time categories of unequal size (i.e. $\leqslant$3, >3 to $\leqslant$4, >4 to $\leqslant$ 5, >5 to $\leqslant$ 7, and >7 to $\leqslant$10 minutes), which is not supported by any relevant secondary endpoints, together with all other shortcomings of this trial (e.g. small sample size, no prespecified subgroup analyses, multitudes of protocol deviations...) are seen as prohibitive to the utilisation of this trial as the sole support for a possible MA of FS Grifols.

Major concerns still remaining include the lack of secondary endpoints, the limited information based on the small sample size gained from subgroup analyses regarding consistency, and the representativeness of the study population to allow generalization to a wider patient population. Beyond this, despite it is accepted that a treatment effect in the overall trial population is demonstrated, the extent of the treatment effect size of Veraseal is not well established. This is partly based on the statistical analyses provided, but beyond this is also seriously affected by imprecise categorical data collection for the primary haemostasis endpoint.

Furthermore, the fact that the phase II/III study IG402 is only a small part of the clinical investigation programme, which consists of 3 additional ongoing phase III studies (in soft tissue surgery, parenchymal organ surgery and peripheral vascular surgery) is seen as an indication that the Applicant did not initially intend to rely on a one pivotal trial strategy.

However, the final integrated inspection report has made clear that the quality and integrity of the data from this trial are not robust enough to be accepted as support of a MA and should be disregarded by the CHMP. As trial IG402 is the sole trial contained in the dossier, no reliable data to demonstrate the efficacy of FS Grifols remain.

## 3.3.8. Clinical safety

### Patient exposure

In the submitted trial 186 patients received the investigational product. Subjects who were randomized to MC but received FS Grifols at the TBS in error or received FS Grifols at a non-TBS were categorized to FS Grifols for safety analyses. Thus the safety population differs from the ITT population.

Subjects were monitored from the time of informed consent to Post-Operative Week 6 ± 4 days for assessment of AEs, adverse drug reactions, and SAEs.

The mean amount of FS Grifols used at the TBS was 4.5 mL among subjects in the safety population treated with FS Grifols (pooled), but exposure was lower in the Preliminary Part (I) (3.7 mL) than in the Primary Part (II) (5.0 mL).

The amount of FS Grifols used in non-TBS sites is not shown. This is due to the fact that the amount of product applied was not captured in the CRF.

**14.3.1 Exposure to Study Treatment (Safety)**

| Variable | FS Grifols Preliminary Part(I) (N = 72) | FS Grifols Primary Part(II) (N = 115) | FS Grifols Pooled Part (I) + Part(II) (N = 187) | MC Primary Part(II) (N = 52) |
|---|---|---|---|---|
| FS Grifols used at TBS (mL) | | | | |
| n | 72 | 114 | 186 | 0 |
| Mean (std) | 3.69 (2.686) | 5.00 (2.972) | 4.49 (2.928) | NA |
| Median | 3.00 | 4.80 | 3.96 | NA |
| Q1, Q3 | 1.50, 5.25 | 3.00, 6.00 | 1.98, 6.00 | NA |
| Min, Max | 0.3, 12.0 | 0.0, 12.0 | 0.0, 12.0 | NA |
| Additional (non-TBS) sites treated with FS Grifols [n (%)] | | | | |
| Yes | 31 ( 43.1) | 50 ( 43.5) | 81 ( 43.3) | NA |
| Vascular bleeding | 26 ( 36.1) | 41 ( 35.7) | 67 ( 35.8) | NA |
| Soft tissue bleeding | 0 | 3 ( 2.6) | 3 ( 1.6) | NA |
| Other | 10 ( 13.9) | 9 ( 7.8) | 19 ( 10.2) | NA |
| No | 41 ( 56.9) | 65 ( 56.5) | 106 ( 56.7) | NA |

FS Grifols = Fibrin Sealant Grifols, MC = Manual Compression, TBS = Target Bleeding Site, NA = Not Applicable
Note: Patient 21-013 was randomized to MC but received FS Grifols at the target bleeding site (TBS) in error; patients 11-011, 15-004, 21-016, and 21-029 were randomized to MC but received FS Grifols at a non-TBS. These patients are categorized under FS Grifols Part(II) for all safety summaries. "FS Grifols used" for these subjects is summarized even if it was used at a non-TBS; patient 11-011 had no FS Grifols volume recorded and is missing from the "FS Grifols used" summary.

Source: Listing 16.2.5, Dataset: ADEX, Program: t_expose.sas, Output: t14-3-1-expose.rtf, Generated on: 23SEP2014 18:39
Page 1 of 1

## Adverse events

**Table 11. Overall Summary of Adverse Events (Safety)**

| | FS Grifols Preliminary Part (I) | | FS Grifols Primary Part (II) | | FS Grifols Pooled Part (I) + Part (II) | | MC Primary Part (II)) | |
|---|---|---|---|---|---|---|---|---|
| | AEs (N=330) n (%) | Subjects (N=72) n (%) | AEs (N=498) n (%) | Subjects (N=115) n (%) | AEs (N=828) n (%) | Subjects (N=187) n (%) | AEs (N=228) n (%) | Subjects (N=52) n (%) |
| Any adverse event | 330 (100.0) | 67 (93.1) | 498 (100.0) | 102 (88.7) | 828 (100.0) | 169 (90.4) | 228 (100.0) | 47 (90.4) |
| Any severe adverse event | 38 (11.5) | 21 (29.2) | 83 (16.7) | 35 (30.4) | 121 (14.6) | 56 (29.9) | 39 (17.1) | 17 (32.7) |
| Any potentially related adverse event | 8 (2.4) | 5 (6.9) | 36 (7.2) | 11 (9.6) | 44 (5.3) | 16 (8.6) | 3 (1.3) | 2 (3.8) |
| Any potentially related adverse event attributable to the technique of application | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Any severe potentially related adverse event | 1 (0.3) | 1 (1.4) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (0.5) | 0 (0.0) | 0 (0.0) |
| Any severe potentially related adverse event attributable to the technique of application | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Any adverse event with outcome of death | 5 (1.5) | 5 (6.9) | 2 (0.4) | 2 (1.7) | 7 (0.8) | 7 (3.7) | 2 (0.9) | 1 (1.9) |
| Any adverse event leading to withdrawal | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Any serious adverse event | 27 (8.2) | 18 (25.0) | 33 (6.6) | 29 (25.2) | 60 (7.2) | 47 (25.1) | 13 (5.7) | 9 (17.3) |
| Any potentially related serious adverse event | 2 (0.6) | 2 (2.8) | 1 (0.2) | 1 (0.9) | 3 (0.4) | 3 (1.6) | 0 (0.0) | 0 (0.0) |
| Any potentially related serious adverse event attributable to the technique of application | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Any intra-operative adverse events | 32 (9.7) | 25 (34.7) | 54 (10.8) | 39 (33.9) | 86 (10.4) | 64 (34.2) | 29 (12.7) | 25 (48.1) |
| Of which imputed due to missing data | 1 (0.3) | 1 (1.4) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (0.5) | 0 (0.0) | 0 (0.0) |
| Any surgical adverse events | 115 (34.8) | 51 (70.8) | 125 (25.1) | 63 (54.8) | 240 (29.0) | 114 (61.0) | 73 (32.0) | 29 (55.8) |
| Of which imputed due to missing data | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Any non-surgical adverse events | 183 (55.5) | 55 (76.4) | 319 (64.1) | 78 (67.8) | 502 (60.6 ) | 133 (71.1) | 126 (55.3 ) | 37 (71.2) |
| Of which imputed due to missing data | 1 (0.3) | 1 (1.4) | 3 (0.6) | 1 (0.9) | 4 (0.5) | 2 (1.1) | 0 (0.0) | 0 (0.0) |

FS Grifols = Fibrin Sealant Grifols, MC = Manual Compression
Note: Only adverse events that occurred on the date of informed consent or with a start date through the Week 6 visit are summarized. For the subjects column of each category, subjects are included only once, even if they experienced multiple events in that category. Potentially related AEs are Unlikely, Possibly, or Probably related. Date imputation algorithm is described in the Statistical Analysis Plan.

Source: Listing 16.2.7, Dataset: ADAE, Program: t_aesum.sas, Output: t14-3-2-1-aesum.rtf, Generated on:23 SEP 2014 20:10
Source: Table 14.3.2.1, Listing 16.2.7

Adverse Events by Relationship

In the FS Grifols pooled group, 16 subjects (8.6%) experienced any AE that was considered potentially related. In the MC group, 2 subjects (3.8%) experienced any AE that was considered potentially related.

Among subjects in the FS Grifols pooled group, no AEs were reported that were considered probably related to the study treatment, 2 subjects (1.1%) each experienced an AE that was considered to be possibly related to the study treatment (post-procedural hemorrhage and wound infection), and 14 subjects (7.5%) experienced at least 1 event that was considered unlikely related to the study medication. All other events were considered unrelated to the study treatment (with the exception of 1 AEs with missing causality). Among subjects in the MC group, no AEs were reported that were considered to be possibly or probably related to the study treatment, and 2 subjects (3.8%) experienced AEs that were considered unlikely to be related to treatment. All other events were considered unrelated to the study treatment.

In addition to the subjects who had AEs classified as possibly or probably related described previously, 14 subjects (7.5%) in the FS Grifols pooled group experienced at least 1 event that was considered unlikely related to the study medication. With the exception of nausea, hematoma, and pyrexia (each 2 subjects, 1.1%), no event was reported as unlikely related for more than 1 subject. These events were procedural pain, wound complication, wound dehiscence, post procedural discharge, graft hemorrhage, seroma, wound hemorrhage, vomiting, dyspepsia, abdominal pain, abdominal distension, hypotension, postoperative wound infection, wound infection, hepatic enzyme increased, blood creatinine increased, headache, atelectasis, food intolerance, anemia, back pain, pruritus, and rash. In the MC group, the AEs that were considered unlikely to be related to treatment were peripheral edema, decreased hemoglobin, and arrhythmia.

Graft hemorrhage was considered potentially related to FS Grifols and reported as severe for 1 subject (0.5% of the FS Grifols pooled group).

Moderate events that were potentially related were reported for 7 subjects (3.7%) in the FS Grifols pooled group: nausea and wound infection (each 2 subjects [1.1%]) and, in 1 subject (0.5%) each, abdominal pain, vomiting, post procedural hemorrhage, procedural pain, wound hemorrhage, hematoma, pruritus, and rash.

## Serious adverse events and deaths

Serious adverse events

Three subjects in the FS Grifols pooled group (1.6%) and no subjects in the MC group experienced SAEs that were considered potentially related to study treatment: post procedural hemorrhage was possibly related, graft hemorrhage was unlikely related, and wound infection was unlikely related.

Subject 23-004, treated with FS Grifols in the Preliminary Part (I), experienced an AE of moderate peripheral artery aneurysm. Although the reported action taken was hospitalization or prolonged hospitalization, the event was not reported as an SAE, per protocol, because it was an elective procedure performed due to a preexisting condition that had not worsened from baseline.

Deaths

Seven subjects (3.7%) in the FS Grifols pooled group and 1 subject (1.9%) in the MC group had any AE with outcome of death. The events with outcome of death that were reported for subjects treated with FS Grifols were myocardial infarction, acute myocardial infarction, cardiac failure, chronic cardiac failure, cardio-respiratory arrest (in the SOC cardiac disorders) and cerebrovascular accident and cerebral infarction (in the SOC nervous system disorders). The subject in the MC group experienced post procedural complication (acutely ischemic colon in the SOC injury, poisoning, and procedural complications) and multi-organ failure (in the SOC general disorders and administration site conditions) with outcome of death.

All events with outcome of death were considered unrelated to study treatment, and all were reported as severe. The cerebrovascular accident (FS Grifols, Preliminary Part [I]) and the multi-

organ failure with post procedural complication (MC) were categorized as surgical AEs, defined as events that happened from the end of the surgery (after the completion of the surgical closure by layers of the last exposed surgical field [TCompletion] until 24 hours after the end of surgery or until recovery from anesthesia, whichever was later. All other AEs with outcome of death occurred after that time.

### Laboratory findings

Laboratory investigations comprised complete blood count, serum clinical chemistry, urinanalyses parameters, coagulation parameters and viral safety.

For complete blood count and serum clinical chemistry comparisons of change from baseline cannot be assessed since several baseline assessments were not done. The applicant acknowledged that assessment of several laboratory parameters was not done at baseline. Although these missing data are captured as protocol violations this is another hint for demonstrating the poor conduct of this clinical trial. Since this is the only trial submitted for this application the final outcome of the inspection report should be awaited before a final conclusion can be drawn.No concerns arise from the virology results.

### Safety in special populations

Elderly were included in the clinical trial. No safety data are available in the paediatric population.

### Immunological events

Patients were only tested for antibodies against human coagulation factor V, human thrombin and human fibrinogen if they had prolonged postoperative coagulation times that were not explained by any of the medical conditions listed in the protocol.

No new positive results were observed at the end of the study. Of the 15 subjects who met the protocol criteria for antibody testing, only Subject 15-003 in the FS Grifols pooled group was found to have a post-baseline positive result for anti-factor V antibodies, but further investigation revealed that the subject had a positive result at baseline as well.

**Figure 1.** SOPs and validation reports for antibody testing (ELISA based) against human Thrombin, human Factor V/Va and human Fibrinogen were provided within the responses to the D120 LoQ. SOPs include detailed descriptions of assay instructions as well as continuative guidance in case a sample reveals to be “potentially positive”. Such samples have to be investigated for their specificity with regard to the respective antibody (i.e. antibodies against Thrombin, Factor V/Va, Fibrinogen).

### Safety related to drug-drug interactions and other interactions

No specific interaction studies were performed.

The information given in the SmPC corresponds to the applicable Core SmPC for fibrin sealants.

### Discontinuation due to AES

No subject discontinued due to an adverse event according to table 14.1.1.3 Subject Disposition (ITT).

## 3.3.9. Discussion on clinical safety

Safety data are derived from one submitted clinical study investigating safety and efficacy of FS Grifols in vascular surgery. The safety population comprises 186 patients. Since some of the patients randomized to MC received FS Grifols at the target bleeding site in error or received FS Grifols at non target bleedings sites, the number of patients in the safety population differs from the ITT population.

The amount of FS Grifols used in non-TBS sites (81) cannot be presented with respect to description of non-TBS sites and the estimate amount of FS Grifols since documentation of this information was not foreseen in the study protocol.

In the FS Grifols pooled group (Preliminary and Primary Part) adverse events that were considered potentially related were reported for 16 subjects (8.6%) while in the MC group 2 subjects (3.8%) experienced any AE that was considered potentially related. All potentially related AEs occurring in the FS Grifols pooled group are adequately reflected in the SmPC.

Safety with regards to adverse events related to thrombotic events, immunogenicity, anaphylactic reactions and adverse events potentially related to (re)bleeding at TBS seems to be comparable between patients receiving VeraSeal and patients receiving MC.

Three subjects in the FS Grifols pooled group (1.6%) and no subjects in the MC group experienced SAEs that were considered potentially related to study treatment: post procedural hemorrhage was possibly related, graft hemorrhage was unlikely related, and wound infection was unlikely related. Seven subjects (3.7%) in the FS Grifols pooled group and 1 subject (1.9%) in the MC group had any AE with outcome of death. All events with outcome of death were considered unrelated to study treatment.

No concerns regarding immunogenicity arise from the presented data.

The applicant acknowledged that assessment of several laboratory parameters was not done at baseline. Although these missing data are captured as protocol violations this is another hint for demonstrating the poor conduct of this clinical trial. The final integrated inspection report confirms that data from this trial are not robust enough to support a MAA and should be disregarded by the CHMP.

### 3.3.10. Conclusions on clinical safety

The safety database is considered rather small for a new product and also compared to that of other licensed fibrin sealants. In addition, findings from a GCP inspection of the study sites raised serious questions about the data from the main study submitted in support of the application.

As trial IG402 is the sole trial contained in the dossier, no reliable data to demonstrate the safety of FS Grifols remain.

## *3.4. Pharmacovigilance system*

The CHMP considers that the Pharmacovigilance system summary submitted as described by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC. The applicant's pharmacovigilance system summary includes a reference to the location where the pharmacovigilance system master file for the medicinal product is kept and provides proof that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC.

## *3.5. Risk management plan*

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

The PRAC considered that the risk management plan version 1.1 is acceptable.

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

# 4. Orphan medicinal products

N/A

# 5. Benefit risk assessment

## *Benefits*

### Beneficial effects

The VeraSeal kit is composed of 2 syringes containing sterile frozen solutions of human fibrinogen and human thrombin with calcium chloride assembled on a syringe holder. VeraSeal is intended for local application by dripping onto the bleeding site.

The efficacy of VeraSeal was investigated in a single blind, randomized phase II/III study in subjects undergoing one of 20 predefined kinds of peripheral vascular surgery. The study consisted of two parts: in the preliminary part, the first 2 patients per centre were treated open label with VeraSeal, in the primary part, subjects were randomized 2:1 to FS Grifols or manual compression. The primary endpoint was defined as time to haemostasis in minutes, investigated in a 10 minute observational window. However, TTH was not reported in minutes, but in 5 haemostatic categories, e.g <3 minutes, ≥3 but <5 minutes and so on.

In the primary part of the trial, 110 patients were treated with VeraSeal and 57 with MC. Of those patients in the ITT analysis population, 46.4% vs. 26.3% achieved haemostasis in less than 3 minutes, while 11.8 % vs. 28.1 % of patients experienced treatment failure (defined as TTH > 10 minutes). The PP analysis produces similar results.

The Grifols sealer components production processes include a double nanofiltration step to remove especially small viruses like Parvo B 19 virus and HAV.

### Fibrinogen (component 1)

The applicant supposes that the double nanofiltration step of the fibrinogen production process can be considered as a double virus removal step. Nanofiltration through Planova 35N is used to pre-filter the spiked material to guarantee monodispersed viruses in the material to be filtered through Planova 20N. The results have shown that most viruses larger than 35 nm are removed by filtration through Planova 35N, with no residual infectivity detected in the Planova 35N filtrate in any of the cases, recovering most of the spiked viruses in the Planova 35N retentate. The filtration through Planova 20N increases the safety of the step even further with respect to small type of virus.

For Fibrinogen 20nm nanofiltration showed a good virus removal capacity for HAV and PPV (as a model virus for Parvo B 19 virus).

### Thrombin (component 2)

For component 2 nanofiltration is performed with two 15nm filters. The company could show in the virus removal studies that the larger viruses (HIV, Pseudorabies Virus, Bovine Viral Diarrhoea VirusandWest Nile Virus) were removed effectively through the Planova 15N filters with no residual infectivity detected in any of the experiments performed.

The smallest viruses assessed (HAV and PPV) provided a Reduction Factor of 6.56 log10/ml and 6.14 log10/ml respectively.

The nanofiltration data provided show that the virus removal steps in the manufacturing processes of the two components of VeraSeal contribute effectively to the safety of the product. With regard

to technical innovation the CHMP cannot identify new or innovative technical improvement in this manufacturing step as the applied technique is widely used in plasma fractionation for just a long time.

It is of course acknowledged that the implementation of double nanofiltration adds to additional viral safety and leads therefore to a final product with a high safety standard.

## Uncertainty in the knowledge about the beneficial effects

The primary endpoint is not supported by clinically relevant secondary endpoints, like transfusion requirements, postoperative rebleeding at the target bleeding site (TBS), reoperation at TBS, postoperative blood loss, graft thrombosis or occlusion, length of hospital stay, as they were not investigated in this trial. The efficacy observation is limited to the 10 minute evaluation.

Initially, no subgroup analyses were foreseen for trial IG402, which is not in accordance with the GL on Points to Consider on Application with One Pivotal Trial (CPMP/EWP/2330/99). Such analyses would have been especially relevant for this application as IG402 is the sole source of clinical data for FS Grifols at the time being. The Applicant has now submitted post hoc subgroup analyses regarding gender, age >/<65, type of bleeding at TBS and type of graft. Although the selected subgroups can be considered as relevant, the performed subgroup analyses have limited convincing power. Methodologically, the CMH test is not sensitive and informative to address consistency of treatment effects, and therefore additional analyses using the POM are requested. Nevertheless, the limited value of the subgroup analyses is also based on their small sample sizes, leaving room for large uncertainty, questioning the generalizability to a larger patient population.

The duration of this small study is excessively long, the actual time to finish the trial was 6 years (Oct 2008 - May 2014). The long timeframe can have introduced bias into the study as the fields of vascular surgery and anaesthesia continually evolve and the standard treatment modalities are subject to change, e.g. suture materials, suture techniques, improved management of anticoagulation during and after surgical procedures, novel anticoagulants, perioperative medication with statins and antiplatelet drugs, improved fluid and blood products management. The claim that the clinical situation has remained unchanged was not further substantiated by the applicant. While some additional analyses have been provided to investigate consistency of the treatment effect over time, further more sensitive statistical analyses would have been requested to assess whether the overall treatment effect is driven by a specific time-period.

6 of 18 treatment centres contributed in the preliminary part, but did not enrol patients in the primary part. The reasons for this cited by the company include lack of resources, lack of interest or internal issues which is a reflection of poor selection of treatment centres.

With respect to single-blinding the long study duration and the changes made in the statistical analysis plan on the primary endpoint are of concern. For this single pivotal trial strong statistical evidence is needed. While the statistical test performed could achieve a level of $p<0.00125$, the sole p-value of a test statistic is however only one aspect. The applicant has changed the statistical test following a pre-test, inflating the type I error. Furthermore changes on the statistical test were introduced during the course of the single blinded trial and some ambiguity in the specifications remained. While it could be shown that relevant analyses resulted in the same conclusions, some remaining issues on consistency of the results prior and after the changes and the robustness of the primary analysis model need to be addressed.

The trial results are still not reassuring regarding the study's internal consistency and external validity. Subgroup analyses are based on small sample sizes, and further analyses investigating treatment effect sizes would have been requested. Altogether these deficiencies undermine the convincing power of the trial and do not contribute to establishing compelling evidence. In addition,

findings from a GCP inspection of the study sites raised serious questions about the data from the main study submitted in support of the application. As data from trial IG402 have to be disregarded, no proof of efficacy for FS Grifols remains as the dossier is currently based only on data from this single phase II/III study.

Furthermore, three phase III studies in surgery are ongoing and indicate that the phase II/III study IG402 was not intended as a one pivotal trial.

## *Risks*

### Unfavourable effects

Safety data are derived from one submitted clinical study investigating safety and efficacy of FS Grifols in vascular surgery. The safety population comprises 186 patients including all patients from the preliminary (n=72) and primary part (n=114) who received FS Grifols. Since some of the patients randomized to MC received FS Grifols at the target bleeding site in error or received FS Grifols at non target bleedings sites, the number of patients in the safety population differs from the ITT population. Patients were monitored from the time of informed consent to post-operative week 6 ± 4 days for assessment of AEs, adverse drug reactions and SAEs.

Adverse events that were considered potentially related were reported for 16 subjects (8.6%) receiving FS Grifols and for 2 subjects (3.8%) treated by manual compression, respectively.

Three subjects in the FS Grifols pooled group (1.6%) and no subjects in the MC group experienced SAEs that were considered potentially related to study treatment: post procedural hemorrhage was possibly related, graft hemorrhage was unlikely related, and wound infection was unlikely related. Seven subjects (3.7%) in the FS Grifols pooled group and 1 subject (1.9%) in the MC group had any AE with outcome of death. All events with outcome of death were considered unrelated to study treatment.

### Uncertainty in the knowledge about the unfavourable effects

Safety data are derived from only one submitted study and the safety database is considered rather small for a new product and also compared to that of other licensed fibrin sealants.

Furthermore, some of the patients received VeraSeal at non target bleeding sites after application to the target bleeding site and efficacy evaluation. However, no efficacy evaluation was foreseen for using VeraSeal at non target bleeding sites and no detailed information can be given about the amount of VeraSeal used at non TBS. Although all subjects receiving VeraSeal are included in the safety population regardless if they received VeraSeal at TBS or non TBS, a thorough assessment might be hampered by missing details about the use of this new investigational product. However, the applicant is not able to retrospectively collect all the requested information since this was not foreseen in the study protocol and therefore no such data are available for all patients.

Assessment of several laboratory parameters was not done at baseline. This included parameters defined as exclusion criteria in the protocol (e.g. coagulation, hepatic or renal parameters > 2x ULN) Although these missing data are captured as protocol violations this is another hint for demonstrating the poor conduct of this clinical trial. Findings from a GCP inspection of the study sites raised serious questions about the data from the main study submitted in support of the application As data from trial IG402 have to be disregarded, no proof of safety for FS Grifols remains as the dossier is currently based only on data from this single phase II/III study.

# Balance

## Importance of favourable and unfavourable effects

The achievement of reliable haemostasis of surgically inflicted injuries to tissues and vessels is a necessary part of every operation. VeraSeal has shown that it shortens the time to achievement of haemostasis after vascular surgery at a target bleeding site with mild to moderate bleeding in comparison with manual compression and also has a reduced rate of treatment failure, where the bleeding site had to be treated with further haemostatic options after the end of the 10 minutes efficacy period. The observed adverse events are comparable to those of other fibrin sealants. However, as the submitted efficacy and safety data cannot be regarded as reliable, no definitive conclusions can be drawn.

## Benefit-risk balance

The favourable short-term primary efficacy endpoint is not supported by clinically relevant secondary endpoints, which could extend the efficacy evaluation beyond the 10 minute observation period, or corroborated by appropriate subgroup or sensitivity analyses. In addition, the incomplete picture on adverse events of special interest together with the many protocol violations where prescribed laboratory tests were not done, the limited size of the safety database and the profound weaknesses of the methodological approach do not allow a comprehensive overview of the intended and unintended consequences of administration of VeraSeal. In summary, this clinical study is not considered able to generate the necessary compelling evidence expected from a single pivotal trial.

### *Discussion on the benefit-risk assessment*

In general, the imprecise primary endpoint with haemostatic time categories of unequal size (i.e. ⩽3, >3 to ⩽4, >4 to ⩽ 5, >5 to ⩽7, and >7 to ⩽10 minutes), which is not supported by any relevant secondary endpoints, together with all other shortcomings of this trial (e.g. small sample size, no prespecified subgroup analyses, multitudes of protocol deviations...) are seen as prohibitive to the utilisation of this trial as the sole support for a possible MA of FS Grifols.

Major concerns that still apply include the lack of secondary endpoints, the limited information based on the small sample size gained from subgroup analyses regarding consistency, and the representativeness of the study population to allow generalization to a wider patient population. Beyond this, despite it is accepted that a treatment effect in the overall trial population is demonstrated, the extent of the treatment effect size of Veraseal is not well established. This is partly based on the statistical analyses provided, but beyond this is also seriously affected by imprecise categorical data collection for the primary haemostasis endpoint.

In addition to the inherent shortcomings already discussed, findings from a GCP inspection of the study sites raised serious questions about the data from the main study submitted in support of the application. Therefore data from trial IG402 study have to be disregarded. In consequence, no proof of efficacy or safety for FS Grifols remains as the dossier is currently based only on data from this single phase II/III study.

## *5.1. Conclusions*

The overall Benefit /Risk of Veraseal is negative.