Application Type	Original Application
STN	125640/0
CBER Received Date	November 4, 2016
PDUFA Goal Date	November 3, 2017
Division / Office	DCEPT / OTAT
Committee Chair	Natalya Ananyeva, Ph.D.
Project Manager	Yu Do, M.S.
Priority Review	No
Clinical Reviewer	Agnes Lim, M.D. Agnes Lim -S Digitally signed by Agnes Lim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Agnes Lim -S, 0.9.2342.19200300.100.1.1=1300395678 Date: 2017.10.24 12:18:03 -04'00' APPROVED By Agnes Lim at 1:56 pm, Oct 16, 2017
Review Completion Date / Stamped Date	October 16, 2017
Supervisory Concurrence	APPROVED By Ilan Irony, M.D. at 8:28 pm, Oct 16, 2017 Concur
	For Division - Concur APPROVED By Ilan Irony, M.D. at 11:03 am, Oct 19, 2017
Applicant	Instituto Grifols, S.A.
Established Name	Fibrin Sealant (Human)
(Proposed) Trade Name	
Pharmacologic Class	Hematology
Formulation(s), including Adjuvants, etc	N/A
Dosage Form(s) and Route(s) of Administration	Frozen solutions for topical application
Dosing Regimen	N/A
Indication(s) and Intended Population(s)	An adjunct to hemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical.
Orphan Designated (Yes/No)	No

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GLOSSARY

Abbreviation	Meaning
ADR	adverse drug reaction
AE	adverse event
ATC	anatomical therapeutic chemical
BLA	biologics license application
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CR	complete response
CSR	clinical study report
DE	Division of Epidemiology
eCTD	electronic Common Technical Document
FDA	Food and Drug Administration
FS	fibrin sealant
FS Grifols	Fibrin Sealant Grifols
HTC	hemostatic time category
HF	Human Factors
ICF	informed consent form
iPSP	initial pediatric study plan
ISE	integrated summary of efficacy
ISS	integrated summary of safety
ITT	intent-to-treat
IU	international unit
MC	manual compression
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
min	minute
mL	milliliter
N/A	not applicable
NHTC	non-hemostatic time category
OBE	Office of Biostatistics and Epidemiology
OR	odds ratio
PeRC	FDA Pediatric Review Committee
PI	package insert
PK	pharmacokinetics
PP	per-protocol
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PT	preferred term, MedDRA
PTFE	polytetrafluoroethylene
RBC	red blood cell
REMS	risk evaluation and mitigation strategy

RR	risk ratio
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class, MedDRA
T10	hemostatic assessment at 10 minutes following T_{Start}
T2	hemostatic assessment at 2 minutes following T_{Start}
T3	hemostatic assessment at 3 minutes following T_{Start}
T4	hemostatic assessment at 4 minutes following T_{Start}
T5	hemostatic assessment at 5 minutes following T_{Start}
T7	hemostatic assessment at 7 minutes following T_{Start}
TBS	target bleeding site
$T_{Closure}$	time of completion of the surgical closure by layers of the exposed surgical field containing the TBS
T_{Start}	time of start of initial study treatment (FS Grifols, Surgicel, or MC) application
TEAE	treatment-emergent adverse events
TTH	time to hemostasis
US	United States
WBC	white blood cell
WFI	water for injection
WHO-DD	World Health Organization Drug classification Dictionary

1. Executive Summary

Instituto Grifols has submitted STN125640 for a fibrin sealant product, Fibrin Sealant Grifols (identified as FS Grifols in this review memorandum), for the following indication:

> FS Grifols is a fibrin sealant (human) indicated as an adjunct to hemostasis for mild to moderate bleeding in adults (b) (4) undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. ~~VeraSeal~~ FS Grifols is effective in heparinized patients.

Reviewer Comments:

1. (b) (4)

   The Applicant has agreed to conduct a post-marketing prospective, controlled pediatric study, if the BLA is approved. The proposed pediatric protocol (IG1 405) that was submitted under IND 14986 was previous reviewed and approved. The Applicant's deferral request for study IG1 405 for the pediatric population zero to less than 18 years of age was reviewed by PeRC on September 6, 2017. PeRC agreed with CBER/OTAT's recommendation to grant the deferral.
2. *The Proprietary Name review team rejected the proposed Trade name, VERASEAL. No new acceptable Trade name has been submitted. The product will be identified as FS Grifols in this review.*

Product

FS Grifols is a frozen, sterile, two-component fibrin sealant solution obtained from human plasma pools. FS Grifols consists of human fibrinogen (component 1) and human thrombin with calcium chloride (component 2) solutions filled in syringes, assembled on a syringe holder. FS Grifols is being submitted as a combination product and is packaged with a spray device.

The human fibrinogen solution contains:

- Human fibrinogen: 80 mg/ml solution
- Other ingredients: sodium citrate, sodium chloride, arginine, L-isoleucine, L-glutamic acid monosodium and water for injection.

The human thrombin solution contains:

- Human thrombin: 500 IU/ml solution
- Other ingredients: calcium chloride, human albumin, sodium chloride, glycine and water for injection.

FS Grifols is intended for topical application to exert a local effect by dripping or spraying. When applied to a bleeding surface, the solutions generate a cross-linked fibrin

clot in a process that mimics the last stage of the human coagulation system. FS Grifols is intended for use intraoperatively by a surgeon or qualified health care provider only.

Clinical Development – Pivotal Studies IG1 101, IG1 102, and IG1 103

The Applicant's clinical program was designed to assess the safety and efficacy of Fibrin Sealant Grifols (FS Grifols) in the surgical setting as an adjunct to local hemostasis. The program consists of three Phase 3 randomized clinical trials: IG1101, IG1102, and IG1103. The Applicant is seeking approval to market FS Grifols for the therapeutic indication as an adjunct to hemostasis in surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. Each trial evaluated one of three surgery types: vascular surgery in study IG1101, parenchymous tissue surgeries in study IG1102, and soft tissue surgeries in study IG1103. In all three trials, the efficacy of FS Grifols was directly compared with an active control: Manual Compression (MC) (superiority studies IG1101) or oxidized cellulose polymer, Surgicel®, (non-inferiority in studies IG1102 and IG1103). The three Phase 3 studies are summarized in Table 1.

Table 1. List of All Three Phase 3 Clinical Trials

Study no.	**Surgery Type**	**Active Control**	**Hypothesis testing**	**Target Bleeding Site Intensity**	**Primary Efficacy Endpoint**
IG1101	Vascular Surgery	Manual Compression	Superiority	Moderate	Proportion of subjects achieving hemostasis (Yes/No) at the target bleeding site by 4 minutes (T4)
IG1102	Parenchymous (hepatic)	Surgicel	Non-inferiority	Moderate	
IG1103	Soft Tissue	Surgicel	Non-inferiority	Moderate	

All three pivotal trials had similar study designs. Each trial consisted of two parts: a Preliminary Part I and a Primary Part II. The purpose of the Preliminary Part I was to ensure that local study teams familiarized themselves with the technique for FS Grifols application and with intra-operative procedures required by the protocol of the clinical trial. In study IG1101, all subjects enrolled in the Preliminary Part I were treated with FS Grifols. In studies IG1102 and IG1103, subjects were randomized in Preliminary Part I to a 1:1 ratio into 1 of 2 treatment groups: FS Grifols or Surgicel.

The Primary Part II of the trial was designed to provide sufficient evidence to support the safety and efficacy of FS Grifols as an adjunct to hemostasis in surgery. Primary Part II of the trial was to start only after enrollment of 2 subjects in Preliminary Part I in study IG1101 and 4 subjects in studies IG1102 and IG1103.

In study IG1101, subjects in Primary Part II were randomized in 2:1 ratio into FS Grifols or MC treatment groups. In studies IG1102 and IG1103, subjects in Primary Part II were randomized in 1:1 ratio into FS Grifols or Surgicel treatment groups.

In both parts of the clinical trials, subjects were scheduled to undergo an elective (non-emergency), open (non-laparoscopic), vascular (non-endovascular) surgical procedure in study IG1101, parenchymous tissue (i.e., hepatic) surgical procedure in tudy IG1102, and soft tissue surgical procedure in study IG1103, wherein a Target Bleeding Site (TBS) was identified intra-operatively and a topical hemostat was indicated, were eligible to participate after informed consent was obtained. A specific bleeding area/site was defined as the TBS when it was determined by the investigator (the surgeon) that control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) was ineffective or impractical, and required an adjunct treatment to achieve hemostasis. The size of the TBS was not defined in study IG1 101. In studies IG1 102 and IG1 103, the approximate size of the TBS was rated by the investigator (the surgeon) using a 3-point scale: Small: TBS ≤10 cm2, Medium: 10 cm2 <TBS ≤100 cm2 or Large: TBS >100 cm2. For both parts of all three trials, only subjects with a TBS with bleeding of moderate intensity could be enrolled.

The primary efficacy endpoint for all three clinical trials was the proportion of subjects in the Primary Part II of the study achieving hemostasis (Yes/No) at the TBS by 4 minutes (T4), following the start of treatment application without occurrence of re-bleeding and re-application of study treatment after T4 and until the completion of the surgical closure. Secondary endpoints included proportion of subjects achieving hemostasis at the TBS at 2, 3, 5, 7, and 10 minutes, time to hemostasis (TTH), categorized from ≤2 minutes to ≤10 minutes, and prevalence of treatment failures.

In all three trials, the safety analysis population included all subjects enrolled.

Study Results

Subject Disposition

Overall, in Primary Part II of the three clinical trials, subject disposition was consistent between treatment groups across studies. See the review of the individual trials for details.

Demographics

Overall, across the three studies, the percentages or numbers of subjects in Primary Part II were balanced between treatment groups regarding gender, age, and race. Of 336 subjects who were randomized to FS Grifols, 89.3% (300/336) of the total enrolled subjects were White, 8.6% (29/336) were Black, and 2.1% (7/336) were Asian. Enrollment in other race groups was too small to permit valid conclusions within these groups. In regard to sex, overall, 48.8% (164/336) were male and 51.2% (172/336) were

female, maintaining an approximately equal ratio in both treatment groups. The mean age of the subjects who were randomized to FS Grifols was 64 years old in study IG1 101, 60 years old in study IG1 102, and 49 years old in study Ig1 103. In Primary Part II, there were no pediatric subjects enrolled in study IG1101 and IG1102, and only 1 pediatric subject in study IG1103.

Primary Efficacy Analyses

The primary efficacy endpoint for all three clinical trials was the proportion of subjects in the Primary Part II of the study achieving hemostasis (Yes/No) at the TBS by 4 minutes (T4) following the start of treatment application (T_{Start}), without occurrence of re-bleeding and re-application of study treatment after T4 and until the completion of the surgical closure by layers of the exposed surgical field containing the TBS ($T_{Closure}$), brisk bleeding, and use of alternative hemostatic treatment after T_{Start} and until $T_{Closure}$. Hemostasis was defined as an absence/cessation of bleeding at the TBS according to the investigator's (the surgeon's) judgment, so that the surgical closure of the exposed field could be started. Re-bleeding was defined as bleeding from the TBS requiring further hemostatic intervention (e.g., manual pressure) after hemostasis was previously achieved at the TBS.

Study IG1 101 was a superiority study. The proportion of hemostasis by T4 (Primary efficacy) was 76.1% (83/109 subjects) in the FS Grifols group and 22.8% (13/57 subjects) in the MC control group. The 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to MC was 3.339 (2.047, 5.445). The proportion of hemostasis by T4 was significantly higher in the FS Grifols group compared to the MC group (p-value <0.001), indicating that FS Grifols is superior to MC and that the primary efficacy objective was achieved.

Studies IG102 and IG103 were designed as non-inferiority trials against an approved product (Surgicel), with a margin of 0.8 for the ratio of proportions of subjects achieving hemostasis by T4.

In study IG1102, the proportion of hemostasis by T4 (Primary efficacy) was 92.8% (103/111 subjects) in the FS Grifols treatment group and 80.5% (91/113 subjects) in the Surgicel treatment group. The 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.152 (1.038, 1.279), indicating that FS Grifols is both non-inferior and superior to Surgicel. The proportion of hemostasis by T4 was significantly higher in the FS Grifols group compared to the Surgicel group (p-value = 0.010).

In study IG1103, the proportion of hemostasis by T4 (Primary efficacy) was 82.8% (96/116 subjects) in the FS Grifols group and 77.8% (84/108 subjects) in the Surgicel group. The 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.064 (0.934, 1.213), indicating that FS Grifols is non-inferior to Surgicel.

There were no missing data in any of the three studies. Results of the primary efficacy endpoint, hemostasis by T4, for the three studies are summarized in Table 2.

Table 2. Primary Efficacy (Hemostasis by T4) in Primary Part II of the Three Phase 3 Trials (ITT Population)

Study No.	FS Grifols % (n/N)	Control % (n/N)	Risk Ratio* (95% CI)	P-value	Efficacy Result
IG1 101	76.1 (83/109)	MC 22.8 (13/57)	3.339 (2.047, 5.445)	<0.001	FS Grifols is superior to MC
IG1 102	92.8 (103/111)	Surgicel 80.5 (91/113)	1.152 (1.038, 1.279)	0.010	FS Grifols is non-inferior to Surgicel**
IG1 103	82.8 (96/116)	Surgicel 77.8 (84/108)	1.064 (0.934, 1.213)	0.401	FS Grifols is non-inferior to Surgicel

*Risk Ratio (RR): estimated ratio of the proportion of subjects meeting the primary efficacy endpoint in the two treatment groups in Primary Part II (FS Grifols relative to MC or Surgicel)
** The lower limit of the 95% CI above 1, indicates FS Grifols is superior to Surgicel.

Additionally, in all three Phase 3 studies, the secondary efficacy endpoints results were supportive in all three trials. Thus, the positive efficacy results from all three trials support the use of FS Grifols as an adjunct to hemostasis for moderate bleeding in adults during surgery.

Summary of Safety Analyses

The safety evaluations for all three trials were based on the pooled safety population, defined as all subjects from Preliminary Part I + Primary Part II of the study. A total of approximately 500 subjects were treated with FS Grifols, 320 subjects were treated with Surgicel, and 57 subjects were treated with MC over the three Phase 3 trials. The safety and tolerability of FS Grifols was assessed by analyzing adverse events (AEs), adverse drug reactions (ADRs), laboratory values (including virus safety assessments and immunogenicity), vital signs, and physical assessments. All reported AEs were coded and summarized by system organ class (SOC) and preferred term (PT) according to MedDRA version 16.0.

The concentration of FS Grifols administered to all subjects in the three trials was the same; however, the volume of FS Grifols administered was up to 6 mL in study IG1 101 (vascular surgery) and up to 12 mL in studies IG1 102 (parenchymous surgery) and IG1 103 (soft tissue surgery). The actual volume of FS Grifols applied varied for each individual subject and was based on the investigator's determination of the volume needed to achieve hemostasis at the TBS. A total of 57 subjects in the control group received manual compression (MC) in the vascular surgery study IG1 101. A total of 162

subjects in study IG1 102 and a total of 160 in study IG1 103 in the control groups received Surgicel. The mean volume of FS Grifols applied among all trials was 6.78 mL, with a median of 6.00 mL and a range of 0.3 to 18.0 mL. The mean number of Surgicel treatment sheets applied was 1.59 sheets, and the median value was 1.00 sheets.

The overall summary of treatment-emergent AEs (TEAEs) in all three studies is provided in Table 3. The overall number of TEAEs was similar for the FS Grifols group (83.8%), the Surgicel group (86.9%), and the manual compression group (77.2%). Treatment-emergent serious AEs (SAEs) were reported in 81/500 (16.2%) subjects in the FS Grifols treatment group, 41/320 (12.8%) subjects in the Surgicel treatment group, and 11/57 (19.3%) subjects in the MC treatment group. There were 13/500 (2.6%) deaths in the FS Grifols group and 4/320 (1.3%) deaths in the Surgicel group and no deaths in the MC treatment group. The occurrence of deaths varied from a few days to weeks after treatment administration (see review Section 8.4.1 for more details). In the FS Grifols treatment group, 64/500 (12.8%) subjects experienced an adverse drug reaction (ADR), compared with 27/320 (8.4%) subjects in the Surgicel treatment group and 3/57 (5.3%) subjects in the MC group.

TEAEs reported for at least 5% of subjects occurred with similar incidence in both groups, with procedural pain and nausea occurring most frequently. Serious TEAEs of special interest included: Myocardial Infraction, occurring in 0.4% in Grifols vs. 0 in Surgicel vs. 1.8% in MC. Respiratory failure occurred in 1.2% in Grifols vs. 0.3% in Surgicel vs. 0 in MC. Vascular Graft thrombosis occurred in 0.2% in Grifols vs. 0 in Surgicel vs. 1.8% in MC. No subject discontinued the study due to an AE in any treatment groups in all three studies.

Table 3 Summary of Treatment-Emergent Adverse Events (TEAEs) reported for ≥5% in All Three Studies

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

Source: Table 5.3/1.2 of ISS in Module 5.3.5.3

The three most frequent TEAEs for FS Grifols by preferred term (PT) reported for at least 5% of subjects within a treatment group for all clinical trials combined were procedural pain 209/500 (41.8%), nausea 67/500 (13.4%), and pyrexia 50/500 (10%). Overall, the incidences of the most frequently reported TEAEs were generally similar between the FS Grifols, Surgicel, and MC treatment groups.

Additionally, viral nucleic acid testing (NAT) or viral serology testing did not detect any treatment-emergent viral infection in any of the three clinical trials.

Adverse Drug Reactions

When an AE was assessed for causal relationship to study treatment by the investigator as definitely related, probably related, possibly related, or unlikely related, the event was defined as an ADR. Overall, there were no substantial differences in the ADR incidences noted among the FS Grifols, Surgicel or MC groups. For ADRs that occurred in ≥1% in the safety population of the FS Grifols treatment group, the most common ADRs were procedural pain and nausea (Table 4).

Table 4. ADRs that occurred in ≥1% in the Safety Population of the FS Grifols Treatment Group in All Three Trials

MedDRA Preferred Term	**FS Grifols**		
	N=500 n (%)	**Causal Relationship n**	
Subjects with any Adverse Drug Reaction (ADR)	64 (12.8)	50	Unlikely
		13	Possibly
		0	Probably
		1	Definitely
Procedural Pain	10 (2.0)	8	Unlikely
		1	Possibly
		1	Definitely
Nausea	6 (1.2)	6	Unlikely

Source: Tables 5.3/1.4 and 5.3/1.7 of ISS in Module 5.3.5.3

Deaths

Thirteen of 500 (2.6%) subjects in the FS Grifols treatment group, 4/320 (1.3%) subjects from the Surgicel treatment group, and no subjects from the MC treatment group died from one or more treatment-emergent SAEs. All SAEs with a fatal outcome in the three trials, regardless of treatment group, were considered unrelated to study treatment by the Applicant. See Section 8.4.1 for a review of deaths reported in the three trials.

Immunogenicity

No immunogenicity occurred with the treatment with FS Grifols in studies IG1101, IG1102, or IG1103.

Safety Conclusions

The results from all three trials showed that the FS Grifols product was reasonably safe and well tolerated as a local adjunct hemostatic agent in various surgery types. Although more deaths were reported with the use of FS Grifols across all three studies as compared to the comparator groups, the proportion of deaths reported were within the range expected for the types of surgical procedures and underlying diseases or conditions these subjects had, and are reviewed in the context of the known thromboembolic nature of the class of fibrin sealant products.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

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

Reviewer Comment: In both parts of each of the three trials, a specific bleeding area/site was defined as the target bleeding site (TBS) when it was determined by the investigator that control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) was ineffective or impractical and required an adjunct treatment to achieve hemostasis. As defined in the protocol, when the TBS was identified, the investigator was to rate the intensity of the bleeding at the TBS according to a 3-point scale (mild, moderate, severe). For both parts of the study, only subjects with a TBS with bleeding of moderate intensity could be enrolled. The protocol specifically excluded patients with severe bleeding intensity. Although no patient with mild bleeding intensity was evaluated across the three trials, based on known benefits and risks of FS Grifols as an adjunct to hemostasis, I believe that it would be reasonable to extrapolate trial results in moderate bleeding to situations of mild bleeding. However, the study data cannot be extrapolated to severe bleeding in the absence of safety and efficacy data specific for severe bleeding.

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

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

2.3 Safety and Efficacy of Pharmacologically Related Products

The safety of fibrin sealant products is acceptable, and not substantially different among licensed adjunct fibrin sealants products.

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

FS Grifols has not been approved for marketing in any country.

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

- November 4, 2016, STN 125640/0 submitted for FS Grifols
- September 6, 2017, PeRC agreed with the deferral request for the PMR pediatric study
- November 4, 2017, action due date (approval) for STN 125640/0

2.6 Other Relevant Background Information

The Proprietary Name review team, APLB, found the Applicant's proposed trade name, VERASEAL, unacceptable. There is no Trade name on record at the time of this review.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

STN125640/0 is of acceptable quality and is complete in the clinical studies sections.

3.2 Compliance with Good Clinical Practices and Submission Integrity

Clinical studies in STN125640/0 conform to Good Clinical Practice with good integrity.

3.3 Financial Disclosures

The financial disclosure statements for study IG1 101, study IG1 102, and study IG1 103 were provided in the BLA. Each of the statements contained a list of clinical investigators and sites: total of 50 investigators for IG1 101, 46 investigators for IG1 102, and 44 investigators for IG1 103. For all three studies, no investigator was identified to be sponsor employee and no investigator had disclosable financial interests/arrangements.

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

4.1 Chemistry, Manufacturing, and Controls

FS Grifols is a 2-component frozen sterile fibrin sealant solution manufactured and supplied by Instituto Grifols, S.A., Barcelona, Spain. FS Grifols contains human fibrinogen 80 mg/mL (component 1) and human thrombin 500 IU/mL (component 2). Each component is a sterile solution containing sodium chloride and other excipients. Both components are isolated from Source Plasma following a fractionation process based on the Cohn method. Due to continuous manufacturing process of both components of FS Grifols from fractionation to the final component, there is no distinct intermediate Drug Substance stage. (b) (4) is used in

the manufacture of Human Fibrinogen. No other materials of animal or human origin are used in the manufacture of fibrinogen.

Fibrinogen and thrombin solutions were supplied in separate (b) (4) glass syringes, each containing 3 mL frozen solution. Both fibrinogen and thrombin syringes were assembled on a syringe holder and sealed in a double plastic pouch (inner pouch and outer pouch). The syringe holder was a plastic device consisting of 1 syringe holder and 1 plunger link. This device allowed for the simultaneous application of equal amounts of fibrinogen and thrombin. The kit containing 6 mL of solution in total was packaged in a cardboard case.

Other reagents used in the manufacturing process are:

- (b) (4)
- Water for injection (WFI)
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- Tri-n-butyl phosphate
- Polysorbate 80
- Glycine
- (b) (4)

After thawing, FS Grifols can be maintained for not more than 48 hours at 2 ºC - 8ºC [36 ºF - 46 ºF] or 24 hours at room temperature (20 °C – 25 °C [68 ºF - 77 ºF]) before use if it remains sealed in the original packaging. Once the packaging is opened, FS Grifols should be used immediately.

FS Grifols is applied by dripping or spraying. When applying FS Grifols using a spray device, it has to be ensured that the pressure and the distance from the tissue are within the recommended ranges. The volume of FS Grifols to be applied should be sufficient to entirely cover the intended application area by a thin, even layer.

4.2 Assay Validation

Not applicable.

4.3 Nonclinical Pharmacology/Toxicology

See Pharmacology/Toxicology review of STN 125640.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

FS Grifols is human fibrinogen (component 1) and human thrombin with calcium chloride (component 2) frozen solutions, which, when mixed, generate a cross-linked fibrin clot in a process that mimics the last stage of the human coagulation system.

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

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

4.4.2 Human Pharmacodynamics (PD)

Not applicable.

4.4.3 Human Pharmacokinetics (PK)

Not applicable.

4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses cited by the Applicant were supported by the submitted data. See statistical review of STN 125640/0.

4.6 Pharmacovigilance

The pharmacovigilance reviewer concluded that the safety data for FS Grifols do not suggest any new safety concerns following application during vascular, parenchymal or soft tissue surgery, that have not been previously identified for fibrin sealants as a class. The available data do not suggest a safety signal that would trigger a Risk Evaluation and Mitigation Strategy (REMS). Routine postmarketing surveillance is recommended to monitor the risks associated with FS Grifols, should the product be licensed. See pharmacovigilance review of STN 125640/0.

In addition, the Human Factors review team identified deficiencies regarding packaging and the Instruction for Use in the initial human factors study conducted in February 2017. The Applicant has agreed to perform a new human factors study to address these deficiencies under protocol IG-PETC-000430_ING. Because the Applicant has already committed to conduct a (deferred) prospective postmarketing pediatric clinical trial, and the BLA review team did not want to delay an action on this application, the review team thought it would be sufficient to incorporate the human factors study as a subpart of the deferred pediatric trial. This modification is not expected to substantively impact the pediatric trial design or risk to subjects. The Applicant has agreed to conduct the new human factor at the same centers participating in the planned pediatric clinical trial in the United States.

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

5.1 Review Strategy

Studies IG1 101, IG1 102, and IG1 103 enrolled subjects undergoing peripheral vascular surgery, parenchymous tissue surgery, and soft tissue surgery, respectively. The outcome for these surgery types are presented and analyzed as representative of general surgery procedures in this review.

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

The clinical trials were conducted under the following INDs:

- IND 14986 (soft tissue surgery),
- IND 14987 (parenchymous tissue surgery), and
- IND 14988 (peripheral vascular surgery)

STN125640/0 contains all the clinical information reviewed for this submission.

5.3 Table of Studies/Clinical Trials

Table 5. Pivotal Studies IG1 101, IG1 102, and IG1 103

Studies	Surgery Type	Study and Control Treatments, Dose	Number of Subjects	Primary Endpoint*
IG1101 Phase 3; 35 sites in Hungary, Russia, Serbia and US; Completed 12/26/2015	Vascular	FS Grifols (≤6 mL), Single intra- operative administration MC, Single intra-operative administration	Total: 225 FS Grifols: 168 (59 in Preliminary Part I, 109 in Primary Part II) MC: 57 in the Primary Part II	Superiority study Proportion of subjects achieving hemostasis at the TBS by T4
IG1102 Phase 3; 33 sites in Hungary, Russia, Serbia and US; Completed 12/28/2015	Parenchymous (hepatic)	FS Grifols (≤12 mL), Single intra-operative administration Surgicel® (≤4 sheets), Single intra-operative administration	Total: 325 FS Grifols: 163 (52 in Preliminary Part I, 111 in Primary Part II) Surgicel: 162 (49 in Preliminary Part I, 113 in Primary Part II)	Non-inferiority study Proportion of subjects achieving hemostasis at the TBS by T4
IG1103 Phase 3; 31 sites in Hungary, Serbia and US; Completed 6/4/2015	Soft tissue	FS Grifols (≤12 mL), Single intra-operative administration Surgicel® (≤4 sheets), Single intra-operative administration	Total: 327 FS Grifols: 167 (51 in Preliminary Part I, 116 in Primary Part II) Surgicel: 160 (52 in Preliminary Part I, 108 in Primary Part II)	Non-inferiority study Proportion of subjects achieving hemostasis at the TBS by T4

*T4 = hemostatic assessment at 4 minutes following the start of treatment

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

STN 125640/0 was not presented to the Blood Products Advisory Committee because the product is not the first in its class, the clinical study design and safety profile are like other products in this class, and there were no new questions regarding safety or efficacy, or other public health questions or controversial issues that would have required an advisory committee discussion.

5.4.2 External Consults/Collaborations

There were no external consults.

5.5 Literature Reviewed (if applicable)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1, study IG1 101: "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"

Study IG1101 was a Phase 3 study, conducted under IND 14988.

6.1.1 Objectives (Primary, Secondary, etc.)

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

The secondary objectives evaluate hemostasis at other various time points, time to hemostasis, and prevalence of treatment failures.

6.1.2 Design Overview

This prospective, multicenter, single-blind trial consisted of two parts: a Preliminary Part I and a Primary Part II. All subjects enrolled in non-randomized Preliminary Part I was treated with FS Grifols. The main objective of this part was to ensure that local study teams become familiarized with the technique for FS Grifols application and with intra-operative procedures required by the protocol of this study. For each study participating center, the first 2 subjects were to be enrolled in the Preliminary Part I. Subjects in the Primary Part II were to be randomized in a 2:1 ratio into FS Grifols or manual compression (MC) treatment groups. Randomization was stratified by 1) study center and 2) type of intervention (peripheral arterial bypass vs. upper extremity vascular access for hemodialysis). This part had two main objectives: 1) to assess the safety of FS Grifols and 2) to assess the efficacy of FS Grifols. For each study center, the Primary Part II was to start only after enrollments of 2 subjects in the Preliminary Part I.

In both parts of this study, a specific bleeding area/site was defined as the target bleeding site (TBS) when it was determined by the investigator that control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) was ineffective or impractical and required an adjunct treatment to achieve hemostasis. When the TBS was identified, the investigator was to rate the intensity of the bleeding at the TBS according to a 3-point scale (mild, moderate, severe), as shown below.

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

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

For both parts of the study, only subjects with a TBS with bleeding of moderate intensity could be enrolled.

6.1.3 Population

This clinical trial included both adult and pediatric subjects who were undergoing an elective (non-emergency), open (non-laparoscopic, non-endovascular), peripheral vascular surgical procedure where a TBS was identified. Upon the identification of a TBS with moderate bleeding on the proximal anastomosis, the subject was deemed eligible for enrollment into the study.

Inclusion Criteria

1. Sign the written Informed Consent Form (ICF).
2. Male or female.
3. At least 18 years old with no upper age limit.
4. Hemoglobin (Hgb) ≥ 8.0 g/dL at Baseline (within 24 hours prior to surgical procedure).
5. Require an elective (non-emergency), primary, open (non-laparoscopic; non-endovascular) peripheral vascular surgical procedure.
6. Require one of peripheral vascular procedures listed below involving a proximal end-to-side arterial anastomosis utilizing coated or uncoated PTFE grafts:
   a. Femoral-femoral bypass grafting
   b. Femoral-popliteal bypass grafting
   c. Femoral-distal bypass grafting
   d. Ilio-iliac bypass grafting
   e. Ilio-femoral bypass grafting
   f. Ilio-popliteal bypass grafting
   g. Aorto-iliac bypass grafting
   h. Aorto-femoral bypass grafting
   i. Axillo-femoral bypass grafting
   j. Upper extremity vascular access for hemodyalisis (arteriovenous graft formation).
7. Intra-operative inclusion criterion:
   a. A TBS can be identified according to the investigator's judgment, and
   b. The TBS has a moderate arterial bleeding according to the Investigator's judgment

Exclusion Criteria

1. Undergoing a re-operative procedure defined as a second, or successive, surgical procedure on the same anatomic location (i.e., same anastomotic site)
2. Undergoing other vascular procedures during the same surgical session (stenting and/or endarterectomy of the same artery were allowed)
3. Infection in the anatomic surgical area

4. History of severe (e.g., anaphylactic) reactions to blood or to any blood-derived (human or animal) product
5. Previous known sensitivity to any FS Grifols, heparin, or protamine component
6. Known (documented) previous exposure to thrombin-containing (bovine, human, or recombinant) products
7. Were unlikely to adhere to the protocol requirements or to be cooperative during the study conduct
8. Females who were pregnant or nursing a child
9. Currently participating or had participated in another clinical study in the context of which they had received investigational drug or device within 3 months from the Screening Visit, or were scheduled to participate during the course of this study
10. Had undergone a therapeutic surgical procedure within 30 days from the Screening Visit
11. Previously enrolled in clinical studies with FS Grifols
12. Intra-operative exclusion criteria:
    - A TBS could not be identified according to the investigator's judgment
    - The TBS had mild or severe bleeding according to the investigator's judgment
    - Occurrence of major intra-operative complications that required resuscitation or deviation from the planned surgical procedure
    - Intraoperative change in planned surgical procedure which resulted in a subject no longer meeting preoperative inclusion and/or exclusion criteria (eg, abandonment of PTFE graft placement or change in the procedure to a different artery, not included in the acceptable procedures list)

Intra-operative inclusion criteria:
Surgery:

- The surgeon performed the surgical intervention according to his/her standards as well as the respective institution's standards. The use of polypropylene sutures (3-0, 4-0, 5-0 or 6-0) with 13 or 26 mm 3/8 or 1/2 circle taper point needles for the proximal anastomosis was required.
- Anticoagulation with heparin before arterial clamping was required.

At the time of surgery, the following was considered:

- When it was determined by the investigator (the surgeon) that the control of bleeding from the proximal anastomosis by conventional surgical techniques (including suture, ligature and cautery) was ineffective or impractical and required an adjunct treatment as to achieve hemostasis, this specific bleeding area/site was identified and defined as the TBS.
- A TBS identified according to the investigator's judgment and the TBS had a moderate arterial bleeding according to the investigator's judgment; the intensity of the arterial bleeding at the TBS was rated by the investigator using the previously predefined 3-point scale:

If the nature of the bleeding from the TBS was severe according to the scale above, the surgeon could have used standard surgical modalities (additional stitches, for instance) in order to control the bleeding. If, once these primary hemostatic measures were taken, the nature of the bleeding became moderate, the subject could have been considered eligible for enrollment. If the nature of the bleeding became mild or remained severe, the subject was withdrawn from the study and would have been considered a screen failure. In these cases, the surgeon could use all necessary measures at his/her discretion as deemed necessary (FS Grifols could not be used for this purpose).

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects were treated intra-operatively with FS Grifols or MC application. Anticoagulation with heparin before arterial clamping was required. FS Grifols-treated subjects could receive up to 6 mL of FS Grifols by dripping application. Subjects receiving FS Grifols were treated intra-operatively with a single administration. The initial volume of FS Grifols applied to the target surface area was sufficient to entirely cover the intended application area by a thin, even layer. If the hemostatic effect was incomplete once clamps were released after the initial application of FS Grifols and before the assessment of the primary efficacy endpoint at T4, additional amounts of FS Grifols could have been applied at the TBS up to the maximum allowed volume of 6 mL, if necessary. No additional amounts of FS Grifols could be applied beyond the primary efficacy endpoint assessment time point at T4.

Manual Compression (MC), a standard hemostatic action, was selected as the active control. Direct MC with dry gauze/laparotomy pads was applied to the TBS completely covering the study suture line and the arterial flow was re-established by releasing the clamps. The actual time of the start of application of MC was recorded (T_{Start}). There was no limitation to the number of gauzes/laparotomy pads applied to the TBS for achieving hemostasis. Manual compression could be applied as necessary during the 10-minute observational period, including reapplication beyond the primary efficacy endpoint assessment time point at T4.

6.1.5 Directions for Use

Application by dripping: FS Grifols must be applied with the cannula provided with the product, or an equivalent cannula (including open surgery and laparoscopic or endoscopic use devices) cleared by FDA for this use. When dripped, the tip of the applicator should be kept as close as possible to the tissue surface, but without touching the tissue during application. Individual drops should be applied to the area to be treated.

The dose to be applied is governed by variables including, but not limited to, the type of surgical intervention, the size of the area and the mode of intended application, and the number of applications. The initial volume of the product to be applied at a chosen anatomic site or target surface area should be sufficient to entirely cover the intended application area. FS Grifols should be applied as a thin layer. The application can be repeated, if necessary. The lower and upper size limits of the TBS were not defined in this study. Application of the product must be individualized by the treating physician.

6.1.6 Sites and Centers

Study IG1 101 was conducted at 35 study sites in the Hungary, Russia, Serbia, and US.

6.1.7 Surveillance/Monitoring

Study visit schedules are shown in Tables 6 and 7 (during surgery).

Table 6. Study Visit/Assessment Schedule

Procedures and Assessments	**Screening Visit**	**Baseline Visit**	**Surgical Procedure (Day 0)**	**Post-op Day 1**	**Post-op Day 2 (±1Day)**	**Post-op Day 3**	**Post-op Day 7**	**Post-op Day 14**	**Post-op Wk 6 (±4 Days)**
Consent/Assent	X		See Table 7						
HIPPA	X								
Subject #	X								
Subject screening log	X								
Demographics	X								
Med & Surgical Hx	X	X							
Abnornal Bleeding Hx	X								
Topical Hemostats Hx	X								
Medications	X	X		X	X	X	X	X	X
Height/Weight	X								
Inc/Exc Criteria	X	X							
Physical Exam		X		X	X	X	X	X	X
Vital Signs		X		X	X	X	X	X	X
Pregnancy Test		X							
Coagulation Panel		X		X	X	X	X	X	X
CBC		X		X	X	X	X	X	X
Serum Chem		X		X	X	X	X	X	X
Viral Panel		X					X	X	X
Immunigenicity Panel		X						X	X
Adverse Event		X		X	X	X	X	X	X

Table 7. Clinical Trial IG1101: Study Procedures and Assessments on Day 0 (During Surgery)

Procedure and Assessment	Before Surgery	Beginning of Surgery	Intra-Surgery	10-Minute Observational Period	Within 6 Hrs Post-Surgery
FS Grifols and MC Prep	X				
Medication		X	X		X
Vital Signs		X	X	X	X
TBS Identification			X		
Rating bleeding at TBS Intra-op Inc/Exc Criteria			X		
T_{On} Registration			X		
Randomization			X		
T_0 Registration			X		
FS Grifols or MC Application			X		
T_{Start} Registration			X		
T_{End} Registration			X		
T_{Off} Registration			X		
T_{Start2} Registration			X		
T_{End2} Registration			X		
MC Application			X		
T_4, T_5, T_7, T_{10}				X	
$T_{Closure}$ Registration			X		
$T_{Completion}$ Registration			X		
Coagulation Panel					X
CBC					X
Serum Chemistry					X
Adverse Events		X	X		X

6.1.8 Endpoints and Criteria for Study Success

The study endpoints and criteria for success are similar for all three Phase 3 trials.

Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of subjects in the Primary Part II of the study achieving hemostasis (Yes/No) at TBS by T4 without occurrence of re-bleeding or reapplication of study treatment after T4 until the time of completion of closure by layers of the exposed surgical field containing the TBS ($T_{Closure}$) without brisk bleeding or use of alternative hemostatic treatment after time of start of initial study treatment (T_{Start}) and until $T_{Closure}$. The definition of the primary efficacy endpoint of hemostasis by T4 is shown in Table 8.

Table 8. Primary Efficacy Endpoint of Hemostasis by T4

Scenario	Hemostasis Achieved?						Study Treatment re-applied at the TBS after T_4 and Before $T_{closure}$	Brisk bleeding, re-bleeding, or alternative hemostatic treatment?[a]	Primary efficacy endpoint: hemostatic response by T_4?
	T_2	T_3	T_4	T_5	T_7	T_{10}			
1	Either Yes or No		Yes	Yes	Yes	Yes	No	No	**Yes**
2	Either Yes or No		No	Either Yes or No at any time point			Either Yes or No	Either Yes or No	**No**
3	Either Yes or No		Either Yes or No	No at any timepoint			Either Yes or No	Either Yes or No	**No**
4	Either Yes or No at any time point						Yes		**No**
5	Either Yes or No at any time point						Either Yes or No	Yes	**No**

Note: TStart = start of treatment application; T2 = hemostatic assessment at 2 minutes following TStart (this assessment not scheduled in study IG1101); T3 = hemostatic assessment at 3 minutes following TStart (this assessment not scheduled in study IG1101); T4 = hemostatic assessment at 4 minutes following TStart; T5 = hemostatic assessment at 5 minutes following TStart; T7 = hemostatic assessment at 7 minutes following TStart; T10 = hemostatic assessment at 10 minutes following TStart; TClosure = time of completion of the surgical closure by layers of the exposed surgical field containing the TBS.
a Did the target bleeding site (TBS) re-bleed after T4, or was alternative hemostatic treatment used, or was there brisk bleeding during the 10-minute observation period and until TClosure?
Source: STN 125640 Clinical Report page 47

Secondary Efficacy Endpoints

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

1. Proportion achieving hemostasis at TBS by time points T2, T3, T5, T7, T10

2. Time to hemostasis (TTH), categorized from ≤2 min. to ≤10 min.

   The TTH was measured from T_{Start} to the achievement of hemostasis at the TBS, or to the end of the 10-minute observational period when hemostasis had not yet been achieved. In the latter case, the TTH was considered as censored at the end of the 10-minute observational period. The TTH was quantified in minutes according to its nominal time point.

If the TBS re-bled but cessation of bleeding was again achieved at a later time point, the effective hemostatic time point was considered to be the time point when the cessation of rebleeding occurred. The TTH was the time from T_{Start} to that last effective hemostatic time point.

The TTH was an incremental time as shown below. If hemostasis was not achieved at 1 assessment time point but was achieved at the next assessment time point, it was inferred that the true TTH was between the 2 assessment time points. Therefore, TTH, although not observed directly, was ascertained as falling into the following hemostatic time categories (HTCs):

- ≤4 minutes from TStart to hemostasis (HTC ≤4).
- >4 minutes to ≤5 minutes from TStart to hemostasis (HTC >4 to ≤5).
- >5 minutes to ≤7 minutes from TStart to hemostasis (HTC >5 to ≤7).
- >7 minutes to ≤10 minutes from TStart to hemostasis (HTC >7 to ≤10).

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

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

3. Prevalence of treatment failures

   The following cases were considered treatment failures:
   - Persistent bleeding at the TBS beyond T4.
   - The event of breakthrough (brisk and forceful) bleeding from the TBS that jeopardized subject safety according to the investigator's judgment at any moment during the 10-minute observational period and until TClosure.
   - Re-bleeding at the TBS after the assessment of the primary efficacy endpoint at T4 and until TClosure.
   - Use of alternative hemostatic treatments or maneuvers (other than the study treatment) at the TBS during the 10-minute observational period and until TClosure or use of study treatment at the TBS beyond T4 and until TClosure. Reversal of heparin, if necessary according to surgeon's judgment after the primary endpoint assessment, was not considered as an alternative hemostatic treatment in this regard. Therefore, reversal of heparin with protamine after the primary endpoint assessment did not render a subject as a treatment failure.

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

considered a treatment failure. The alternative treatment used was recorded in the subject's source documents and eCRF.

6.1.9 Statistical Considerations & Statistical Analysis Plan

See statistical review of STN 125640/0. The determination of efficacy was based on statistical review of the primary efficacy endpoint and secondary endpoints data, based on the ITT population of Primary Part II of the completed study IG1 101. This study was intended to demonstrate superiority of FS Grifols as an adjunct to achieve hemostasis at 4 minutes (T4) as compared to manual compression alone.

Efficacy Analysis

Primary Efficacy Analysis:

For primary efficacy analysis, only the data from the Primary Part II of the study were used. FS Grifols would be deemed superior to MC if the 2-sided test was statistically significant at the 5% level and FS Grifols had a greater proportion of subjects with achievement of hemostasis by T4 than MC. Additionally, the primary efficacy endpoint of the proportion of subjects achieving hemostasis by 4 minutes at TBS was analyzed using the Per-protocol (PP) population.

Secondary Efficacy Analysis:

For secondary efficacy analysis, the time to hemostasis (TTH) was measured from T_{Start} to the achievement of hemostasis at the TBS, or to the end of the 10-minute observation period when hemostasis had not yet been achieved; in latter case, the TTH was considered as censored at the end of the 10-minute observation period. The TTH was quantified in minutes according to its nominal time point.

If the TBS re-bled but cessation of bleeding was again achieved at a later time point, then the effective hemostatic time point would be the last one where the cessation of bleeding happened. The TTH would be the time passed from T_{Start} to that last effective hemostatic time point.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Study Populations

Three analysis populations were defined for this study:

- Intent-to-treat (ITT):

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

For the Primary Part II of the study, the ITT population included all subjects randomized to FS Grifols or MC.

- Per-protocol (PP):

Included all subjects in the ITT population, excluding any subject for whom there was at least 1 major protocol deviation that might have an impact on the primary efficacy assessment. The major protocol deviations were determined at a data review meeting and were documented in a data review report prior to the database lock.

- Safety population:

The safety population consisted of all subjects who received any amount of FS Grifols or MC.

Missing Data Handling

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

6.1.10.1.1 Demographics

Subject demographics by treatment group and by Preliminary Part I and Primary Part II are summarized using the ITT population in Table 9. In Preliminary Part I and Primary Part II, the FS Griofols group consisted of approximately 70% males and 30% females. The ratio of males and females was relatively balanced in the MC group (54% males vs. 46% female). The majority of subjects were White/Caucasian (86.2%). There were no pediatric subjects enrolled in this study.

Table 9. Demographics, Study IG1 101, (ITT Population)

Characteristics	Preliminary Part (I)	Preliminary Part (II)		Part (I) + Part (II)	Total (N=225) n (%)
	FS Grifols (N=59) n (%)	FS Grifols (N=109) n (%)	MC (N=57) n (%)	FS Grifols (N=168) n (%)	
Sex – n (%)					
Male	41 (69.5)	76 (69.7)	31 (54.4)	117 (69.6)	148 (65.8)
Female	18 (30.5)	33 (30.3)	26 (45.6)	51 (30.4)	77 (34.2)
Age (years)					
Mean (SD)	63.53 (9.343)	63.72 (8.908)	62.04 (10.734)	63.65 (9.036)	63.24 (9.496)
Median	64.0	64.0	61.0	64.0	63.0
Min, Max	41.0, 82.0	44.0, 84.0	22.0, 82.0	41.0, 84.0	22.0, 84.0
Age Category (years) – n (%)					
≤11	0	0	0	0	0
12-17	0	0	0	0	0
18-64	32 (54.2)	58 (53.2)	32 (56.1)	90 (53.6)	122 (54.2)
≥65	27 (45.8)	51 (46.8)	25 (43.9)	78 (46.4)	103 (45.8)
65-84	27 (45.8)	51 (46.8)	25 (43.9)	78 (46.8)	103 (45.8)
≥85	0	0	0	0	0
Race – n (%)					
White (Caucasian)	44 (74.6)	101 (92.7)	49 (86.0)	145 (86.3)	194 (86.2)
Black or African American	13 (22.0)	6 (5.5)	8 (14.0)	19 (11.3)	27 (12.0)
Asian	0	2 (1.8)	0	2	2 (0.9)
Native Hawaiian or Other Pacific Islander	1 (1.7)	0	0	1 (0.6)	1 (0.4)
Multi-racial	1	0	0	1	1 (0.4)

Source: BLA 125640/0; Module 5.3.5.1; IG1 101 Clinical Report

6.1.10.1.3 Subject Disposition

Preliminary Part I:

During Preliminary Part I of the study, 90 subjects were screened, and there were 31 screen failures. A majority of subjects who failed screening did not meet the enrollment criteria (19/31, 61.3%). A total of 59 subjects who met the intra-operative inclusion criterion and whom the investigator therefore intended to treat with FS Grifols were enrolled (ITT Population). All 59 subjects received FS Grifols.

Primary Part II:

During Primary Part II of the study, 193 subjects were screened; 27 were screen failures. A majority of subjects who failed screening did not meet the enrollment criteria (20/27, 74.1%). A total of 166 subjects were randomized (Table 10). Of 166 subjects, 109 were randomized to FS Grifols (ITT Population), and 57 were randomized to MC (ITT Population). In general, there were no major differences between the FS Grifols treatment group and the MC treatment group in subject disposition.

A summary of subject disposition in the Primary Part II of the clinical studies in the ITT Population is shown in Table 10. In general, there were no major differences between the FS Grifols treatment group and the MC treatment group in subject disposition.

Table 10. Subject Disposition in Primary Part (II), Study IG1 101

Number of Subjects:	**FS Grifols n (%)**	**MC n (%)**	**Overall N**
Randomized (ITT Population)	109	57	166
Completed Study	106 (97.2)	56 (98.2)	162
Premature Discontinuation	3 (2.8)	1 (1.8)	4
Withdrew Consent	1 (0.9)	0	1
Lost to Follow-up	0	1 (1.8)	1
Death	2 (1.8)	0	2
Other	0	0	0
Premature Discontinuation before Virology Follow-up	10 (9.2)	2 (3.5)	12

Source: BLA 125640/0; Module 5.3.5.1, CSR IG1 101

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The results of the primary efficacy analysis of hemostasis at the TBS by T4 was performed using the ITT population in the Primary Part II of the study (Table 11). The rate of hemostasis by T4 was statistically and significantly higher in the FS Grifols group compared to the MC group (p-value <0.001) in each study center, indicating that FS Grifols is superior to MC and that the primary efficacy objective was met in the ITT population. The supportive analysis in the PP population showed similar results.

Table 11. Primary Efficacy Results in Primary Part (II)

Analysis Population	FS Grifols	MC	RR (95% CI)[a]	p-value[b]
ITT	83/109 (76.1%)	13/57 (22.8%)	3.339 (2.05, 5.45)	<0.0001
PP	75/97 (77.3%)	12/52 (23.1%)	3.351 (2.02, 5.57)	<0.0001

a RR was the ratio of proportion of subjects meeting the efficacy endpoint in the two treatment groups in Primary Part (II) (FS Grifols relative to MC).
b P-value was calculated from Fischer Exact Test.

6.1.11.2 Analyses of Secondary Endpoints

To control for multiple comparison/multiplicity, the superiority for the secondary endpoints were tested after the superiority for the primary efficacy endpoint was demonstrated. For secondary efficacy endpoints, a fixed-sequence testing method was employed for handling the multiplicity issue to maintain the overall family-wise alpha level at 0.05. The order in which the null hypotheses were tested was predetermined as shown below for the secondary efficacy variables:

1. Cumulative proportion of subjects having achieved hemostasis at the TBS by 5 minutes (T5)
2. Cumulative proportion of subjects having achieved hemostasis at the TBS by 7 minutes (T7)
3. Cumulative proportion of subjects having achieved hemostasis at the TBS by 10 minutes (T10)

The median TTH was statistically and significantly shorter (p-value <0.001) in the FS Grifols group (4.0 minutes) compared to the MC group (≥10.0 minutes), demonstrating that FS Grifols is superior to MC.

The results for proportion of subjects achieving hemostasis at the TBS by T5, T7, and T10 are positive, as shown in Table 12.

Table 12. Analysis of Hemostasis by T5, T7, and T10 at TBS (ITT Population)

	Primary Part (II)			
	FS Grifols N=109 N (%)	MC N=57 N (%)	RR (95% CI)[a]	p-value[b]
Hemostasis by T5	88 (80.7)	16 (28.1)	2.876 (1.879, 4.402)	<0.001
Hemostasis by T7	92 (84.4)	20 (35.1)	2.406 (1.675, 3.455)	<0.001
Hemostasis by T10	96 (88.1)	26 (45.6)	1.931 (1.442, 2.585)	<0.001

a RR was the ratio of proportion of subjects meeting the efficacy endpoint in the two treatment groups in Primary Part (II) (FS Grifols relative to MC).
b p-value was calculated from Fischer Exact Test.
Source: Original BLA 125640/0; Module 5.3.5.1, Clinical Study Report for Study IG1101.

Treatment Failures

In the Primary Part II of the study, the rate of treatment failures was 23.9% in the

FS Grifols treatment group and was 77.2% in the MC treatment group. The rate of treatment failures was significantly lower in the FS Grifols treatment group compared to the MC treatment group (p-value <0.001). In both treatment groups, the most common reason for treatment failure was persistent bleeding. Details are summarized in Table 13.

Table 13. Treatment Failure at TBS (ITT Population), Study IG1 101

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

a RR was the proportion of subjects meeting the efficacy endpoint in the two treatment groups
b p-value was calculated from Fisher Exact Test
For the MC group only, treatment could be reapplied beyond T4 and until the completion of the surgical closure, bout would be consistent a treatment failure.
Source: BLA 125640/0, Post-text Table 14.2.3

6.1.11.3 Subpopulation Analyses

The subgroup analyses by sex, race, and age categories are shown in Table 14. The rates of hemostasis at the TBS by T4 in the FS Grifols and MC treatment groups were similar in the 18 to 64-year-old and ≥65 year old age groups, and were consistent with the overall primary efficacy analysis for both treatment groups in the Primary Part II of the study. The rates of hemostasis at the TBS by T4 in the FG Grifols treatment group were similar in the male (77.6%) and female (72.7%) subject populations in the Primary Part II of the study. In the MC treatment group, female subjects had a higher rate of hemostasis (34.6%) compared to male subjects (12.9%).

Table 14. Analysis of Hemostasis by T4 at TBS by Subgroups (ITT Population)

Subgroup	FS Grifols (N=109)	MC (N=57)
Sex		
Male	59/76 (77.6%)	4/31 (12.9%)
Female	24/33 (72.7%)	9/26 (34.6%)
Age		
18-64 years	45/58 (77.6%)	8/32 (25%)
≥65 years	38/51 (74.5%)	5/25 (20.0%)
Race		
White (Caucasian)	77/101 (76.2%)	11/49 (22.5%)
Black or African American	4/6 (66.7%)	2/8 (25%)
Asian	2/2 (100%)	0

Pediatric subjects were eligible to enroll in both the Preliminary Part I and the Primary Part II of the clinical study. However, there were no pediatric enrolled in either Preliminary Part I or Primary Part II of the trial. The absence of pediatric enrollment was attributed to the low prevalence of children who need vascular surgery.

6.1.11.4 Dropouts and/or Discontinuations

There were no dropouts or discontinuation due to adverse events. All subjects were followed for the 4 minutes to hemostasis assessment because they were in surgery in the operating room.

6.1.12 Safety Analyses

The safety evaluations were based on the pooled safety population, which includes all subjects from Preliminary Part I + Primary Part II of the study. FS Grifols was applied by dripping at the TBS during vascular surgery. The proportion of subjects in whom treatment-emergent adverse events (TEAEs) were reported in ≥ 5% of subjects was similar between the treatment groups (FS Grifols, 138/168 (81%); MC, 44/57 (77.2%), see Table 15. The most frequently reported TEAE preferred terms, occurring in more than 5% of subjects, were procedural pain (34.5% in FS Grifols vs. 36.8% in MC), pyrexia (11.3% in FS Grifols vs.10.5% in MC), and peripheral edema (7.7% in FS Grifols vs. 1.8% in MC). Vascular Graft thrombosis occurred in 1.2% of FS Grifols subjects compared to 5.3% of MC subjects.

Additionally, severe TEAEs that were reported in ≥ 2 subjects are shown in Table 16. These severe TEAEs were reported infrequently, but included myocardial, pulmonary, and wound infections AEs.

Table 15. Study IG1 101: Treatment-Emergent Adverse Events Reported in ≥ 5% of Subjects within Treatment Group

Preferred Term	FS Grifols , N=168 (%)	MC, N=57 (%)
Any TEAE	138 (81.0)	44 (77.2)
Procedural Pain	58 (34.5)	21 (36.8)
Pyrexia	19 (11.3)	6 (10.5)
Peripheral Edema	13 (7.7)	1 (1.8)
Body temperature increased	10 (6.0)	4 (7.0)
Anemia	10 (6.0)	2 (3.5)
Nausea	10 (6.0)	2 (3.5)
Post op anemia	9 (5.4)	2 (3.5)
Constipation	7 (4.2)	4 (7.0)
Vomiting	4 (2.4)	3 (5.3)
Vascular Graft Thrombosis	2 (1.2)	3 (5.3)

Table 16. Study IG1 101: Severe Treatment-Emergent Adverse Events Reported in ≥ 2 Subjects

Preferred Term	**FS Grifols N=168 (%)**	**MC N=57 (%)**
Myocardial Infarction	2 (1.2)	1 (1.8)
Post-op wound infection	2 (1.2)	1 (1.8)
Wound infection	2 (1.2)	0
Reocclusion	2 (1.2)	0
Pneumonia	2 (1.2)	0
Acute Respiratory Infection	2 (1.2)	0

6.1.12.1 Methods

6.1.12.2 Overview of Adverse Events

6.1.12.3 Deaths

Deaths were reported in 4/168 (2.4%) of subjects who received FS Grifols, The cause of death included myocardial infarction, gastrointestinal hemorrhage, and multi-organ failure. All deaths were considered unrelated to study treatment by investigators. No death occurred in the MC group. Death AEs are further discussed in Section 8.4.1.

6.1.12.4 Nonfatal Serious Adverse Events

Thirty-four of 168 (20.2%) subjects in the FS Grifols group (pooled safety population) experienced 60 serious adverse events (SAEs) vs. 11 of 57 (19.3%) subjects in the MC group experienced 14 SAEs. In the both FS Grifols group and MC groups, many of the SAEs were reported in a single subject.

In this study, all except 5 SAEs were considered by investigators not related to study treatment: 4 SAEs in the FS Grifols group and 1 SAE in the MC treatment group. Three SAEs (2 FS Grifols subjects and 1 MC subject) were considered unlikely related to study treatment, and 2 SAEs from the FS Grifols group were considered possibly related.

6.1.12.5 Adverse Events of Special Interest (AESI)

Two subjects in the FS Grifols group (2/168; 1.2%) and three subjects in the MC group (3/57; 5.3%) each experienced a vascular graft thrombosis event.

6.1.13 Study Summary and Conclusions

Overall, data demonstrate the hemostatic efficacy of FS Grifols and support the use of FS Grifols as an effective local hemostatic agent in vascular surgery. Primary efficacy analysis of hemostasis at the TBS by T4 demonstrated that the rate of hemostasis at the TBS by T4 was statistically and significantly higher in the FS Grifols treatment group (76.1%) as compared to the MC treatment group (22.8%; p-value <0.001) and that FS Grifols was superior to MC. The results of secondary efficacy endpoints provided additional support for FS Grifols as an effective local hemostatic agent in vascular surgery, with an acceptable safety profile.

6.2 Trial #2, Study IG1102: "A Prospective, Single-blind, Randomized, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Hemostasis During Parenchymous Tissue Open Surgeries."

Study IG1102 was a Phase 3 study, conducted under IND 14987.

6.2.1 Objectives (Primary, Secondary, etc.)

The primary objective of the study was to evaluate the hemostatic efficacy of FS Grifols in parenchymous tissue open surgery.

The secondary objectives evaluate hemostasis at other various time points and prevalence of treatment failures.

6.2.2 Design Overview

The design of Study IG1 102 was similar to Study IG1 101. This was a randomized, controlled, single-blind, multicenter study consisting of 2 parts: a Preliminary Part I and a Primary Part II. Subjects in the Preliminary Part I were randomized in a 1:1 ratio into

either FS Grifols or Surgicel (control). The main objective of this part of the clinical study was to ensure that local study teams become familiarized with the technique for FS Grifols application and with intra-operative procedures required by the protocol of this study. For each study participating center, the first 4 subjects were to be enrolled in the Preliminary Part I. Subjects in the Primary Part II were randomized in a 1:1 ratio into either the FS Grifols or Surgicel (control) treatment groups. Primary Part II assessed the safety and efficacy of FS Grifols. For each study center, the Primary Part II of the study was to start only after enrollment of 4 subjects in the Preliminary Part I. Randomization was stratified by study center.

In both parts of this study, a specific bleeding area/site was defined as the TBS when it was determined intra-operatively by the investigator that control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) was ineffective or impractical and required an adjunct treatment to achieve hemostasis. When the TBS was identified, the investigator rated the intensity of the bleeding according to a 3-point scale (mild, moderate, severe) at the TBS. The approximate size of the bleeding surface was rated small, medium, or large. The grading scales are defined below.

The intensity of the bleeding at the TBS was rated by the investigator (surgeon) using the following 3-point scale:

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

The approximate size of the TBS was rated by the investigator (the surgeon) using a 3-point scale:

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

For both parts of the study, only subjects with a TBS with bleeding of moderate intensity could be enrolled.

6.2.3 Population

Inclusion criteria:

1. Sign the written Informed Consent Form (ICF).
2. Male or female.
3. At least 18 year old with no upper age limit.
4. Hemoglobin (Hgb) ≥ 8.0 g/dL at Baseline (within 24 hours prior to surgical procedure).
5. Require an elective (non-emergency), open (non-laparoscopic) hepatic resection (anatomic or non-anatomic resections of at least one anatomical hepatic segment, or equivalent tissue volume).
    - Where TBS is identified on the cut raw liver surface (resection area).

6. Intra-operative inclusion criteria: a TBS can be identified according to the investigator's judgment, and
   - The TBS has moderate bleeding according to the investigator's judgment.
   - The intensity of the bleeding at the TBS will be rated by the investigator using a pre-defined three-point scale.

Exclusion criteria:

1. Require hepatic resection due to trauma.
2. Infection in the anatomic surgical area.
3. History of severe (e.g. anaphylactic) reactions to blood or to any blood-derived (human or animal) product.
4. Previous known sensitivity to any FS Grifols component or any Surgicel® component.
5. Are unlikely to adhere to the protocol requirements, or to be cooperative, during the study conduct.
6. Females who are pregnant or nursing a child at Baseline (within 24 hours prior to surgical procedure).
7. Receiving an organ transplant during the same surgical procedure.
8. Undergoing another concurrent major surgical intervention beyond the liver.
9. Currently participating or have participated in another clinical study in the context of which have received investigational drug or device within 3 months from the screening visit, or are scheduled to participate during the course of this study.
10. Undergone a therapeutic surgical procedure within 30 days from the screening visit.
11. Previously enrolled in clinical trials with FS Grifols.
12. Intra-operative exclusion criteria:
    - A TBS (as defined in section 7.1.3.1) cannot be identified according to the investigator's judgment.
    - The TBS has a mild or severe bleeding according to the investigator's judgment.
    - Occurrence of major intraoperative complications that require resuscitation or deviation from the planned surgical procedure.
    - Application of any topical hemostatic material on the resection surface of the liver prior to application of the study treatment.
    - Radiofrequency precoagulation of the liver resection surface, except focal use of radiofrequency as primary hemostatic treatment.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Subjects were treated intra-operatively with either FS Grifols or Surgicel to the TBS.

FS Grifols is composed of frozen solutions of human fibrinogen and human thrombin with calcium chloride. The fibrinogen and thrombin solutions are supplied in a kit in separate glass syringes, each containing 3 mL frozen solution. The syringes are assembled on a syringe holder device with a plunger allowing for the simultaneous application of equal amounts of fibrinogen and thrombin. For subjects randomized to the

FS Grifols group, FS Grifols was applied at the TBS up to 12 mL. No additional amounts of FS Grifols could be applied beyond T4.

Surgicel is a sterile, absorbable, knitted fabric prepared by the controlled oxidation of regenerated cellulose. For subjects randomized to the Surgicel group, up to four 4" × 8" sheets of Surgicel were applied to the TBS. No additional Surgicel sheets could be applied at the TBS beyond T4.

6.2.5 Directions for Use

The initial volume of FS Grifols applied in the target surface area was sufficient to entirely cover the intended application area by a thin, even layer. For every subject, FS Grifols was administered by spraying onto the TBS surface with the use of an applicator. Before application of FS Grifols to the TBS, the target area should have been as dry as possible. For FS Grifols applied by spraying, the recommended distance between the spray applicator and the surface of the target area was 10 cm and the sterile gas pressure must have been regulated at a pressure of 15 psi (1 bar) to 25 psi (1.75 bar). The time of start of initial study treatment application (T_{Start}) was recorded, and the primary efficacy endpoint was the hemostatic assessment at 4 minutes following T_{Start} (T4). The time of end/completion of initial study treatment application before T4 (T_{End}) was also recorded.

For every subject, FS Grifols will be administered by spraying onto the TBS surface. Before any application of FS Grifols to the TBS, target area should be as dry as possible. When FS Grifols is applied by spraying, the recommended distance between the spray applicator and the surface of the target area is 10 cm, and the sterile gas pressure must be regulated at a pressure of 15 psi (1 bar) to 25 psi (1.75 bar). FS Grifols can only be applied to the TBS in this study. Application by spraying: FS Grifols must be applied with the spray device supplied separately (Fibrijet Gas assisted applicator), or an equivalent spray device (including open surgery and laparoscopic or endoscopic use devices) cleared by FDA for this use. The product should then be sprayed onto the surface of the tissue in short bursts (0.1 – 0.2 mL) to form a thin, even layer.

If the hemostatic effect is incomplete after the initial application of FS Grifols and before the Primary Efficacy Endpoint at T4, additional amounts of FS Grifols may be applied at the TBS up to the maximum allowed volume of 12 mL (equivalent to the full content of 2 FS Grifols kits), if necessary. It is recommended to remove accumulated blood from the surrounding tissues, and the target area to be treated according to normal practice in order to have a dry field prior to application of FS Grifols (e.g., by means of suction, sponges or sterile gauzes). The time of start (TStart2) and end of FS Grifols re-application (TEnd2) will be recorded. No additional amounts of FS Grifols may be applied beyond the primary efficacy endpoint assessment time point at T4. The approximate total amount of FS Grifols applied to the TBS will be documented.

Patients in the FS Grifols group should not receive any alternative hemostatic product or treatment (including application of manual pressure) during the 10-minute observational period, apart from re-application of FS Grifols before the Primary Efficacy Endpoint at

T4, unless there is a brisk and forceful bleeding (breakthrough bleeding) at the TBS that jeopardizes subject safety according to surgeon's judgment, in which case the surgeon may use any other hemostatic measure at his/her discretion (the use of FS Grifols or other plasma-derived hemostatic agents is not allowed in this case). In this case, the patient will be considered a treatment failure. The alternative treatment applied will be recorded in subject's source documents and CRF.

For subjects randomized to the Surgicel group in both parts of the trial, an appropriate number of Surgicel Original sheets of the appropriate size will be applied, as per the Package Insert Instructions and according to the surgeon's usual clinical practice, immediately after randomization. Up to four 4" x 8" sheets will be allowed per subject. The number of sheets applied to the TBS will be documented.

6.2.6 Sites and Centers

Study IG1 102 was conducted in 33 study centers in Hungary, Russia, Serbia and the US.

6.2.7 Surveillance/Monitoring

The study schedules of events/monitoring are similar to study IG1 101; See Tables 6 and 7.

6.2.8 Endpoints and Criteria for Study Success

The study endpoints and criteria for success are similar for all three Phase 3 trials.

Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of subjects in the Primary Part (II) of the study achieving hemostasis (Yes/No) at the TBS by T4 without occurrence of re-bleeding and re-application of study treatment after T4 and until $T_{Closure}$ without brisk bleeding and use of alternative hemostatic treatment after T_{Start} and until $T_{Closure}$.

Secondary Efficacy Endpoints

- Time to hemostasis, which was measured from T_{Start} to the achievement of hemostasis at the TBS, or to the end of the 10-minute observational period when hemostasis had not yet been achieved.
- Cumulative proportion of subjects achieving hemostasis at the TBS by each of the following time points: T2, T3, T5, T7, and T10.

Safety Endpoints

- AEs, ADRs and SAEs
- Vital signs
- Physical assessments
- Laboratory tests
- Viral markers
- Antibodies

6.2.9 Statistical Considerations & Statistical Analysis Plan

See statistical review of STN 125640/0. The determination of efficacy was based on the statistical review of the primary efficacy endpoint and secondary endpoints data, based on the ITT population of Primary Part II of the completed study IG1 102. This study was intended to demonstrate non-inferiority of FS Grifols as an adjunct to achieve hemostasis at 4 minutes (T4), as compared to Surgicel.

Analysis Populations

- ITT population: The ITT population included all subjects randomized to FS Grifols or Surgicel. The efficacy analysis was performed using the ITT population.

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

- Safety population: The safety population consisted of all subjects who received any amount of FS Grifols or Surgicel. Safety analyses were based on the safety population.

Analysis for Primary Efficacy Endpoint

For primary efficacy analysis, only the data from the Primary Part II of the study were used. The primary efficacy endpoint was analyzed by providing the ratio of hemostasis rates by T4 in the 2 treatment groups (FS Grifols relative to Surgicel). FS Grifols would be considered non-inferior to Surgicel if the lower limit of the 95% CI exceeded 0.8; 0.8 is an acceptable non-inferiority margin that was agreed to before the trial was initiated. If non-inferiority was established, superiority may have been additionally claimed if the 95% CI was entirely above 1.

Analysis for Secondary Efficacy Endpoint

- Time to hemostasis was tested using Log Rank test.

- Cumulative proportion of subjects achieving hemostasis at the TBS by T5, T7, and T10 were analyzed by providing the ratio of proportion of subjects meeting the secondary efficacy endpoints and its 95% CI for subjects in the Primary Part II of the study.

The superiority for the secondary endpoints would only be tested if the non- inferiority for the primary efficacy endpoint was demonstrated. For secondary efficacy endpoints, a fixed-sequence testing method was employed for handling the multiplicity issue to maintain the overall familywise alpha level at 0.05. Each subsequent hypothesis was tested only if the superiority for the previous comparisons was shown at a 2-sided

significance level of 5%. The order in which the null hypotheses were tested was predetermined as below for the secondary efficacy variables:

1. Cumulative proportion of subjects having achieved hemostasis at the TBS by T3.
2. Time to hemostasis.
3. Proportion of subjects having achieved hemostasis at the TBS by T2.

Missing Data Handling

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

6.2.10 Study Population and Disposition

During the Primary Part II of the study, a total of 224 subjects were randomized into either FS Grifols treatment group or Surgicel treatment group (Table 18).

6.2.10.1 Populations Enrolled/Analyzed

6.2.10.1.1 Demographics

Subject demographics by treatment and by Preliminary Part I and Primary Part II are summarized in Table 17. In Part I + Part II (ITT population), the FS Grifols group consisted of 52.1% male and 47.9% female subjects. Similar results were seen in the Surgicel group (i.e. 52.5% male and 47.5% female subjects). The mean ages of subjects were comparable in the FS Grifols (58.8 years) and Surgicel (57.0 years) groups. The majority of subjects in the ITT population were Whites (90.8%).

Table 17. Demographics, Study IG1 102, (ITT Population)

Characteristics	Preliminary Part I	Preliminary Part II		Part I + Part II	Total (N=225) n (%)
	FS Grifols (N=59) n (%)	FS Grifols (N=109) n (%)	MC (N=57) n (%)	FS Grifols (N=168) n (%)	
Sex – n (%)					
Male	41 (69.5)	76 (69.7)	31 (54.4)	117 (69.6)	148 (65.8)
Female	18 (30.5)	33 (30.3)	26 (45.6)	51 (30.4)	77 (34.2)
Age (years)					
Mean (SD)	63.53 (9.343)	63.72 (8.908)	62.04 (10.734)	63.65 (9.036)	63.24 (9.496)
Median	64.0	64.0	61.0	64.0	63.0
Min, Max	41.0, 82.0	44.0, 84.0	22.0, 82.0	41.0, 84.0	22.0, 84.0
Age Category (years) – n (%)					
≤11	0	0	0	0	0
12-17	0	0	0	0	0
18-64	32 (54.2)	58 (53.2)	32 (56.1)	90 (53.6)	122 (54.2)
≥65	27 (45.8)	51 (46.8)	25 (43.9)	78 (46.4)	103 (45.8)
65-84	27 (45.8)	51 (46.8)	25 (43.9)	78 (46.8)	103 (45.8)
≥85	0	0	0	0	0
Race – n (%)					
White (Caucasian)	44 (74.6)	101 (92.7)	49 (86.0)	145 (86.3)	194 (86.2)
Black or African American	13 (22.0)	6 (5.5)	8 (14.0)	19 (11.3)	27 (12.0)
Asian	0	2 (1.8)	0	2	2 (0.9)
Native Hawaiian or Other Pacific Islander	1 (1.7)	0	0	1 (0.6)	1 (0.4)
Multi-racial	1	0	0	1	1 (0.4)

Source: BLA 125640/0; Module 5.3.5.1; IG1 101 Clinical Report

In the Preliminary Part I, 2 pediatric subjects (≤11 years) were randomized to the FS Grifols group. No pediatric subjects were enrolled in the Primary Part II of the study.

6.2.10.1.3 Subject Disposition

Subject disposition is summarized in Table 18.

Table 18. Subject Disposition in Primary Part (II), Study IG1 102

Number of Subjects:	FS Grifols n (%)	Surgicel n (%)	Overall N
Randomized (ITT Population)	111	113	224
Completed Study	100 (90.1)	108 (95.6)	208
Premature Discontinuation	11 (9.9)	5 (4.4)	16
Withdrew Consent	2 (1.8)	4 (3.5)	6
Lost to Follow-up	4 (3.6)	0	4
Death	4 (3.6)	1 (0.9)	5
Other	1 (0.9)	0	1
Premature Discontinuation before Virology Follow-up	15 (13.5)	11 (9.7)	26

Source: BLA 125640/0; Module 5.3.5.1, CSR IG1 102

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The rate of hemostasis by T4 was 92.8% (103/111 subjects) in the FS Grifols treatment group and was 80.5% (91/113 subjects) in the Surgicel treatment group. The 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.152 (1.038, 1.279), indicating that FS Grifols is non-inferior to Surgicel (i.e. the lower limit of the 95% CI $\geq$ 0.8). Additionally, the lower limit of the 95% CI above 1 indicates that FS Grifols is superior to Surgicel. The rate of hemostasis by T4 was significantly higher in the FS Grifols group compared to the Surgicel group (p-value = 0.010). The supportive analysis in the PP set showed similar results. Detailed results are shown in Table 19.

Table 19. Study IG1 102: Primary Endpoint Results in Primary Part

Analysis Population	FS Grifols	Surgicel	RR (95% CI)[a]	p-value[b]
ITT	103/111 (92.8%)	91/113 (80.5%)	1.152 (1.038, 1.279)	0.01
PP	86/87 (98.9%)	85/100 (85.0%)	1.163 (1.068, 1.267)	<0.001

a RR was the ratio of proportion of subjects meeting the efficacy endpoint in the two treatment groups in Primary Part (II) (FS Grifols relative to Surgicel).
b P-value was calculated from Fischer Exact Test.

6.2.11.2 Analyses of Secondary Endpoints

To control for multiple comparison/multiplicity, the superiority for the secondary endpoints were tested after the non-inferiority for the primary efficacy endpoint was

demonstrated. Secondary endpoints were analyzed according to the sequence described in Section 6.2.9.

In the ITT population, the rate of hemostasis by T3 was 85.6% (95/111 subjects) in the FS Grifols group and was 62.8% (71/113 subjects) in the Surgicel group. The 95% CI of proportion of subjects achieving hemostasis by T3 in subjects receiving FS Grifols relative to Surgicel was 1.362 (1.160, 1.600), indicating that FS Grifols is superior to Surgicel at T3. The rate of hemostasis by T3 was superior in the FS Grifols group compared to the Surgicel group (p-value <0.001).

The median TTH was significantly shorter (p-value <0.001) in the FS Grifols treatment group (2.0 minutes) compared to the Surgicel treatment group (3.0 minutes), indicating that FS Grifols is superior to Surgicel.

The results for cumulative proportion of subjects achieving hemostasis at the TBS by T2, T5, T7, and T10 show a similar pattern as the primary efficacy analysis in favor of FS Grifols (Table 20).

Table 20. Study IG1 102: Analysis of Hemostasis by T2, T3, T5, T7, and T10 at Target Bleeding Site (ITT Population)

	Primary Part II			
	FS Grifols N=111 n (%)	**Surgicel N=113 n (%)**	**RR (95% CI)[a]**	**P-value[b]**
Hemostasis by 2 minutes	62 (55.9)	47 (41.6)	1.343 (1.021, 1.766)	0.045
Hemostasis by 3 minutes	95 (85.6)	71 (62.8)	1.362 (1.160, 1.600)	<0.001
Hemostasis by 5 minutes	108 (97.3)	96 (85.0)	1.145 (1.053, 1.245)	0.002
Hemostasis by 7 minutes	108 (97.3)	99 (87.6)	1.111 (1.029, 1.198)	0.010
Hemostasis by 10 minutes	109 (98.2)	104 (92.0)	1.067 (1.005, 1.133)	0.059

a RR was the ratio of proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in Primary Part II (FS Grifols relative to Surgicel)
b P-value was calculated from Fischer Exact Test.
Source: Original BLA 125640/0; Module 5.3.5.1, Clinical Study Report for Study IG1102, p91.

6.2.11.3 Subpopulation Analyses

Subgroup analyses by sex, race and age categories using the ITT population is shown in Table 21. The results show a similar direction as the primary efficacy analysis in favor of FS Grifols in each subgroup.

Table 21. Study IG1 102: Analysis of Hemostasis by T4 at TBS by Treatment and Subgroups (ITT Population, Primary Part (II))

Subgroup	FS Grifols (N=111)	Surgicel (N=113)
Sex		
Male	56/59 (90.9%)	56/63 (88.9%)
Female	47/52 (90.4)	35/50 (70%)
Age		
18-64 years	64/70 (91.4%)	59/76 (77.6%)
≥65 years	39/41 (95.1%)	32/37 (86.5%)
Race		
White (Caucasian)	98/106 (92.5%)	84/103(81.6%)
Black or African American	1/1 (100%)	0/2 (0%)
Asian	4/4 (100%)	5/6 (83.3%)
American Indian or Alaska Native	0/0 (0%)	1/1 (100%)

6.2.11.4 Dropouts and/or Discontinuations

There were no dropouts or discontinuation due to adverse events. All subjects were followed for the 4 minutes to hemostasis assessment because they were in surgery in the operating room.

6.2.12 Safety Analyses

6.2.12.1 Methods

The safety evaluations were based on the pooled safety population of Preliminary Part I and Primary Part II of study IG1 102. In this study, FS Grifols was administered by topical spraying. A total of 134/163 (82.2%) subjects in the FS Grifols group and 139/162 (85.8%) subjects in Surgicel group experienced TEAEs. In the FS Grifols group, 11/163 (6.7%) subjects experienced an ADR, compared with 3/162 (1.9%) subjects in the Surgicel group. Table 22 summarizes the safety analysis by treatment arms.

Table 22. Study IG1 102: Safety Analysis by Treatment Arms

	Pooled Safety Population	
	FS Grifols N=163 n (%)	**Surgicel N=162 n(%)**
Subjects with any TEAE Total number of TEAEs	134 (82.2) 737	139 (85.8) 694
Subjects with any ADR Total number of ADRs	11 (6.7) 24	3 (1.9) 10
Subjects with any ADR attributable to application technique Total number of ADRs attributable to application technique	0 0	0 0
Subjects with any SAE Total number of SAEs	30 (18.4) 78	23 (14.2) 38
Subjects with any TEAE with outcome of death	7 (4.3)	3 (1.9)
Subjects with any serious ADR Total number of serious ADRs	4 (2.5) 9	0 0
Subjects with any AE leading to withdrawal Total number of AEs leading to withdrawal	0 0	0 0
Subjects with any intra-operative AE Total number of intra-operative AEs	55 (33.7) 109	56 (34.6) 96
Subjects with any surgical AE Total number of surgical AEs	104 (63.8) 275	101 (62.3) 284
Subjects with any nonsurgical AE Total number of nonsurgical AEs	107 (65.6) 447	115 (71.0) 398

6.2.12.2 Overview of Adverse Events

6.2.12.3 Deaths

A total of 10 deaths occurred in this study. AEs with the outcome of death were more frequently reported in FS Grifols the group. There were 7 (4.3%) deaths in the FS Grifols group vs. 3 (1.9%) in the Surgicel group. All death outcomes were considered not related to study treatment by investigators and the Applicant. Death AEs are further discussed in Section 8.4.1.

6.2.12.4 Nonfatal Serious Adverse Events

Thirty out of 163 (18.4%) subjects in the FS Grifols group experienced 78 SAEs, and 23 out of 162 (14.2%) subjects in the Surgicel group experienced 38 SAEs. In the FS Grifols group, 38/78 SAEs (48.7%) occurred in only single subjects. In the Surgicel group, 30/38 SAEs (78.9%) were reported in only single subjects. Of the total 78 SAEs occurring in 30 FS Grifols subjects in this study, the SAEs were considered not related to study treatment in all except 4 subjects in which the SAEs were considered unlikely related to study treatment; this included SAEs of pulmonary embolism and deep vein thrombosis considered as unlikely related to study treatment. All of the 38 SAEs occurring in 23 Surgicel subjects were considered not related to study treatment.

Reviewer Comment: Upon further review by the PVP clinical reviewer of the SAEs of pulmonary embolism and deep vein thrombosis that were assessed as unlikely related to

study treatment, Dr. Barash disagrees with the attributions and considers the pulmonary embolism and deep vein thrombosis SAEs as possibly related in the context of fibrin sealant use, which is well known to be thrombogenic. I agree with Dr. Barash, and I also agree that routine PVP would be sufficient to continue to monitor these adverse events.

The most frequently reported TEAEs, as shown in Table 23, occurring in more than 5% of subjects, were procedural pain, 59/163 (36.2%) in the FS Grifols group and 61/162 (37.7%) in the Surgicel group, followed by nausea, 20.9% in the FS Grifols group vs. 23.5% in the Surgicel group. Hypotension was report at 14.1% in the FS Grifols group vs. 6.2% in the Surgical group.

Table 23. Study IG1 102: Treatment-Emergent Adverse Events Reported in ≥ 5% of Subjects within Treatment Group

Preferred Term	FS Grifols, N=163 (%)	Surgicel, N=162 (%)
Any TEAE	134 (82.2)	139 (85.8)
Procedural Pain	59 (36.2)	61 (37.7)
Nausea	34 (20.9)	38 (23.5)
Hypotension	23 (14.1)	10 (6.2)
Pyrexia	17 (10.4)	20 (12.3)
Tachycardia	14 (8.6)	24 (14.8)
Hypertension	14 (8.6)	12 (7.4)
Peripheral Edema	14 (8.6)	11 (6.8)
Vomiting	13 (8.0)	17 (10.5)
Pruritis	12 (7.4)	12 (7.4)
Incisional site pain	12 (7.4)	11 (6.8)
Pleural effusion	12 (7.4)	9 (5.6)
Atelectasis	11 (6.7)	10 (6.2)
Abdominal Pain	11 (6.7)	3 (1.9)
Procedural Hemorrhage	9 (5.5)	4 (2.5)
Dyspnea	3 (1.8)	11 (6.8)

6.2.12.5 Adverse Events of Special Interest (AESI)

Three subjects in the FS Grifols group (3/163; 1.8%) experienced a deep vein thrombosis. Of these, one of the thrombotic events was considered unrelated, and two were considered unlikely related to study treatment by investigators and the Applicant. One subject in the Surgicel group (1/162; 0.6%) experienced a deep vein thrombosis that was considered unrelated to study treatment by the investigator.

6.2.13 Study Summary and Conclusions

Overall, efficacy data are positive for FS Grifols and support the use of FS Grifols as an effective local hemostatic agent in parenchymous tissue (liver) surgery. Primary efficacy analysis of hemostasis at the TBS by T4 demonstrated that the rate of hemostasis by T4

was statistically and significantly higher (p-value = 0.010) in the FS Grifols treatment group (92.8%), compared to the Surgicel treatment group (80.5%). Additionally, data shows FS Grifols is superior to Surgicel.

The results of all secondary efficacy endpoints provided additional support for FS Grifols as an effective local hemostatic agent in parenchymous tissue surgery.

6.3 Trial #3, IG1 103: "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."

Study IG1103 was a Phase 3 trial, conducted under IND 14986.

6.3.1 Objectives (Primary, Secondary, etc.)

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

The secondary objectives evaluate hemostasis at other various time points, time to hemostasis, and prevalence of treatment failures.

6.3.2 Design Overview

Study IG1 103 was a randomized, single-blind, multicenter clinical trial to evaluate the safety and efficacy of FS Grifols. The study consisted of 2 parts: a Preliminary Part I and a Primary Part II. Subjects in the Preliminary Part I were randomized in a 1:1 ratio into 1 of 2 treatment groups: FS Grifols or Surgicel. The main objective of this part of the clinical study was to ensure that local study teams become familiarized with the technique for FS Grifols application and with intra-operative procedures required by the protocol of this trial. For each study participating center, the first 4 subjects were to be enrolled in the Preliminary Part I. Subjects in the Primary Part II were to be randomized in a 1:1 ratio into FS Grifols or Surgicel treatment groups. For each study center, the Primary Part II of the study was to start only after enrollment of 4 subjects in the Preliminary Part I. Randomization was stratified by study center.

In both parts of this study, a specific bleeding area/site was defined as the TBS when it was determined intra-operatively by the investigator that control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) was ineffective or impractical and required an adjunct treatment to achieve hemostasis. When the TBS was identified, the investigator rated the intensity of the bleeding according to a 3-point scale (mild, moderate, severe) at the TBS. The approximate size of the bleeding surface was rated small, medium, or large. The grading scales are defined below.

The intensity of the bleeding at the TBS was rated by the investigator (surgeon) using the following 3-point scale:

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

The approximate size of the TBS was rated by the investigator (the surgeon) using a 3-point scale:

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

For both parts of the study, only subjects with a TBS with bleeding of moderate intensity could be enrolled.

6.3.3 Population

Inclusion Criteria:

1. Sign the written ICF.
2. Male or female.
3. No lower or upper age limit.
4. Hemoglobin (Hgb) ≥ 8.0 g/dL at Baseline (within 24 hours prior to surgical procedure).
5. Require an elective (non-emergency), open (non-laparoscopic;) surgical procedure involving soft (non-parenchymous) tissue:
   - Where TBS is identified on soft tissue during following urologic, gynecologic or general surgery procedures:
     i. Simple or radical nephrectomies.
     ii. Total adrenalectomies.
     iii. Radical prostatectomies.
     iv. Pyeloplasties.
     v. Radical cystectomies.
     vi. Simple or radical hysterectomies.
     vii. Lymphadenectomies (in the retroperitoneal or pelvic region only).
     viii. Retroperitoneal tumor resections.
     ix. Mastopexies.
     x. Abdominoplasties.

6. Intra-operative inclusion criteria: a TBS can be identified according to the investigator's judgment, and
   - The TBS has a moderate bleeding according to the investigator's judgment.
   - The intensity of the bleeding at the TBS will be rated by the investigator using a pre-defined three-point scale

Exclusion Criteria:

1. Require thoracic, abdominal, retroperitoneal or pelvic surgery due to trauma.
2. Infection in the anatomic surgical area.

3. History of severe (e.g. anaphylactic) reactions to blood or to any blood derived (human or animal) product.
4. Previous known sensitivity to any FS Grifols component or any Surgicel® component.
5. Are unlikely to adhere to the protocol requirements, or to be cooperative during the study conduct.
6. Females who are pregnant or nursing a child at Baseline (within 24 hours prior to surgical procedure).
7. Receiving an organ transplant during the same surgical procedure.
8. Currently participating or have participated in another clinical study in the context of which have received investigational drug or device within 3 months from the screening visit, or are scheduled to participate during the course of this study.
9. Undergone a therapeutic surgical procedure within 30 days from the screening visit.
10. Previously enrolled in clinical trials with FS Grifols.
11. Intra-operative exclusion criteria:
    - A TBS (as defined in section 7.1.3.1) cannot be identified according to the investigator's judgment.
    - The TBS has a mild or severe bleeding according to the investigator's judgment.
    - Occurrence of major intraoperative complications that require resuscitation or deviation from the planned surgical procedure.
    - Application of any topical hemostatic material on the cut soft tissue surface identified as the TBS prior to application of the study treatment.
12. Known (documented) history of thrombophilia.
13. Known (documented) history of IgA deficiency.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Subjects were treated intra-operatively with either FS Grifols or Surgicel to the TBS.

FS Grifols is composed of frozen solutions of human fibrinogen and human thrombin with calcium chloride. The fibrinogen and thrombin solutions are supplied in a kit in separate glass syringes, each containing 3 mL frozen solution. The syringes are assembled on a syringe holder device with a plunger allowing for the simultaneous application of equal amounts of fibrinogen and thrombin. For subjects randomized to the FS Grifols group, FS Grifols was applied at the TBS up to 12 mL. No additional amounts of FS Grifols could be applied beyond T4.

6.3.5 Directions for Use

The initial volume of FS Grifols applied in the target surface area was sufficient to entirely cover the intended application area by a thin, even layer. For every subject, FS Grifols was administered by dripping or by spraying onto the TBS surface with the use of an applicator. Before application of FS Grifols to the TBS, the target area should have been as dry as possible. If FS Grifols was applied by dripping, the tip of the applicator should have been kept as close to the tissue surface as possible without touching the

tissue during application. If FS Grifols was applied by spraying, the recommended distance between the spray applicator and the surface of the target area was 10 cm and the sterile gas pressure must have been regulated at a pressure of 15 psi (1 bar) to 25 psi (1.75 bar). The time of start of initial study treatment application (TStart) was recorded, and the primary efficacy endpoint was the hemostatic assessment at 4 minutes following TStart (T4). The time of end/completion of initial study treatment application before T4 (TEnd) was also recorded.

If the hemostatic effect was incomplete after TStart and before the primary efficacy endpoint assessment time point, T4, additional amounts of FS Grifols may have been applied at the TBS up to the maximum allowed volume of 12 mL (equivalent to the full content of 2 FS Grifols kits), if necessary. It was recommended to remove accumulated blood from the surrounding tissues and the target area to be treated according to normal practice in order to have a dry field prior to application of FS Grifols (e.g., by means of suction, sponges, or sterile gauzes). These additional applications of FS Grifols may have been done with either spray or drip applicator tips, according to the surgeon's preference and the nature of the remaining bleeding area. No additional amounts of FS Grifols could be applied beyond the primary efficacy endpoint assessment time point at T4. Only FS Grifols could be applied to the TBS in this study.

In subjects randomized to the Surgicel group, if the hemostatic effect was incomplete after TStart and before T4, additional sheets of Surgicel Original may have been applied, if deemed necessary by the surgeon, at the TBS, up to four 4” × 8” sheets. No additional Surgicel sheets could be applied at the TBS beyond T4.

6.3.6 Sites and Centers

This study was conducted in 31 study centers in Hungry, Serbia, and the US.

6.3.7 Surveillance/Monitoring

The study schedules of events/monitoring are the similar to study IG1 101; See Tables 6 and 7.

6.3.8 Endpoints and Criteria for Study Success

The study endpoints and criteria for success are similar for all three Phase 3 trials.

Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of subjects in the Primary Part II of the study achieving hemostasis (Yes/No) at the TBS by T4 without occurrence of re-bleeding and re-application of study treatment after T4 and until $T_{Closure}$ without brisk bleeding and use of alternative hemostatic treatment after T_{Start} and until $T_{Closure}$.

Secondary Efficacy Endpoints

- Time to hemostasis, which was measured from T_{Start} to the achievement of hemostasis at the TBS, or to the end of the 10-minute observational period when hemostasis had not yet been achieved.

- Cumulative proportion of subjects achieving hemostasis at the TBS by each of the following time points: T2, T3, T5, T7, and T10.

Safety Endpoints

- AEs, ADRs and SAEs.
- Vital signs.
- Physical assessments.
- Laboratory tests.
- Viral markers.
- Antibodies.

6.3.9 Statistical Considerations & Statistical Analysis Plan

See statistical review of STN 125640/0. The determination of efficacy was based on the statistical review of the primary efficacy endpoint and secondary endpoints data, based on the ITT population of Primary Part II of the completed study IG1 103. This study was intended to demonstrate non-inferiority of FS Grifols as an adjunct to achieve hemostasis at 4 minutes (T4), as compared to Surgicel.

Analysis Populations

- ITT population: The ITT population included all subjects randomized to FS Grifols or Surgicel. The efficacy analysis was performed using the ITT population.
- PP population: The PP population included all subjects in the ITT population excluding any subject for whom there was at least 1 major protocol deviation that might have an impact on the primary efficacy assessment.
- Safety population: The safety population consisted of all subjects who received any amount of FS Grifols or Surgicel. Safety analyses were based on the safety population.

Analysis for Primary Efficacy Endpoint

For primary efficacy analysis, only the data from the Primary Part II of the study were used. The primary efficacy endpoint was analyzed by providing the ratio of hemostasis rates by T4 in the 2 treatment groups (FS Grifols relative to Surgicel) and its 2-sided asymptotic 95% CI. FS Grifols would be considered non-inferior to Surgicel if the lower limit of the 95% CI exceeded 0.8. If non-inferiority was established, superiority may have been additionally claimed if the 95% CI was entirely above 1.

Analysis for Secondary Efficacy Endpoint

- Time to hemostasis was tested using Log Rank test.
- Cumulative proportion of subjects achieving hemostasis at the TBS by T5, T7, and T10 were analyzed by providing the ratio of proportion of subjects meeting

the secondary efficacy endpoints and its 95% CI for subjects in the Primary Part II of the study.

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

1. Cumulative proportion of subjects having achieved hemostasis at the TBS by T3.
2. Time to hemostasis.
3. Proportion of subjects having achieved hemostasis at the TBS by T2.

Missing Data Handling

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

6.3.10 Study Population and Disposition

During the Primary Part II, a total of 224 subjects were randomized into either FS Grifols treatment group or Surgicel treatment group (Table 25).

Table 24. Subject Populations and Disposition During Primary Part II

	FS Grifols N	Surgicel N	Overall N
Subjects randomized	116	108	224
ITT population	116	108	224
PP population	104	102	206
Safety population	116	108	224
Subjects completed study	103	95	198
Subjects discontinued study	13	13	26
Withdrawal of consent	5	4	9
Lost to follow-up	4	5	9
Death	2	1	3
Other	2	3	5

6.3.10.1 Populations Enrolled/Analyzed

6.3.10.1.1 Demographics

Subject demographics by treatment and by Preliminary Part I and Primary Part II are summarized in Table 26. In the Preliminary Part I, the ITT population consisted of 47.1% male subjects and 52.9% female subjects in the FS Grifols treatment group. Similarly, 46.2% male subjects and 53.8% female subjects in the Surgicel group. In the Primary Part II of the study, there were more female subjects vs male subjects: 75.0% vs 25% in FS Grifols-treated subjects and 79.6% vs 20.4% in the Surgicel-treated subjects. The ages of subjects in both treatment groups across the Preliminary Part I and the Primary Part II of the study were consistent. The mean age of subjects was comparable in the FS Grifols (48.1 years) and Surgicel (46.3 years) groups.

Table 25. Study IG1 103: Demographics, Study IG1 103, (ITT Population)

Characteristics	Preliminary Part (I)	Preliminary Part (II)		Part (I) + Part (II)	Total (N=225) n (%)
	FS Grifols (N=59) n (%)	FS Grifols (N=109) n (%)	MC (N=57) n (%)	FS Grifols (N=168) n (%)	
Sex – n (%)					
Male	41 (69.5)	76 (69.7)	31 (54.4)	117 (69.6)	148 (65.8)
Female	18 (30.5)	33 (30.3)	26 (45.6)	51 (30.4)	77 (34.2)
Age (years)					
Mean (SD)	63.53 (9.343)	63.72 (8.908)	62.04 (10.734)	63.65 (9.036)	63.24 (9.496)
Median	64.0	64.0	61.0	64.0	63.0
Min, Max	41.0, 82.0	44.0, 84.0	22.0, 82.0	41.0, 84.0	22.0, 84.0
Age Category (years) – n (%)					
≤11	0	0	0	0	0
12-17	0	0	0	0	0
18-64	32 (54.2)	58 (53.2)	32 (56.1)	90 (53.6)	122 (54.2)
≥65	27 (45.8)	51 (46.8)	25 (43.9)	78 (46.4)	103 (45.8)
65-84	27 (45.8)	51 (46.8)	25 (43.9)	78 (46.8)	103 (45.8)
≥85	0	0	0	0	0
Race – n (%)					
White (Caucasian)	44 (74.6)	101 (92.7)	49 (86.0)	145 (86.3)	194 (86.2)
Black or African American	13 (22.0)	6 (5.5)	8 (14.0)	19 (11.3)	27 (12.0)
Asian	0	2 (1.8)	0	2	2 (0.9)
Native Hawaiian or Other Pacific Islander	1 (1.7)	0	0	1 (0.6)	1 (0.4)
Multi-racial	1	0	0	1	1 (0.4)

Source: BLA 125640/0; Module 5.3.5.1; IG1 101 Clinical Report

The majority of subjects in the ITT population were Whites (81.3%).

Only one pediatric subject between the ages of 12-17 years was enrolled, in the Primary Part II of the study.

6.3.10.1.3 Subject Disposition

The disposition of subject is summarized in Table 27.

Table 26. Study IG1 103: Subject Disposition in Primary Part II

Number of Subjects:	FS Grifols n (%)	Surgicel n (%)	Overall N
Randomized (ITT Population)	116	108	224
Completed Study	103 (88.8)	95 (88.0)	198
Premature Discontinuation	13 (11.2)	13 (12.0)	26
Withdrew Consent	5(4.3)	4 (3.7)	9
Lost to Follow-up	4 (3.4)	5 (4.6)	9
Death	2 (1.7)	1 (0.9)	3
Other	2 (1.7)	3 (2.8)	5
Premature Discontinuation before Virology Follow-up	20 (17.2)	21 (19.4)	41

Source: BLA 125640/0; Module 5.3.5.1, CSR IG1 103

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

The rate of hemostasis at the TBS by T4 was higher in the FS Grifols treatment group 82.8% (96/116 subjects) vs. 77.8% (84/108 subjects) in the Surgicel group. The 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.064 (0.934, 1.213), indicating that FS Grifols is non-inferior to Surgicel in the ITT population. However, the rate of hemostasis by T4 was not statistically superior in the FS Grifols group compared to the Surgicel group. The supportive analysis in the PP set showed similar results. Results are shown in Table 28.

Table 27. Study IG1 103: Primary Endpoint Results in Primary Part II

Analysis Population	FS Grifols	Surgicel	RR (95% CI)[a]	p-value[b]
ITT	96/116 (82.8%)	84/108 (77.8%)	1.064 (0.934, 1.213)	0.401
PP	87/104 (83.7%)	78/102 (76.5%)	1.094 (0.954, 1.255)	0.224

[a] RR was the ratio of proportion of subjects meeting the efficacy endpoint in the two treatment groups in Primary Part (II) (FS Grifols relative to Surgicel).
[b] P-value was calculated from Fischer Exact Test.

6.3.11.2 Analyses of Secondary Endpoints

To control for multiple comparison/multiplicity, the superiority for the secondary endpoints were tested after the non-inferiority for the primary efficacy endpoint was demonstrated. Secondary endpoints were analyzed according to the sequence described in Section 6.3.9.

In the ITT population, the rate of hemostasis at the TBS by T3 was 75.9% (88/116 subjects) in the FS Grifols group and was 60.2% (65/108 subjects) in the Surgicel group. The 95% CI of proportion of subjects achieving hemostasis at the TBS by T3 in subjects receiving FS Grifols relative to Surgicel was 1.260 (1.048, 1.516), indicating that FS Grifols is superior to Surgicel at T3. The rate of hemostasis at the TBS by T3 was statistically superior in the FS Grifols group compared to the Surgicel group (p-value=0.015). See Table 29.

The median TTH was not significantly shorter (p-value=0.06) in the FS Grifols treatment group (2.0 minutes) compared to the Surgicel treatment group (3.0 minutes), indicating that FS Grifols is not superior to Surgicel.

The results for cumulative proportion of subjects achieving hemostasis at the TBS by T2, T5, T7, and T10 in the ITT population show a similar pattern as the primary efficacy analysis, thus, FS Grifols is non-inferior to Surgicel (Table 29).

Table 28. Study IG1 103: Analysis of Hemostasis by T_2, T_3, T_5, T_7, and T_{10} at Target Bleeding Site (ITT Population)

	Primary Part II			
	FS Grifols N=116 n (%)	**Surgicel N=108 n (%)**	**RR (95% CI)[a]**	**P-value[b]**
Hemostasis by 2 minutes	62 (553.4)	47 (43.5)	1.228 (0.934, 1.615)	0.144
Hemostasis by 3 minutes	88 (75.9)	65 (60.2)	1.260 (1.048, 1.516)	0.015
Hemostasis by 5 minutes	97 (83.6)	85 (78.8)	1.062 (0.936, 1.206)	0.394
Hemostasis by 7 minutes	100 (86.2)	88 (81.5)	1.058(0.942, 1.188)	0.367
Hemostasis by 10 minutes	104 (89.7)	90 (83.3)	1.076 (0.969, 1.194)	0.176

a RR was the ratio of proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in Primary Part II (FS Grifols relative to Surgicel)
b P-value was calculated from Fischer Exact Test.
Source: Original BLA 125640/0; Module 5.3.5.1, Clinical Study Report for Study IG1103, p92.

6.3.11.3 Subpopulation Analyses

Subgroup analyses by sex, race and age categories using the ITT population is shown in Table 30. The results show a similar direction as the primary efficacy analysis.

Table 29. Study IG1 103: Analysis of Hemostasis by T4 at TBS by Treatment and Subgroups (ITT Population, Primary Part II)

Subgroup	FS Grifols (N=116)	Surgicel (N=108)
Sex		
Male	22/29 (75.9%)	18/22 (81.8%)
Female	74/87 (85.1%)	66/86 (76.7%)
Age		
12-17 years	1/1 (100%)	0/0 (0%)
18-64 years	64/70 (91.4%)	59/76 (77.6%)
≥65 years	39/41 (95.1%)	32/37 (86.5%)
Race		
White (Caucasian)	77/93 (82.8%)	68/81 (84.0%)
Black or African American	18/22 (81.8%)	14/25 (56%)
Asian	1/1 (100%)	1/1 (100%)
American Indian or Alaska Native	0/0 (0%)	1/1 (100%)

6.3.11.4 Dropouts and/or Discontinuations

There were no dropouts or discontinuation due to adverse events. All subjects were followed for the 4 minutes to hemostasis assessment because they were in surgery in the operating room.

6.3.12 Safety Analyses

The safety evaluations were based on the pooled safety population, which includes all subjects from Preliminary Part (I) + Primary Part (II) of the study. A total of 149 (88.2%) subjects in the FS Grifols group and 139 (88.0%) subjects in Surgicel group experienced TEAEs. In the FS Grifols group, 32 (18.9%) subjects experienced an ADR compared with 24 (15.2%) subjects in the Surgicel group. Table 31 summarizes the safety analysis by treatment arms.

Table 30. Study IG1 103: Safety Analysis by Treatment Arms

	Pooled Safety Population	
	FS Grifols N=169 n (%)	**Surgicel N=158 n(%)**
Subjects with any TEAE Total number of TEAEs	149 (88.2) 597	139 (88.0) 569
Subjects with any ADR Total number of ADRs	32 (18.9) 65	24 (15.2) 55
Subjects with any ADR attributable to application technique Total number of ADRs attributable to application technique	1 (0.6) 2	0 0
Subjects with any SAE Total number of SAEs	17 (10.1) 29	18 (11.4) 27
Subjects with any TEAE with outcome of death	2 (1.2)	1 (0.6)
Subjects with any serious ADR Total number of serious ADRs	1 (0.6) 2	0 0
Subjects with any AE leading to withdrawal Total number of AEs leading to withdrawal	0 0	0 0
Subjects with any intra-operative AE Total number of intra-operative AEs	37 (21.9) 64	37 (23.4) 63
Subjects with any surgical AE Total number of surgical AEs	127 (75.1) 295	120 (75.9) 270
Subjects with any nonsurgical AE Total number of nonsurgical AEs	98 (58.0) 299	87 (55.1) 294

Source: BLA 125640/0; Module 5.3.5.1, Clinical Study Report for Study IG1 103, p100.

6.3.12.1 Methods

6.3.12.2 Overview of Adverse Events

6.3.12.3 Deaths

A total of 3 deaths occurred in 2 (1.2%) FS Grifols subjects and 1 (0.6%) Surgicel subjects during the study. All death outcomes were considered not related to study treatment. See Section 8.4.1 for further details.

6.3.12.4 Nonfatal Serious Adverse Events

Seventeen out of 169 (10.1%) subjects in the FS Grifols treatment group experienced 29 SAEs, and 18 out of 158 (11.4%) subjects in the Surgicel treatment group experienced 27 SAEs. In the FS Grifols treatment group, 19/29 (65.5%) SAEs were reported in only single subjects, while 20/27 (74.0%) SAEs were reported in only single subjects in the Surgicel treatment group,

A total of 29 SAEs occurring in 17 subjects in the FS Grifols treatment group in this study. Of these, all were considered not related by investigators, except for 2 SAEs (abdominal wound dehiscence and peritonitis) that were considered possibly related, but were also considered attributable to application technique. All of the 27 SAEs occurring in 18 Surgicel-treated subjects were considered not related to study treatment.

6.3.12.5 Adverse Events of Special Interest (AESI)

One subject in the FS Grifols group (1/169; 0.6%) and one subject in the Surgicel group (1/158; 0.6%) each experienced a deep vein thrombosis event.

6.3.13 Study Summary and Conclusions

Overall, data demonstrate the hemostatic efficacy of FS Grifols and support the use of FS Grifols as an effective local hemostatic agent in soft tissue surgeries. Primary efficacy analysis of hemostasis rate by T4 demonstrated that FS Grifols is non-inferior to Surgicel and that the rate of hemostasis by T4 in the FS Grifols treatment group (82.8%) was higher, but not statistically superior (p-value = 0.401) to the Surgicel treatment group (77.8%).

The results of all secondary efficacy endpoints provided additional support for FS Grifols as an effective local hemostatic agent in soft tissue surgery.

7. INTEGRATED OVERVIEW OF EFFICACY

All 3 Phase 3 trials met their designated primary endpoint: one was a superiority trial in vascuilar surgery against manual compression, the other two were non-inferiority trials against Surgicel. In the second trial (IG1 102), FS Grifolds not only met the primary efficacy non-inferiority endpoint, but also was shown to be superior (lower bound of the 95% of the ratio of proportion of subjects achieving hemostasis by T4 was above "1"). Results of the primary efficacy endpoint, hemostasis by T4, for the three studies are summarized in Table 32. Additionally, the secondary efficacy endpoints results were supportive in all three Phase 3 trials.

Table 31. Primary Efficacy (Hemostasis by T4) in Primary Part II of the Three Phase 3 Trials

Study No.	FS Grifols % (n/N)	Control % (n/N)	Risk Ratio* (95% CI)	P-value	Efficacy Result
IG1 101 Vacular	76.1 (83/109)	MC 22.8 (13/57)	3.339 (2.047, 5.445)	<0.001	FS Grifols is superior to MC
IG1 102 Liver	92.8 (103/111)	Surgicel 80.5 (91/113)	1.152 (1.038, 1.279)	0.010	FS Grifols is non-inferior to Surgicel**
IG1 103 Soft Tissue	82.8 (96/116)	Surgicel 77.8 (84/108)	1.064 (0.934, 1.213)	0.401	FS Grifols is non-inferior to Surgicel

*Risk Ratio (RR): estimated ratio of the proportion of subjects meeting the primary efficacy endpoint in the two treatment groups in Primary Part II (FS Grifols relative to MC or Surgicel)
** The lower limit of the 95% CI above 1, indicates FS Grifols is superior to Surgicel.

8. INTEGRATED OVERVIEW OF SAFETY

Three Phase 3 clinical trials have been completed using Fibrin Sealant Grifols as an adjunct to hemostasis during vascular surgery, parenchymous tissue surgery, and soft tissue surgery. The data from these studies are intended to show that FS Grifols is safe and effective as an adjunct to hemostasis. All subjects participating in Studies IG1101, IG1102, and IG1103 were monitored for safety throughout the study from screening visit to final visit. The safety of FS Grifols was evaluated in these studies by assessing the nature, severity, and frequency of adverse events (AEs) and serious adverse events (SAEs) reported over the course of the studies (post-operative Week 6). Additional assessments of safety included evaluation of clinical laboratory parameters, virus safety, immunogenicity, vital signs, and physical assessments. In these studies, the last visit for collecting viral panel samples for adult subjects took place at either Month 3 or Month 6.

Among the 3 clinical trials that included Preliminary Part I plus Primary Part II, 877 subjects were assigned or randomized to specific study treatment. Of these 877 subjects, 498 were randomized to receive FS Grifols (ITT Population), 322 subjects were randomized to receive Surgicel (ITT Population), and 57 subjects were randomized to receive MC (ITT Population). Due to 2 subjects who were initially randomized to Surgicel but actually received FS Grifols, the Safety Population included a total of 500 subjects treated with FS Grifols, 320 subjects treated with Surgicel, and 57 subjects treated with MC. All subjects received treatment and are included in the Safety Population based on actual treatment received and used for safety analysis.

8.1 Safety Assessment Methods

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

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety population consists of all subjects enrolled in Preliminary Part I and Primary Part II of all three Phase 3 trials.

All 3 clinical trials were conducted using the same general trial design with each trial consisting of a Preliminary Part I followed by a Primary Part II. The same subject monitoring and follow-up periods were used in the three trials. The inclusion and exclusion criteria were generally the same for all clinical trials except for the types of surgeries included in each study: vascular surgery in IG1 101, parenchymous surgery in IG1 102, and soft tissue surgery in IG1 103.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Duration of Exposure

The concentration of FS Grifols was the same in all trials, although the maximum allowable volume was 6 mL in study IG1101, compared to 12 mL in studies IG1102 and IG1103. When applied by dripping, 1 kit of FS Grifols (6 mL of solution in total) may cover up to 48 cm2 of the surface area in a layer of 1 mm thickness. When applied by spraying, 1 kit of FS Grifols (6 mL of solution in total) may cover up to 957 cm2 of the surface area in a thin layer (thickness not specified). The actual volume of FS Grifols applied varied for each individual subject and was based on the investigator's determination of the volume needed to achieve hemostasis at the TBS, and the number of applications of FS Grifols to the TBS within the protocol-specified time of 4 minutes from the first application was at the discretion of the investigator. Each subject receiving FS Grifols in these trials received the application(s) at a single TBS and for a single surgery.

The mean volume of FS Grifols applied among all 3 studies was 6.78 mL, with a median of 6.0 mL and a range of 0.3 to 18.0 mL (minimum to maximum). The mean volume of FS Grifols applied in study IG1101 was 4.23 mL, with a median of 4.20 mL and a range of 0.3 to 12.0 mL (minimum to maximum). The mean volume of FS Grifols applied in studies IG1102 and IG1103 combined was 8.07 mL, with a median of 6.0 mL and a range of 0.3 to 18.0 mL (minimum to maximum).

For each participating subject receiving manual compression (MC) treatment in study IG1101, dry gauze/laparotomy pads were available and ready for use in the operating room at the time of surgery.

Subjects receiving Surgicel (studies IG1102 and IG1103) were to receive a single intraoperative exposure at the TBS. For each participating subject assigned to receive the Surgicel treatment for parenchymous and soft tissue surgical procedures, four 4"×8" Surgicel Original sheets were allotted. The sheets were available and ready for use in the operating room at the time of surgery if this treatment was assigned. All four Surgicel sheets were allowed to be applied for each subject.

The demographics of subjects in Primary Part II are shown in Table 33.

Table 32. Subject Demographics in Primary Part II (ITT Population)

	IG1 101		IG1 102		IG1 103	
	FS Grifols N=109 n (%)	**MC N=57 n (%)**	**FS Grifols N=111 n (%)**	**Surgicel N=113 n (%)**	**FS Grifols N=116 n (%)**	**Surgicel N=108 n (%)**
Sex - n (%)						
Male	76 (69.7)	31 (54.4)	59 (53.2)	63 (55.8)	29(25.0)	22 (20.4)
Female	33 (30.3)	26 (45.6)	52 (46.8)	50 (44.2)	87 (75.0)	86 (79.6)
Age (years)						
Mean (SD)	63.72 (8.908)	62.04 (10.734)	59.87 (12.222)	57.71 (13.595)	48.51 (14.369)	46.72 (14.330)
Median	64.00	61.00	61.00	61.00	46.00	45.00
Min, Max	44.0, 84.0	22.0, 82.0	25.0, 82.0	19.0, 84.0	15.0, 85.0	21.0, 84.0
Age (yrs) - n (%)						
≤11	0	0	0	0	0	0
12-17	0	0	0	0	1 (0.9)	0
18-64	58 (53.2)	32 (56.1)	70 (63.1)	76 (67.3)	98 (84.5)	90 (83.3)
≥65	51 (46.8)	25 (43.9)	41 (36.9)	37 (32.7)	17 (14.7)	18 (16.7)
65-84	51 (46.8)	25 (43.9)	41 (36.9)	t37 (32.7)	16 (13.8)	18 (16.7)
≥85	0	0	0	0	1 (0.9)	0
Ethnicity - n (%)						
Hispanic/Latino	3 (2.8)	2 (3.5)	5 (4.5)	7 (6.2)	20 (17.2)	12 (11.1)
Not Hispanic/Latino	106 (97.2)	55 (96.5)	106 (97.2)	105 (92.9)	96 (82.8)	96 (88.9)
Not specified	0	0	0	1 (0.9)	0	0
Race - n (%)						
Caucasian	101 (92.7)	49 (86.0)	106 (95.5)	103 (91.2)	93 (80.2)	81 (75.0)
Black/African American	6 (5.5)	8 (14.0)	1 (0.9)	2 (1.8)	22 (19.0)	25 (23.1)
Asian	2 (1.8)	0	4 (3.6)	6 (5.3)	1 (0.9)	1 (0.9)
American Indian/Alaskan	0	0	0	1 (0.9)	0	1 (0.9)
Multi-racial (no primary race)	0	0	0	0	0	0
Other	0	0	0	0	0	0
Not Specified	0	0	0	1 (0.9)	0	0

8.2.3 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0.

8.4 Safety Results

An overall summary of treatment-emergent AEs (TEAEs) in all 3 Studies IG1101, IG1102, and IG1103 is provided in Table 34. The proportions of subjects for whom TEAEs were reported were comparable among the treatment groups (FS Grifols, 83.8%; Surgicel, 86.9%; MC, 77.2%).

Table 33. Summary of Treatment Emergent Adverse Events by Treatment Group in All 3 Studies (Safety Population)

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

Source: Table 5.3/1.2 of ISS in Module 5.3.5.3

Treatment-emergent serious AEs (SAEs) were reported in 81/500 (16.2%) subjects in the FS Grifols treatment group, 41/320 (12.8%) subjects in the Surgicel treatment group, and 11/57 (19.3%) subjects in the MC treatment group. Included were 13/500 (2.6%) deaths in the FS Grifols treatment group, 4/320 (1.3%) deaths in the Surgicel treatment group, and no deaths in the MC treatment group.

TEAEs in ≥5% of Subjects by Preferred Term within a treatment group in all three trials are shown in Table 35. Overall, across all trials, the most frequently reported TEAEs in this table are procedural pain, nausea, and pyrexia.

Table 34. Treatment-Emergent Adverse Events Reported in ≥5% of Subjects by Preferred Term within a Treatment Group in All 3 Studies (Safety Population)

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

Serious Adverse Events

Of the SAEs in the FS Grifols group (72/81 subjects), the majority were considered unrelated to study treatment by investigators in all except 9 subjects (9/81 subjects). Five subjects had SAEs that were considered unlikely related and 4 subjects had SAEs that were considered possibly related to the study treatment. SAEs considered unlikely related to study treatment were: postoperative wound infection, wound infection, abdominal abscess, deep vein thromboses (2 subjects, including 1 right femoral vein and 1 left peroneal vein in 1 subject), pulmonary embolism (2 subjects), postprocedural bile leak (2 subjects), and liver abscess (1 subject). SAEs considered possibly related to study treatment were: cellulitis, parvovirus B19 (B19V) test positive (determined not to be treatment-emergent viral infection.), abdominal wound dehiscence, and peritonitis.

All SAEs in the Surgicel and all SAEs in the MC treatment groups were considered unrelated to study treatment.

Overall, there were no substantial differences noted in SAE incidences among treatment groups, when these SAEs were reviewed within the context of known potential risk of the class of fibrin sealant products.

Reviewer Comment: In Study IG1102, the Sponsor considered an SAEs of pulmonary embolism and deep vein thrombosis as unlikely to be related to study treatment. The

pharmacovigilance reviewer disagrees and considers these SAEs as possibly related in the context of fibrin sealant use, which is well known to be thrombogenic. I agree that the SAEs of pulmonary embolism and deep vein thrombosis could be possibly related.

Adverse Drug Reactions

In the FS Grifols treatment group, 64/500 (12.8%) subjects experienced an adverse drug reaction (ADR) compared with 27/320 (8.4%) subjects in the Surgicel treatment group and 3/57 (5.3%) subjects in the MC group. Of these, 9/500 (1.8%) subjects in the FS Grifols treatment group, 0 subjects in the Surgicel treatment group, and 1/57 (1.8%) subject in the MC group experienced a serious ADR.

No subject in any of the three studies had an AE leading to withdrawal.

8.4.1 Deaths

Thirteen of 500 (2.6%) subjects in the FS Grifols treatment group, 4/320 (1.3%) subjects from the Surgicel treatment group, and no subjects from the MC treatment group died from one or more treatment-emergent SAEs. A summary of deaths in all three clinical trials is shown in Table 36.

Table 35 List of Death Reports in All 3 Studies (Safety Population)

Subject No. / Study	MedDRA Preferred Term	Days After Exposure	Causality by Investigator
FS Grifols (frequency)	13/500 (2.6%)		
1491002 Study IG1 101	Myocardial Infarction	42	Not Related
1321004 Study IG1 101	Death (not otherwise specified)	11	Not Related
4091003 Study IG1 101	Gastrointestinal hemorrhage	35	Not Related
5001032 Study IG1 101	Multi-organ failure	3	Not Related
2072001 Study IG1 102	Respiratory failure Vena cava thrombosis Cardiac arrest	4	Not Related
2072004 Study IG1 102	Hypotension Respiratory failure Hepatic failure	5	Not Related
2312001 Study IG1 102	Septic shock	39	Not Related
2322013 Study IG1 102	Brain injury	23	Not Related
6202008 Study IG1 102	Hepatic necrosis Liver abscess	31	Not Related
6202028 Study IG1 102	Abdominal wound dehiscence Intestinal perforation Wound evisceration Sepsis syndrome	36	Not Related
6212010 Study IG1 102	Deep vein thrombosis	52	Not Related
3073009 Study IG1 103	Cardiac arrest	27	Not Related
4053011 Study IG1 103	Respiratory failure	5	Not Related
Surgicel (frequency)	4/320 (1.3%)		
2042004 Study IG1 102	Multi-organ failure	50	Not Related
4002002 Study IG1 102	Hemorrhage Venous injury Disseminated intravascular coagulation Cardiac arrest	1	Not Related
6222016 Study IG1 102	Hepatic failure	34	Not Related
7203015 Study IG1 103	Death (cause unknown)	45	Not Related

Source: Table 5.3/2.1 of ISS in Module 5.3.5.3

Across all three trials, there was a total of 13 deaths reported with use of FS Grifols (13/500 [2.6%]) as compared to 4/320 [1.3%] in the Surgicel group. Deaths were more frequently reported in study IG1 102; of the 13 deaths reported for FS Grifols, 7 deaths occurred in the IG1 102 trial. The investigator and Applicant assessed all the deaths, including all deaths in the IG1 102 trial, to be unrelated to study treatment. Of the deaths reported in subjects who were treated with FS Grifols, 4 deaths (highlighted in Table 36) occurred less than 1 week of study FS Grifols administration. Safety data for FS Grifols were reviewed within the context of known risks of products in the fibrin sealant class - including thromboses, air embolus, adhesions - and the nature of the surgeries and underlying conditions of the subjects. Although there were more deaths reported with FS Grifols subjects than with the comparator Surgicel, most of the deaths occurred more than one week from the time of exposure, and no discernable pattern was detected from review of the death narratives. Therefore, except for Subject 2072001 (Vena Cava thrombosis occurring 5 days post-exposure), which may be possibly related, the deaths are considered unrelated to the study drug. The safety data do not suggest any new safety concerns following administration during vascular, parenchymal or soft tissue surgery.

Cardiac and thrombotic SAEs occurring after exposure to fibrinogen and thrombin are suspicious for being possibly related, depending on when the event occurred from the time of exposure. Therefore, the case narratives of the four deaths that occurred within one week post exposure to FS Grifols were reviewed to assess for possible relatedness: Subject 500-1032 in study IG1 101, Subject 2072001 in study IG1 102, Subject 2072004 in study IG1 102, and Subject 4053011 in study IG1 103. The narrative reports of these four deaths are summarized below.

1. Subject 500-1032 (study IG1 101): The subject was a 77 year old White male, with an extensive medical history of cardiovascular diseases, chronic chronic obstructive pulmonary disease, hypothyroidism, and possible bronchial tumor, and was on multi-medications to treat these diseases. The subject underwent left aorto-femoral bypass on (b) (6) and was treated with FS Grifols as per protocol. Hypotension and a transient episode of atrial fibrillation were noted on the electrocardiogram after the cross-clamping of the aorta during his surgery. The subject experienced the SAE of multi-organ failure on (b) (6) (Day 2), which resulted in the subject's death on (b) (6) (Day 7). An autopsy noted pulmonary edema, atelectasis, and a lung adenocarcinoma. The investigator considered the SAE of multi-organ failure severe in intensity and not related to the study drug, but related to the subject's underlying chronic obstructive pulmonary disease and ischemic heart disease. The investigator and Applicant assessed the relationship as not related to study drug.

   Reviewer Comment: I agree that the death is not related to study treatment.

2. Subject 2072001 (study IG1 102): The subject was a 61 year old White male with a history of pulmonary embolism, laryngeal cancer, squamous cell carcinoma of the hypopharynx, anaemia, jaundice, dyspnea, dyspepsia, hypokalaemia, and vena cava embolism. His extensive medication for his medical diseases included

fentanyl and hydromorphone. He underwent a right open hepatectomy on (b) (6) and received FS Grifols as per protocol. During surgery, there were some issues of hypotension in the operating room; however, the subject recovered relatively well in the post anesthesia care unit. The subject experienced the SAEs of shock (on (b) (6)), respiratory failure (from (b) (6)), renal failure acute (on (b) (6)), vena cava thrombosis (from (b) (6)), cardiac failure congest (on (b) (6)), and cardiac arrest (on (b) (6)) post-surgery. On (b) (6) (Day 5), the subject continued to worsen, and his family elected comfort care measures only; he was made a do-not-resuscitate (DNR), and expired of cardiac arrest shortly after his wife made the decision to have him terminally extubated. No autopsy was performed. No action was taken with study drug due to the events. The death certificate indicated proximate cause of death was cardiac arrest due to pulmonary failure, renal failure, and clotting disorder. The investigator considered the SAEs of vena cava thrombosis, respiratory failure, renal failure acute, shock, and cardiac arrest as severe in intensity and not related to the study drug. The Sponsor assessed the relationship of the events as not related to study drug.

Reviewer Comment: This subject died from cardiac arrest due to pulmonary failure, renal failure, and clotting disorder five days post hepatectomy. Although it is difficult to assign attribution with certainty, cardiac and thrombotic events are known risks for fibrin sealants if administered intra-vascularly by accident. Dr. Barash, pharmacovigilance reviewer for this BLA, believes that this case of Vena Cava thrombosis, occurring 5 days post-exposure, is possibly related. I agree that this case could be considered possibly related.

3. Subject 2072004 (study IG1 102) was a 75-year old Asian male who underwent a left hepatic lobectomy with a bloc resection of his left hemidiaphragm and microwave ablation of 1.5 centimeters hepatic segment 8 tumor on August 19, 2014. The subject's medical/surgical histories included: back pain, edema, hepatocellular carcinoma, hypertension, lung cancer, abdominal pain, pulmonary tuberculosis, gastric ulcer, anemia, blood creatinine increased, renal cyst, pleural effusion, gastric ulcer surgery, and lung resection. The subject received FS Grifols on (b) (6) (Day 0), as per study protocol. The subject experienced the SAEs of hypotension on (b) (6) (Day 0); hepatic failure on (b) (6) (Day 3); respiratory failure on (b) (6) (Day 3); sepsis on (b) (6) (Day 3); cardiac failure congestive on (b) (6) (Day 3); renal failure acute on (b) (6) (Day 3). On (b) (6) (Day 3), the subject's hemoglobin levels dropped significantly and continued to drop from 10.0 g/dL at 05:54 hours, 9.0 g/dL at 13:37 hours, and 5.6 g/dL. He received a transfusion of red blood cells. On (b) (6) (Day 4). The numerous diagnostic procedures performed did not identify the source of the bleed. There was no evidence of leak or bleeding at the location where the left hepatic duct had been transected and over sewn. The subject's family elected comfort measures only due to the subject's poor prognosis, and he was declared dead hours later.

The death certificate indicated proximate cause of death was hepatic failure due to hepatocellular carcinoma. The investigator considered the SAEs of hypotension, hepatic failure, respiratory failure, sepsis, cardiac failure congestive, acute renal failure, and hemorrhagic anemia to be severe in intensity and not related to study drug.

Reviewer Comment: The cause of death for this subject appears to be hepatic failure due to hepatocellular carcinoma. I believe this death is unrelated to study treatment.

4. Subject 405-3011 was a 69 year old White male who underwent radical cystoprostatectomy with pelvic lymph node dissection, right nephrectomy, ileal conduit construction for urinary diversion, and incisional hernia repairs (b) (6) and received FS Grifols as per protocol. Relevant medical and surgical histories included: renal atrophy, hyperparathyroidism, osteoarthritis, chronic obstructive pulmonary disease (COPD), arteriosclerosis, congestive heart failure, coronary artery disease (CAD), bladder neoplasm (HG T2 disease), myocardial infarction, gallbladder disorder (not otherwise specified [NOS]), biliary tract disorder (NOS), type 2 diabetes mellitus, depression, obesity, peripheral vascular disorder, hypertension, stage 3 chronic kidney disease (CKD), anemia of chronic disease, and bypass surgery. He was on numerous medications to treat his diseases. Postoperative notes estimated a 1500 milliliter blood/fluid loss during the study procedure and he was administered 5 liters of lactated ringer solution, 1 liter of 5% albumin, and was transfused with 3 units of packed red blood cells. Overall, there were no apparent intraoperative complications. The subject was left intubated and taken to the post-anesthesia care unit in stable condition where he was taken to the intensive care unit for overnight care. The subject had experienced an elevation in creatinine (result not provided) on (b) (6) and subsequently had worsening renal failure, thought to be due to acute tubular necrosis, requiring dialysis. On (b) (6), and (b) (6), the subject experienced acute myocardial infarction. Relevant laboratory test results or treatment were not provided. On (b) (6) (Day 4), at an unknown time, the subject experienced respiratory failure. Subsequently on (b) (6), the subject became bradycardic and asystolic. Cardiopulmonary resuscitation was initiated, but was unsuccessful. No autopsy was performed therefore no death certificate was available. The investigator considered the events of respiratory failure, atrial fibrillation, renal failure, and the event of acute myocardial infarction not related to study drug.

Reviewer Comment: Although this subject's postoperative medical complications included cardiac SAEs leading to asystole, there is insufficient information available to attribute the many serious post-operative complications to study treatment with any certainty. Therefore, I do not dispute with the investigator's assessment that this death is unrelated.

8.4.2 Nonfatal Serious Adverse Events

Of the SAEs in the FS Grifols group (72/81 subjects), the majority were considered unrelated to study treatment by investigators in all except 9 subjects (9/81 subjects). In the FS Grifols group, 5 subjects had SAEs that were considered unlikely related; these included postoperative wound infection, wound infection, abdominal abscess, deep vein thromboses, pulmonary embolism, postprocedural bile leak, and liver abscess. In the FS Grifols group, 4 subjects had SAEs that were considered possibly related to the study treatment: cellulitis, parvovirus B19 (B19V) test positive (determined not to be treatment-emergent viral infection.), abdominal wound dehiscence, and peritonitis.

All SAEs in the Surgicel and all SAEs in the MC treatment groups were considered unrelated to study treatment. Overall, there were no substantial differences in SAE incidences were noted among treatment groups.

Reviewer Comment: In Study IG1102, the Sponsor considered an SAEs of pulmonary embolism and deep vein thrombosis as unlikely to be related to study treatment. The pharmacovigilance reviewer disagrees and considers these SAEs as possibly related in the context of fibrin sealant use, which is well known to be thrombogenic. I agree that the SAEs of pulmonary embolism and deep vein thrombosis could be related.

8.4.3 Study Dropouts/Discontinuations

No subjects discontinued the study due to an AE in any treatment group in any of the three trials.

8.4.4 Common Adverse Events

The most common TEAEs reported for at least 5% of subjects within a treatment group in the three treatment groups were similar:

- FS Grifols: procedural pain (41.8%), nausea (13.4%), and pyrexia (10%)
- Surgicel: procedural pain (45.9%), nausea (17.5%), anemia (12.5%), pyrexia (10.9%), constipation (10.6%), and procedural nausea (10.0%)
- MC: procedural pain (36.8%) and pyrexia (10.5%)

No substantial differences in TEAE incidences were noted among treatment groups.

8.4.5 Clinical Test Results

Viral NAT or viral serology testing did not detect any treatment-emergent viral infection in all 3 clinical trials.

8.4.8 Adverse Events of Special Interest

The thrombogenic nature of fibrin sealant products makes thromboembolic events – deep vein thrombosis, pulmonary embolism, and myocardial infraction – of special interest.

The pooled cases of deep vein thrombosis, pulmonary embolism, and myocardial infraction across the three trials are shown in Table 37. All cases were considered unrelated by investigators.

Overall, the number of thromboembolic events reported across the three trials were relatively small. Additionally, the review of these events for FS Grifols were performed within 1) the context of the known thromboembolic risks of the fibrin sealant product class, 2) the fact that the comparators inheren y carry lower risks: manual compression only or Surgicel, a hemostatic pad applied topically as compared to the dripping or spraying route of administration of the FS Grifols liquid solution, and 3) the nature of the surgeries and underlying conditions of the subjects. These factors are taken into consideration in concluding that the safety data for FS Grifols do not suggest any new safety concerns following administration during vascular, parenchymal or soft tissue surgery.

Table 36. Severe Treatment-Emergent Adverse Events of Interest by Selected Preferred Terms (IG1101, IG1102 and IG1103 pooled Safety Population)*

Preferred Term	FS Grifols N=500 n (%)	Surgicel N=320 n (%)	Manual Compression N=57 n (%)
Deep vein thrombosis	2 (0.4)	1 (0.3)	0
Pulmonary embolism	0	0	0
Myocardial infarction	2 (0.4)	0	1 (1.8)

* For each preferred term, subjects are counted only once.

8.5 Additional Safety Evaluations

8.5.8 Immunogenicity (Safety)

No immunogenicity occurred from the treatment with FS Grifols.

Two specimens were found to be positive for antibodies to human thrombin: baseline and Day 14 specimens from 1 subject in the FS Grifols treatment group, with antibody titers of 9363 and 11739, respectively, indicating relatively similar levels. Therefore, no immunogenicity response was observed in patients treated with FS Grifols in the clinical trials.

8.6 Safety Conclusions

The results from all three studies, IG1101, IG1102, and IG1103, demonstrated that FS Grifols was reasonably safe and generally well tolerated as a local adjunct hemostatic agent in various surgery types.

Fibrin Sealants have been available and in use for many years, and are generally considered to be a safe adjunct to hemostasis in surgical procedures. Safety data for FS Grifols were reviewed within the context of known risks of products in the fibrin sealant class, including thromboses, air embolus, adhesions. The safety data do not suggest any

new safety concerns following administration during vascular, parenchymal or soft tissue surgery. Although there were more deaths reported with FS Grifols subjects than with the comparator Surgicel, many of the deaths occurred more than one week from the time of exposure, and no discernable pattern was detected from review of the death narratives. Therefore, except for Subject 2072001 (Vena Cava thrombosis occurring 5 days post-exposure), which may be possibly related, the deaths are considered unrelated to the study drug. The available data do not suggest a safety signal that would trigger a Risk Evaluation and Mitigation Strategy (REMS). The pharmacovigilance review team agrees with the Applicant's proposed pharmacovigilance plan for adverse event reporting as required under 21 CFR 600.80. Also, the Applicant has agreed to conduct a postmarketing prospective, controlled pediatric trial (study IG1 405) that will further evaluate safety (and efficacy), comparing FS Grifols to another frozen 2-component (fibrinogen and thrombin) fibrin sealant (Evicel) as active control. This trial will provide additional post-marketing safety data.

In addition, the Applicant has agreed to conduct a new human factors study (IG-PETC-000430_ING) as a substudy of the pediatric trial IG1 405 to address deficiencies that were identified from the initial human factors study completed in February 2017. Specifically, in the initial study, participants commented that the outer pouch packaging was difficult to open completely and the Instructions for Use for product thawing time and cannula connection were unclear and were not easy to understand. Because the Applicant has already committed to conduct the (deferred) prospective post-marketing pediatric clinical trial, and the BLA review team did not want to delay an action on this application, the review team reasoned that it would be acceptable to incorporate the human factors study as a part (substudy) of the deferred pediatric trial. This modification is not expected to substantively impact the pediatric trial design or risk to subjects. The Applicant has agreed to conduct the new human factor at the same centers participating in the planned pediatric clinical trial in the United States.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There were no reproduction or pregnancy studies.

9.1.2 Use During Lactation

There were no studies on the effects on lactation.

9.1.3 Pediatric Use and PREA Considerations

Children were eligible to enroll in each of the three Phase 3 trials: vascular surgery (study IG1 101; n=225), parenchymous surgery (study IG1 102; n=325) or soft tissue surgery (study IG1 103; n=327). However, there was a large imbalance in the number of adult vs. the number pediatric subjects enrolled. No pediatric subject was enrolled in study IG1 101: low pediatric enrollment was expected, based on the nature of the

vascular surgical procedures. A total of 23 pediatric subjects were enrolled in Preliminary Part I of studies IG1 102 and IG1 103 and only one pediatric subject was enrolled in Primary Part II of study IG1 103.

There were two pediatric subjects in the FS Grifols treatment group who had SAEs. One subject had 2 SAEs (clostridium difficile colitis and febrile neutropenia) and another subject had 1 SAE (laryngospasm). These SAEs were considered unrelated to FS Grifols by the investigator and the subjects recovered. There were 3 pediatric subjects with SAEs in the Surgicel treatment group. One subject had neuralgia, the second subject had enterovirus infection, febrile neutropenia, and rhinovirus infection, and the third subject had urinary tract infection. These SAEs were considered unrelated to Surgicel by the investigator and the subjects recovered (Table 5.3/2.8 of ISS in Module 5.3.5.3).

Although no specific safety signals were identified in the pediatric population, no conclusions can be drawn based on the small number of children enrolled. Overall, the safety and efficacy of FS Grifols as an adjunct to hemostasis during surgery in pediatric subjects was not sufficiently evaluated, but based on the limited pediatric safety data, there was no pattern suggesting a unique safety concern for the pediatric subjects. Therefore, additional safety and effectiveness data are needed.

PREA Considerations

Under the Pediatric Research Equity Act (PREA; 21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and efficacy of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The Applicant has submitted an initial Pediatric Study Plan (iPSP) and a pediatric clinical protocol (IG1 405) under IND 14986. The iPSP and pediatric protocol were review and approved on November 1, 2016. There is no substantive modification to the pediatric protocol included in the BLA submission. In the IG1 405 trial, the different types of surgery (parenchymous and soft tissue) will be evaluated in a single trial, with the stipulation that at least 50% of surgeries must be hepatic. Because there is a low prevalence of pediatric subjects undergoing vascular surgery, it was not considered feasible to include vascular surgery in the planned pediatric trial. The pediatric trial is summarized below.

IG1 405 Title: “A Prospective, Randomized, Active-Controlled, Single-blind, Parallel Group Clinical Trial to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis during Surgery in Paediatric Subjects”

The multicenter Phase 3b trial will enroll a total of 172 subjects, randomized to a 1:1 ratio to FS Grifols vs. control (Evicel) as the comparator group. Evicel is a 2-component (fibrinogen and thrombin) fibrin sealant solution, approved for topical use as an adjunct to hemostasis during surgery. The study is designed to demonstrate non-inferiority if

lower limit of the 2-sided 95% confidence interval (CI) exceeds 0.8. The key study entrance criteria are:

Pre-operative:

1. <18 years of age
2. Requires an elective (non-emergent), open (non-laparoscopic), pelvic, abdominal, or thoracic (non-cardiac) surgical procedure

Intra-operative:

1. Presence of an appropriate target bleeding site (TBS) identified by the investigator surgeon
2. TBS is of Grade 1 (mild) or Grade 2 (moderate) bleeding intensity, rated using a 5-point validated bleeding severity scale

The age groups for the study are defined in Table 38.

Table 37. Study IG1 405: Pediatric Age Groups

Age Group	Number of Subjects Planned
Adolescents (12 to 17 years)	100
Children (2 to 11 years)	50
Infants and toddlers (28 days to 23 months)	16
Preterm (up to gestational age <37 weeks) and term newborn infants (0 to 27 days)	6
The first 24 subjects to be enrolled in the study will be adolescents (age range 12 to 17 years).	

Assessments will be performed at baseline, Day 1, Day 4 and Day 30. Intraoperatively, hemostasis will be evaluated at T4 (primary efficacy endpoint) from start, and at T7 and T10 as secondary efficacy endpoints. Safety will be monitored by AEs, SAEs, ADRs, ARs, discontinuations due to AEs, clinical laboratory panels, physical examinations, and vital signs.

The timelines for the pediatric study are:

Study Initiation: January 2018
Study completion: June 2023
The Clinical Study Report (CSR): June 2024

The Applicant's deferral request for the pediatric study was approved at the September 6, 2017 meeting of the Pedatric Research Committee (PeRC).

The new human factors study, IG-PETC-000430_ING will be conducted as a subpart of this pediatric trial.

9.1.4 Immunocompromised Patients

There were no studies in immunocompromised patients.

9.1.5 Geriatric Use

The TEAE incidence in the subgroup of elderly subjects (≥65 years of age) was evaluated as part of the analysis of age subgroups. Treatment-emergent AEs were evaluated in 288 elderly subjects, with 172 receiving FS Grifols, 91 receiving Surgicel, and 25 receiving MC. The overall TEAE incidence was 143/172 (83.1%) in the FS Grifols treatment group, 77/91 (84.6%) in the Surgicel treatment group, and 20/25 (80.0%) in the MC treatment group.

The incidences of the most frequently reported TEAEs were generally similar between the FS Grifols and Surgicel treatment groups. Several of the most frequently reported TEAEs in the FS Grifols and Surgicel treatment groups were reported less frequently in the MC treatment group: nausea, peripheral edema, incision site pain, hypokalemia, ileus, and atelectasis, although no conclusion about these differences can be made because of the small number of subjects in the MC treatment group.

The incidences of the most commonly reported TEAEs in the elderly subpopulation in the 3 studies were similar to the incidences for the total Safety Population. There were no substantial differences in TEAE incidences found among treatment groups in the elderly subpopulation.

Most SAEs in elderly subjects were reported in only 1 or 2 subjects within a treatment group. No clinically meaningful differences in the incidences of SAEs were noted among treatment groups.

Overall, there was no pattern suggesting a unique safety concern for the elderly subjects. FS Grifols was safe and well tolerated in elderly subjects.

10. CONCLUSIONS

FS Grifols has been demonstrated to be effective as an adjunct to hemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. There do not appear to be safety concerns for the FS Grifols product. Approval is recommended.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Risk-Benefit considerations are summarized in Table 39.

11.2 Risk-Benefit Summary and Assessment

The benefit-risk assessment is favorable.

11.4 Recommendations of Regulatory Actions

I recommend that STN 125640/0 be approved.

11.5 Labeling Review and Recommendations

See the approved package insert document.

11.6 Recommendations on postmarketing Actions

The Applicant has agreed to conduct a deferred postmarketing pediatric trial that will include a human factors substudy. No other postmarketing commitments or requirements are recommended.

Table 39. Risk-Benefit Considerati

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Surgery may create large areas of bleeding that must be addressed before surgical closure.	• FS Grifols has demonstrated safety and efficacy for use as an adjunct to hemostasis in three types of surgery: vascular, hepatic, and soft tissue dissection.
Unmet Medical Need	• There are several fibrin sealant products available for use as an adjunct to hemostasis in various surgical settings.	• There is no unmet medical need.
Clinical Benefit	• The indication for use as an adjunct to hemostasis in adult surgery is supported by the results of the IND study IG1 101, IG1 102 and IG1 103. • Fibrin sealant products, when used as adjuncts to hemostasis, have not been able to demonstrate a traditional clinical benefit based on mortality or morbidity endpoints. For this reason, CBER decided to accept the surrogate endpoints of time-to-hemostasis or percent of subjects achieving hemostasis at a defined time point as acceptable primary endpoints for licensure.	• FS Grifols has demonstrated clinical benefit for use as an adjunct to hemostasis in adult surgery, per the primary endpoint, time-to-hemostasis at 4 minutes.
Risk	• FS Grifols contains human thrombin and human fibrinogen, and therefore, there is a theoretical risk for perturbation of the coagulation system. • Administration by the FS Grifols drip or spray device carries a potential risk of air embolism if used inappropriately.	• All the evidence indicates that the risk associated with the use of FS Grifols as an adjunct to hemostasis is minor. There is no evidence of an increased risk for thrombogenicity or increased immunogenicity, however, continued surveillance for these events is advisable.
Risk Management	• Thromboembolic events, disseminated intravascular coagulation, and anaphylactic reactions may occur, if human plasma-derived fibrin sealant is unintentionally applied intravascularly. • Potential for air embolism	• Routine monitoring could detect thromboembolic and allergic adverse events. • Labeling and routine monitoring could prevent or detect potential air embolism problems.