Official 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

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[redacted]	Owner	11-Nov-2021 08:06:01

Clinical Study Protocol

Protocol 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
Investigational Product:	Fibrin Sealant Grifols (FS Grifols)
Sponsor's Name and Address:	Instituto Grifols, S.A. Can Guasch, 2 08150 Parets del Vallès Barcelona, Spain
Sponsor's Telephone Number:	[redacted] MD [redacted]
Study Number/Protocol Version Number/Date:	IG1405/Refer to left margin
EUDRACT Number:	2016-004489-24
IND Numbers:	14986
Development Phase:	Phase 3b
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Confidentiality Statement:

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Protocol Version History

Protocol Version	Date of Approval
5.0 Amendment 4 + Integrated Protocol	See left margin
4.0 Amendment 3 + Integrated Protocol	02 November 2021
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Amendment 4

The protocol for IG1405 (Version 3.0, dated 02 November 2021) has been amended as Protocol Amendment 4, Version 5.0. See Appendix 2 for a summary of changes for Protocol Amendment 4.

PROTOCOL SYNOPSIS

Title of Study: 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

Study Number: IG1405

Phase: 3b

Study Objectives:

The objectives of this study are to evaluate the efficacy and safety of Fibrin Sealant Grifols (FS Grifols) as an adjunct to achieve hemostasis during surgery in pediatric subjects.

Primary Efficacy Objective

- To evaluate if FS Grifols is non-inferior to EVICEL® in terms of the proportion of subjects achieving hemostasis at the target bleeding site (TBS) by 4 minutes (T_4) from the start of treatment application (T_{Start}) with no occurrence of rebleeding until the completion of the surgical closure by layers of the exposed surgical field containing the TBS ($T_{Closure}$).

Secondary Efficacy Objectives

- To determine the cumulative proportion of subjects achieving hemostasis at the TBS by the defined observation time points of 7 minutes (T_7) and 10 minutes (T_{10}) from T_{Start}
- To determine prevalence of treatment failures

Exploratory Efficacy Objectives

- To determine the proportion of subjects achieving at least 1 point decrease in bleeding intensity according to the 5-point validated bleeding severity scale by the defined observation time points of T_4, T_7, and T_{10}
- To determine the mean change from baseline in bleeding intensity according to the 5-point validated bleeding severity scale at the defined observation time points of T_4, T_7, and T_{10}

Safety Objective

To evaluate the safety and tolerability of FS Grifols in pediatric subjects undergoing surgery

Overall Study Design and Description:

This is a prospective, randomized, active-controlled, single-blind, parallel group clinical trial to evaluate the safety and efficacy of FS Grifols as an adjunct to hemostasis during surgery in pediatric subjects.

Pediatric subjects (<18 years of age) requiring an elective (non-emergent), open (non-laparoscopic), pelvic, abdominal, or thoracic (non-cardiac) surgical procedure, wherein a TBS is identified, and a topical hemostatic agent is indicated, will be eligible to participate in the clinical trial.

Preterm (up to gestational age <37 weeks) and term newborn infants (0 to 27 days) requiring either an elective (non-emergent) or an emergency, open (non-laparoscopic) pelvic, abdominal or thoracic (non-cardiac) surgical procedure wherein a TBS is identified, and a topical hemostatic agent is indicated, will be eligible to participate in the clinical trial. The study treatments will be applied on the cut parenchymous surface of a solid organ (i.e., liver) and in soft tissue (i.e., fat, muscle, or connective tissue).

A specific bleeding site will be defined as the TBS when it is determined by the investigator (the surgeon) that control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) is ineffective or impractical and requires an adjunct treatment to achieve hemostasis.

When the TBS is identified, the investigator will record the precise anatomical location of the TBS, rate the intensity of the bleeding at the TBS (Grade 1-4 according to the 5-point validated bleeding severity scale), and record the size of the approximate bleeding surface, (small, medium, and large). For soft tissue surgery only, the investigator will also record the type of soft tissue (i.e., fat, muscle, or connective tissue). In this clinical trial, only subjects with a TBS with bleeding of Grade 1 (mild) or Grade 2 (moderate) intensity will be enrolled.

Subjects will be randomly allocated in a 1:1 ratio into 1 of 2 treatment groups: FS Grifols or EVICEL. The first 24 subjects to be enrolled in the study will be adolescents (age range 12 to 17 years). The term “enrolled” implies that the subject was actually randomized to and treated with either the FS Grifols or EVICEL. Enrollment will be monitored by surgery type to ensure approximately 50% of the surgical procedures are hepatic.

Number of Subjects Planned:

Approximately 172 subjects (86 subjects in the FS Grifols treatment group and 86 subjects in the EVICEL treatment group) are planned to be enrolled. In case any of the age subgroups mentioned below is underrepresented when the target of 172 enrolled subjects is met, the sponsor may allow over-enrollment of a few additional subjects (i.e., not more than 10 additional subjects) in the specific age subgroup.

The approximate number of subjects planned to be randomized according to age range will be as follows:

- Adolescents (12 to 17 years): up to 100, and not less than 50
- Children (2 to 11 years): up to 100, and not less than 50
- Infants and toddlers (28 days to 23 months): up to 100 and not less than 16
- Preterm (up to gestational age <37 weeks) and term newborn infants (0 to 27 days): up to 10

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

A subject must meet all the following inclusion criteria to be eligible for participation in this study.

Pre-operative:

1. Is less than 18 years of age.
2. Requires an elective (non-emergent), open (non-laparoscopic), pelvic, abdominal, or thoracic (non-cardiac) surgical procedure. Or is a preterm (up to gestational age <37 weeks) and term newborn infants (0 to 27 days), who may require either an elective (non-emergent) or an emergency, open (non-laparoscopic) pelvic, abdominal or thoracic (non-cardiac) surgical procedure.
3. Subject and/or subject's legal guardian is willing to give permission for the subject to participate in the clinical trial and provide written informed consent for the subject. In addition, assent must be obtained from pediatric subjects who possess the intellectual and emotional ability to comprehend the concepts involved in the clinical trial.

Intra-operative:

4. Presence of an appropriate (as defined in inclusion criterion 5) parenchymous or soft tissue TBS identified intra-operatively by the investigator (the surgeon).
5. TBS has Grade 1 (mild) or Grade 2 (moderate) bleeding intensity according to the investigator's (the surgeon's) judgment. The intensity of the bleeding at the TBS will be rated by the investigator using the 5-point validated bleeding severity scale.

Exclusion Criteria

A subject meeting any of the following exclusion criteria is NOT eligible for participation in the study.

Pre-operative:

1. Subjects admitted for trauma surgery.
1. Subjects unwilling to receive blood products.
2. Subjects with known history of severe (e.g., anaphylactic) reaction to blood products.
3. Subjects with known history of intolerance to any of the components of the investigational product (IP).
4. Female subjects who are pregnant, breastfeeding or, if of child-bearing potential (i.e., adolescent), unwilling to practice a highly effective method of contraception (e.g., oral, injectable, or implanted hormonal methods of contraception, placement of an intrauterine device or intrauterine system, condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilization, or true abstinence) throughout the study.

True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.).

5. Subjects previously enrolled in a clinical trial with FS Grifols.
6. Subjects currently participating, or during the study is planned to participate, in any other investigational device or medicinal product study.

Intra-operative:

7. An appropriate parenchymous or soft tissue TBS (as defined in exclusion criteria 8 and 9) cannot be identified intra-operatively by the investigator (the surgeon).
8. The TBS has Grade 3 (severe) bleeding according to the investigator's (the surgeon's) judgment that cannot be controlled with conventional surgical techniques to Grade 1 or Grade 2 bleeding. The intensity of the bleeding at the TBS will be rated by the investigator using the 5-point validated bleeding severity scale.
9. The TBS is in an actively infected surgical field.
10. Occurrence of major intra-operative complications that require resuscitation or deviation from the planned surgical procedure.
11. Application of any topical hemostatic agent on the resection surface of parenchyma or soft tissue prior to application of the IP.

Investigational Product, Dose and Mode of Administration

FS Grifols is a frozen, sterile, 2-component fibrin sealant (FS) solution obtained from human plasma pools. FS Grifols consists of human fibrinogen (component 1, 80 mg/mL solution) and human thrombin (component 2, 500 IU/mL solution) solutions filled in syringes and assembled on a syringe holder. The solution is applied topically via drip or spray application.

Duration of Treatment:

The total time of subject's participation in the study is expected to be no longer than 2 months from the Screening Visit to the Post-operative Day 30 (± 7 days) Visit.

Reference Therapy, Dose and Mode of Administration

EVICEL (Omrix Biopharmaceuticals N.V, Diegem, Belgium) is manufactured from pooled human plasma. EVICEL is provided as a single use kit consisting of 2 packages: 1 package containing 1 vial of Biological Active Component 2, a frozen, sterile solution consisting mainly of a concentrate of human fibrinogen (55-85 mg/mL) and 1 vial of thrombin (800-1200 IU/mL); and 1 package containing a sterile spray application device. The 2 components should be mixed and applied topically via drip or spray application.

Key Study Variables:

Primary Efficacy Variable:

The primary efficacy variable is the proportion of subjects achieving hemostasis (binary decision: hemostatic response, Grade 0 = Yes/Grade ≥1 = No) at the TBS by T_4 without occurrence of rebleeding or reapplication of study treatment after T_4 and until the time of completion of the surgical closure by layers of the exposed surgical field containing the TBS ($T_{Closure}$), and without Grade 3 or 4 bleeding or use of alternative hemostatic treatment after T_{Start} and until $T_{Closure}$.

Secondary Efficacy Variables:

The secondary efficacy variables are:

- The cumulative proportion of subjects achieving hemostasis at the TBS by the time points of T_7 and T_{10} defined as an absence/cessation of bleeding (Grade 0) at the TBS by that time point without occurrence of rebleeding, Grade 3 or 4 bleeding, use of alternative hemostatic treatment, and reapplication of study treatment after T_4 and until $T_{Closure}$.
- Prevalence of treatment failures including:
  - Persistent bleeding at the TBS beyond T_4
  - Grade 3 or 4 breakthrough bleeding from the TBS that jeopardizes subject safety according to the investigator's judgment at any moment during the 10-minute observational period and until $T_{Closure}$
  - Use of alternative hemostatic treatments or maneuvers (other than the study treatment) at the TBS during the 10-minute observational period and until $T_{Closure}$ or use of study treatment at the TBS beyond T_4 and until $T_{Closure}$
  - Rebleeding (Grade ≥1) at the TBS after the assessment of the primary efficacy endpoint at T_4 and until $T_{Closure}$

Exploratory Efficacy Variables:

- The proportion of subjects achieving at least 1 point decrease in bleeding intensity according to the 5-point validated bleeding severity scale by the defined observation time points of T_4, T_7, and T_{10}
- The mean change from baseline in bleeding intensity according to the 5-point validated bleeding severity scale at the defined observation time points of T_4, T_7, and T_{10}

Safety:

- Adverse events (AEs) including serious adverse events (SAEs), suspected adverse drug reactions (ADRs)/adverse reactions (ARs), and discontinuations due to AEs
- Clinical laboratory panels (i.e., hematology, serum clinical chemistry, and coagulation panel)
- Physical examination
- Vital signs

Study Assessments and Procedures:

This study consists of a Screening Visit, Baseline Visit, Surgical Visit, and Post-Operative Visits.

Screening Visit (within 21 days prior to surgical procedure)

Following signature of the Informed Consent Form (ICF), screening procedures will be performed. The Screening Visit assessments and activities will include: allocation of subject number, adding subject's data into the Screening Log, documentation of demographics, medical and surgical history for the last 12 months, life time history for the use of topical hemostats and bleeding abnormalities (including inquiry into previous surgery and trauma episodes and the family history), medications that the subject is taking or has taken within the last 3 months (including transfusion of blood or any blood-derived product), review of inclusion/exclusion criteria to confirm subject eligibility.

If suitable due to logistic reasons, procedures scheduled at the Screening Visit may be performed during the Baseline Assessments Visit (i.e., within 24 hours prior to the surgical procedure). In this case, the Screening Visit will be combined with the Baseline Assessments Visit. Assessments required during both visits (Screening and Baseline) must be performed.

Baseline Assessment Visit (within 24 hours prior to surgical procedure)

Baseline assessments will be performed within 24 hours prior to the scheduled surgery (i.e., the baseline assessments can be performed the same day of the surgery). At this visit, confirmation of existing and recording of any new events or changes in the Screening Visit assessments, confirmation of bleeding abnormalities and topical hemostat use, recording of height and weight, physical assessment, recording of vital signs, pregnancy test for women of childbearing potential, coagulation panel, hematology, serum clinical chemistry, assessment of AEs, and review of inclusion/exclusion criteria to confirm subject eligibility will be performed. Once all these assessments have been completed and confirmed, the subject will be randomized.

Surgical Procedure Day 1

Prior to surgery, FS Grifols or EVICEL will be prepared. Confirmation of existing and recording of any new medications (not including gaseous anesthetics), or changes in medications administered to the subject since Baseline Visit assessments (including any blood product administered to the subject) and the use of anticoagulants and any neutralizing agent should also be recorded in detail including dose and time of administration.

Vital signs will be recorded immediately prior to skin incision to expose the surgical field and AEs will be assessed. During surgery, the surgeon will perform the surgical intervention according to his/her standards as well as the respective institution's standards. Complete details of the conventional surgical techniques used in the surgical procedure will be recorded. At the time of surgery, the following will be considered:

- When there is generalized bleeding from the cut parenchymous surface of the solid organ (i.e., liver), or from the cut soft tissue (i.e., fat, muscle, or connective tissue), persisting after conventional resection procedure or dissection, respectively, and primary control of arterial and venous bleeding by sutures, ligations, clips, vascular stapler, point electro-cautery or focal radio-frequency ablation, and it is determined by the investigator (the surgeon) that the control of bleeding by previously mentioned conventional surgical techniques is ineffective or impractical and requires an adjunct treatment to achieve hemostasis, this specific bleeding site will be identified and defined as the TBS.
- The intensity of the bleeding at the TBS will be rated by the investigator (surgeon) using the 5-point validated bleeding severity scale. If the nature of the bleeding from the parenchymous or soft tissue is Grade 3 (severe), the surgeon may use standard conventional surgical techniques (e.g., cautery, sutures, clips, or ligation) again in order to control the bleeding. If the nature of the bleeding becomes Grade 1 (mild) or Grade 2 (moderate) once those primary hemostatic measures are taken, the subject may be considered eligible for enrollment. If the nature of the bleeding becomes or remains Grade 3 or Grade 4, the subject should not be enrolled into the study and should be considered a screen failure. In this case, the surgeon may use all necessary measures at his/her discretion as deemed necessary (FS Grifols, EVICEL, or other plasma-derived hemostatic agents cannot be used for this purpose). The hemostatic treatment received will be recorded in the subject's source documents and electronic case report form.

- Upon the identification of a TBS with Grade 1 or 2 (mild or moderate) bleeding, the subject will be deemed eligible for enrollment into the study.
- The approximate size of the TBS will be rated by the investigator (the surgeon) using a 3-point scale (small, medium, and large) and recorded.
- The anatomical location of the TBS will be recorded.
- For soft tissue surgery only, the type of soft tissue will be recorded (i.e., fat, muscle, or connective tissue).
- If the subject presents with multiple appropriate bleeding sites, the TBS will be the larger or more clinically relevant site, as judged by the investigator (surgeon).
- If the subject does not have an identifiable TBS, the subject should be withdrawn from the study. The subject will be considered a screen failure as they do not meet the intra-operative criteria and will be treated accordingly.
- The TBS will be the only site to be evaluated for hemostasis in this study.

At the time of surgery, the following will be performed:

- Verification of intra-operative inclusion and exclusion criteria.
- Recording of vital signs will be measured and recorded at the time of TBS identification, 30 minutes after T_{Start} (excluding temperature), and every 30 minutes until $T_{Closure}$ (excluding temperature).

- Investigational product application: FS Grifols or EVICEL.
- Assessment of AEs.
- Record $T_{Closure}$, $T_{Completion}$, and treatment failures.

The following cases will be considered treatment failures:

- Persistent bleeding at the TBS beyond the 4-minute time point.
- Grade 3 or 4 breakthrough bleeding at the TBS that jeopardizes subject safety according to the investigator's judgment at any moment during the 10- minute observational period and until $T_{Closure}$.
- Use of alternative hemostatic treatments or maneuvers (other than the study treatment) at the TBS during the 10-minute observational period and until $T_{Closure}$, or use of allocated study treatment (FS Grifols or EVICEL) at the TBS beyond the assessment of the primary efficacy endpoint at T_4 and until $T_{Closure}$.
- Rebleeding (Grade $\geq$1) at the TBS after the assessment of the primary efficacy endpoint at T_4 and until $T_{Closure}$.

Observational Period

An observational period of 10 minutes will occur following T_{Start} to determine whether hemostasis has been achieved at the TBS. During this time, vital signs will be assessed at 5 minutes after T_{Start} and confirmation of existing and recording of any new medications except gaseous anesthetics, or changes in medications administered to the subject since the last assessment (including any blood products administered to the subject), AEs, and treatment failures will be recorded.

- Assessment of Hemostasis will be performed

  Hemostasis at the TBS will be assessed by the investigator (surgeon) at T_4, T_7, and T_{10}. Hemostasis is defined as Grade 0 bleeding at the TBS according to the investigator's (the surgeon's) judgment, so that the surgical closure of the exposed field could begin.

The following will be recorded: $T_{Closure}$, $T_{Completion}$, AEs, and treatment failures.

Post-Operative Day 4 (± 2 days)

At this study visit, concomitant medications assessment, physical assessment, recording of vital signs, clinical laboratory evaluations, and AE assessment will be performed.

Post-Operative Day 30 (± 7 days) – Final Study Visit

At this study visit, concomitant medications assessment, physical assessment, and AE assessment including any potential bleeding related complication will be performed.

Statistical Methods:

Four analysis populations will be defined for efficacy and safety analyses as follows:

The Intent-to-Treat (ITT) population will include all subjects who are randomized, regardless of meeting intra-operative enrollment criteria and regardless of whether the IP was administered to the subject.

The Modified ITT (mITT) population will include all subjects in the ITT population who meet the intra-operative enrollment criteria, and thus treated with any amount of IP.

The Per Protocol (PP) population will include all subjects in the mITT population who do not have any major protocol deviations (to be determined at a data review meeting prior to unblinding) which could impact the primary efficacy endpoint.

The Safety population will include all subjects who receive any amount of IP.

Primary Efficacy Analyses

The efficacy analyses will be performed using the mITT population. Additionally, the primary efficacy endpoint will be also analyzed using the PP population (if different from the mITT population). For sensitivity analysis, the primary efficacy endpoint will be analyzed using ITT population. For subjects in both treatment groups in the ITT population who do not meet the intra-operative criteria and do not receive the study treatment, they will be deemed as not achieving hemostasis for the primary efficacy endpoint.

The primary efficacy endpoint of hemostasis at TBS by T_4 will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by type of surgery (i.e., parenchymous versus soft tissue surgery).The ratio of the proportion of subjects meeting the primary efficacy endpoint in the 2 treatment groups (FS Grifols relative to EVICEL) and its 2-sided asymptotic 95% confidence interval (CI) will be provided. The non-inferiority will be deemed to have been demonstrated if the lower limit of the 95% CI exceeds 0.8. After the non-inferiority of FS Grifols to EVICEL is established, its superiority may be additionally claimed if the 95% CI for the ratio is entirely above 1.

Secondary Efficacy Analyses

Secondary efficacy endpoints will be analyzed by similar methods at other individual assessment time points (i.e., T_7 and T_{10} minutes).

Exploratory Efficacy Analyses

Exploratory efficacy endpoints will be descriptively summarized by treatment group. The proportion of subjects achieving at least 1 point decrease in bleeding intensity according to the 5-point validated bleeding severity scale by each of the defined observation time points (i.e., T_4, T_7, and T_{10}) will be analyzed using CMH test stratified by type of surgery (i.e., hepatic versus soft tissue surgery).

Safety Analysis

The safety analyses will be based on the Safety population. The safety analyses will be addressed by listing and tabulation of AEs and will include suspected ADRs, vital signs, physical assessments, and clinical laboratory tests. Data will be described using descriptive analyses.

Determination of Sample Size

The sample size of the study was estimated to provide sufficient power (at least 80%) to demonstrate the hemostatic efficacy of FS Grifols in parenchymous and soft tissue surgery.

Assuming that the true response rate is 80% for the FS Grifols group, and 80% for the EVICEL group, it can be shown that a sample size of 172 subjects (86 subjects in the FS Grifols group and 86 subjects in the EVICEL group, with a 1:1 assignment ratio) would give a power of at least 80% to establish non-inferiority, with lower 95 % CI for the ratio of the proportion of subjects with hemostasis success by 4 minutes in the 2 treatment groups (FS Grifols relative to EVICEL) above 0.80.

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GLOSSARY AND ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AR	adverse reaction
AST	aspartate aminotransferase
BAC2	Biological Active Component 2
B19V	parvovirus B19
BUN	blood urea nitrogen
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
DBP	diastolic blood pressure
EC	Ethics Committee
eCRF	electronic case report form
FS	fibrin sealant
FS Grifols	Fibrin Sealant Grifols
GCP	Good Clinical Practice
HAV	hepatitis A virus
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
Hct	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
HR	heart rate
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
LDH	lactate dehydrogenase
MC	manual compression
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NAT	nucleic acid testing
PI	package insert
PP	per-protocol
PT	prothrombin time
RBC	red blood cell
RR	respiration rate
SD	standard deviation
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
T	temperature
T_2	hemostatic assessment at 2 minutes following T_{Start}
T_3	hemostatic assessment at 3 minutes following T_{Start}
T_4	hemostatic assessment at 4 minutes following T_{Start}
T_5	hemostatic assessment at 5 minutes following T_{Start}
T_7	hemostatic assessment at 7 minutes following T_{Start}
T_{10}	hemostatic assessment at 10 minutes following T_{Start}
TB	total bilirubin
TBS	target bleeding site
$T_{Closure}$	time of completion of the surgical closure by layers of the exposed surgical field containing the TBS

$T_{Completion}$	time of completion of the surgical incision closure – when the last skin closure stitch is put in – of the last exposed field, regardless of whether it was the field containing the TBS
TEAE	treatment-emergent adverse event
T_{End}	time of end/completion of initial study treatment application before T_4
T_{End2}	time of end/completion of study treatment reapplication after T_{End} and before T_4, if applicable
T_{Start}	time of start of initial study treatment application
T_{Start2}	time of start of study treatment reapplication before T_4, if applicable
TTH	time to hemostasis
US	United States
WBC	white blood cell
WFI	water for injection

1 GENERAL INFORMATION

Protocol title and other key study information are provided on the title page. Information regarding additional key personnel and organizations involved in the conduct of the study, including names and contact details of participating investigators, monitors, clinical laboratories, technical departments and/or institutions, as well as information on members of additional study committees, will be found in the study files of the sponsor and at the investigator sites within the study reference manual/file.

Investigators and staff will receive training either via an investigator's meeting or other appropriate individual site training session(s).

2 BACKGROUND INFORMATION

In addition to the information provided below, please also refer to the Investigator's Brochure ([IB] 1) and any additional data supplied by the sponsor.

In this study, the safety and efficacy of Fibrin Sealant Grifols (FS Grifols) in pediatric subjects undergoing surgical procedures where bleeding is present on the cut parenchymous surface of a solid organ (i.e., liver) or soft tissue (i.e., fat, muscle, or connective tissue) will be examined. The aim of this study is to demonstrate that FS Grifols application is not inferior in providing benefit in terms of hemostasis, when compared to the application of a licensed, widely used adjunct to hemostasis agent, specifically the commercially available fibrin sealant (FS) solution EVICEL® (Omrix Biopharmaceuticals N.V., [Diegem, Belgium]), applied as per its package insert (PI) instructions and according to the surgeons' usual clinical practice (2).

2.1 Name and Description of the Investigational Products

See Section 4.4 Study Treatments for details.

FS Grifols is a 2-component, frozen, sterile FS composed of human fibrinogen (80 mg/mL solution), human thrombin (500 IU/mL solution), and other ingredients including sodium citrate, sodium chloride, arginine, L-isoleucine, L-glutamic acid monosodium, calcium chloride, human albumin, and glycine.

EVICEL is a sterile, frozen FS solution composed of: Biological Active Component 2 ([BAC2] 55-85 mg/mL human fibrinogen), thrombin (800-1200 IU/mL human thrombin), and other ingredients including arginine hydrochloride, glycine, sodium chloride, sodium citrate, calcium chloride, human albumin, mannitol, and sodium acetate.

2.2 Relevant Findings from Nonclinical and Clinical Trials

For nonclinical study results, please refer to the FS Grifols IB (1).

The efficacy and safety of FS Grifols as an adjunct to hemostasis in surgery have been evaluated in a comprehensive clinical development program. The clinical development

program consisted of three pivotal phase 3 clinical trials: IG1101 (vascular surgery), IG1102 (parenchymous surgery), and IG1103 (soft tissue surgery).

All 3 pivotal trials were phase 3, prospective, single-blind, randomized studies to evaluate the safety and efficacy of FS Grifols as an adjunct to hemostasis consisting of 2 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 intraoperative procedures required by the protocol of the clinical study. In study IG1101, all subjects enrolled in the Preliminary Part (I) were treated with FS Grifols and in Primary Part (II) subjects were randomized in a 2:1 ratio to either FS Grifols or manual compression (MC), respectively. In studies IG1102 and IG1103, subjects were randomized in a 1:1 ratio into 1 of 2 treatment groups: FS Grifols solution or Surgicel® oxidized cellulose pads.

In both parts of the clinical studies, subjects undergoing an elective (non-emergency), open (non-laparoscopic), vascular (non-endovascular) surgical procedure (study IG1101), parenchymous tissue (i.e., hepatic) surgical procedure (study IG1102), or soft tissue surgical procedure (study IG1103), wherein a target bleeding site (TBS) was identified and a topical hemostat was indicated, were initially eligible to participate.

The primary efficacy endpoint for all 3 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 (T_4) following the start of treatment application (T_{Start}), without occurrence of rebleeding and reapplication of study treatment after T_4 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 $T_{Closure}$.

The secondary endpoints for all 3 clinical trials were the time to hemostasis (TTH), the cumulative proportion of subjects achieving hemostasis at the TBS by 2 (T_2), 3 (T_3), 5 (T_5), 7 (T_7), and 10 (T_{10}) minutes after T_{Start} (the T_2 and T_3 time points were not applicable to study IG1101), and the prevalence of treatment failures.

In the 3 pivotal studies, approximately 500 subjects were treated with FS Grifols. The results from all 3 pivotal studies IG1101, IG1102, and IG1103 demonstrated that FS Grifols was effective, safe, and well tolerated as a local hemostatic agent in various surgery types.

2.2.1.1 Vascular Surgery (Study IG1101)

A total of 225 subjects were enrolled or randomized into this study; 59 subjects in Preliminary Part (I) and 166 subjects in Primary Part (II). Of the 225 subjects, 168 subjects received FS Grifols and 57 subjects received MC.

Overall, the data demonstrated the hemostatic efficacy of FS Grifols and support the use of FS Grifols as an effective local hemostatic agent in vascular surgery. In Primary Part (II), the rate of hemostasis at the TBS by T_4 was 76.1% (83/109 subjects) in the FS Grifols treatment group and was 22.8% (13/57 subjects) in the MC treatment group. The rate of hemostasis at the TBS by T_4 was statistically and significantly higher in the FS Grifols treatment group

compared to the MC treatment group (p-value <0.001), indicating that FS Grifols was superior to MC and the primary efficacy objective was met.

The results of all secondary efficacy endpoints provided additional support for FS Grifols as an effective local hemostatic agent in vascular surgery. In all parameters, FS Grifols was statistically and significantly superior to Surgicel.

No substantial differences in the incidences of treatment emergent adverse events (TEAEs) were noted between treatment groups.

No clinically relevant changes occurred in vital signs, physical examinations, or clinical laboratory parameters. No treatment-emergent viral infection was detected by viral nucleic acid testing (NAT) or viral serology testing.

2.2.1.2 Parenchymous Tissue Surgery (Study IG1102)

A total of 325 subjects were enrolled or randomized into this study. In Preliminary Part (I), a total of 101 subjects were enrolled; 52 subjects were randomized to the FS Grifols treatment group and 49 subjects were randomized to the Surgicel treatment group. In Primary Part (II), a total of 224 subjects were randomized; 111 subjects were randomized to receive FS Grifols, and 113 subjects were randomized to receive Surgicel.

Overall, the data demonstrate the hemostatic efficacy of FS Grifols and support the use of FS Grifols as an effective local hemostatic agent in parenchymous tissue surgery. In Primary Part (II), the rate of hemostasis at the TBS by T_4 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 rate of hemostasis by T_4 was statistically and significantly higher in the FS Grifols treatment group compared to the Surgicel treatment group (p-value = 0.010). The estimated ratio of proportion achieving hemostasis by T_4 in subjects receiving FS Grifols relative to Surgicel was 1.152 (95% Confidence Interval [CI]: 1.038, 1.279), indicating that FS Grifols was non-inferior to Surgicel and that the primary efficacy objective was achieved. Additionally, the lower limit of the 95% CI was above 1 indicating that FS Grifols was 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. In all parameters, FS Grifols was statistically and significantly superior to Surgicel.

No substantial differences in the incidences of TEAEs were noted between treatment groups.

No clinically relevant changes occurred in vital signs, physical examinations, or clinical laboratory parameters. No treatment-emergent viral infection was detected by viral NAT or viral serology testing.

2.2.1.3 Soft Tissue Surgery (Study IG1103)

A total of 327 subjects were enrolled or randomized into this study. In Preliminary Part (I), a total of 103 subjects were enrolled; 51 subjects were randomized to receive FS Grifols and

52 subjects were randomized to receive Surgicel. In Primary Part (II), a total of 224 subjects were randomized: 116 subjects were randomized to receive FS Grifols and 108 subjects were randomized to receive Surgicel.

Overall, the 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. In Primary Part (II), the rate of hemostasis by T_4 was 82.8% (96/116 subjects) in the FS Grifols treatment group and 77.8% (84/108) in the Surgicel treatment group. The rate of hemostasis by T_4 was higher in the FS Grifols treatment group compared to the Surgicel treatment group, but the difference was not statistically significant (p-value = 0.401). The estimated ratio of proportion achieving hemostasis by T_4 in subjects receiving FS Grifols relative to Surgicel was 1.064 (95% CI: 0.934, 1.213), demonstrating that FS Grifols was non-inferior to Surgicel and the primary endpoint was met.

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

No substantial differences in the incidences of TEAEs were noted between treatment groups.

No clinically relevant changes occurred in vital signs, physical examinations, or clinical laboratory parameters. No treatment-emergent viral infection was detected by viral NAT or viral serology testing.

2.2.1.4 Safety of Fibrin Sealant Grifols in Pediatric Subjects in Studies IG1101, IG1102, and IG1103

Only 23 pediatric subjects were evaluated in 2 of the 3 clinical trials. A total of 22 pediatric subjects were randomized in Preliminary Part (I) of studies IG1102 and IG1103 and only 1 subject was enrolled in Primary Part (II) in study IG1103. No pediatric subjects were enrolled in Study IG1101 as there is a low prevalence of pediatric subjects undergoing vascular surgery. For the pediatric subjects evaluated, there were no unique safety concerns.

Overall, 11 pediatric subjects ranging from 3 to 16 years old were enrolled in the FS Grifols treatment group in clinical studies IG1102 and IG1103. Similarly, 12 pediatric subjects were also enrolled in the Surgicel treatment group.

Treatment-emergent AEs were summarized separately for pediatric subjects (≤16 years of age) and for adults (>16 years of age). The small number of pediatric subjects and the large imbalance in the number of adult and pediatric subjects makes a comparison of the TEAE incidence rates between these subgroups difficult. Many of the most frequent TEAEs reported in adults were either not reported in pediatric subjects or were reported in only a single pediatric subject within a treatment group. In addition, there were no major differences between the pediatric subjects in the FS Grifols treatment group compared with the Surgicel treatment group.

There were 2 pediatric subjects in the FS treatment group who had serious adverse events (SAEs). One subject had 2 SAEs (clostridium difficile colitis and febrile neutropenia) and another subject had 1 SAE (laryngospasm). These SAEs were considered by the investigator

to be unrelated to FS Grifols 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 by the investigator to be unrelated to Surgicel and the subjects recovered.

Overall, there was no pattern suggesting a unique safety concern for the pediatric subjects.

2.3 Known and Potential Risks and Benefits to Human Subjects

2.3.1 Benefits

The data obtained through the three pivotal phase 3 studies IG1101, IG1102, and IG1103, provides substantial evidence of the efficacy/benefit of FS Grifols as an effective local hemostasis agent in surgery. The benefits of FS Grifols as an effective local hemostasis agent in surgery include the following:

Superiority of FS Grifols relative to MC in Achieving Hemostasis in Vascular Surgery (Study IG1101)

The analysis of the primary efficacy endpoint indicated that the rate of hemostasis at the TBS by T_4 in the FS Grifols treatment group in vascular surgery was 76.1%, which was statistically and significantly higher than the rate of hemostasis of 22.8% in the MC treatment group (p-value <0.001). This result demonstrated that FS Grifols is superior to MC in achieving hemostasis in vascular surgery.

The analysis of the secondary endpoints provided further evidence that FS Grifols is superior to MC in achieving hemostasis. The results showed that FS Grifols is superior to MC in the median TTH (4.0 minutes in the FS treatment group versus ≥10.0 minutes in the MC treatment group) (p-value <0.001).

FS Grifols was superior to MC in the rates of hemostasis at all time points evaluated (by T_5, T_7, and T_{10}). In the FS Grifols treatment group, the rates of hemostasis at the TBS by T_5, T_7, and T_{10} were 80.7%, 84.4%, and 88.1%, respectively. In the MC treatment group, the rates of hemostasis at the TBS by T_5, T_7, and T_{10} were 28.1%, 35.1%, and 45.6%, respectively. At each time point, the rates of hemostasis were statistically and significantly higher in the FS Grifols treatment group compared to the MC treatment group (p-value <0.001).

In the Primary Part (II) of the study, the rate of treatment failures was significantly lower (p-value <0.001) in the FS Grifols treatment group (23.9%) compared to the MC treatment group (77.2%). The estimated ratio of proportion of treatment failure in subjects receiving FS Grifols relative to MC was 0.309 (95% CI: 0.215, 0.445).

Superiority of FS Grifols Relative to Surgicel in Achieving Hemostasis in Parenchymous (Hepatic) Tissue Surgery (Study IG1102)

The analysis of the primary efficacy endpoint indicated that the rate of hemostasis at the TBS by T_4 in the FS Grifols treatment group in parenchymous (hepatic) tissue surgery was 92.8%,

which was statistically and significantly higher compared to the rate of 80.5% in the Surgicel treatment group (p-value = 0.010). The estimated ratio of proportion achieving hemostasis at the TBS by T_4 in subjects receiving FS Grifols relative to Surgicel was 1.152 (95% CI: 1.038, 1.279), indicating that FS Grifols is non-inferior to Surgicel. Additionally, the lower limit of the 95% CI above 1 indicated that FS Grifols is superior to Surgicel.

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

The rates of hemostasis by T_2 and T_3 were higher and statistically superior in the FS Grifols treatment group compared to the Surgicel treatment group (p-value = 0.045 and <0.001, respectively). Inferential analyses of the ratio and 95% CI of the proportion of subjects achieving hemostasis by T_5, T_7, and T_{10} in subjects receiving FS Grifols relative to Surgicel indicated that FS Grifols was superior to Surgicel.

The rate of treatment failure was statistically and significantly lower (p-value = 0.010) in the FS Grifols treatment group (7.2% subjects) compared to the Surgicel treatment group (19.5% subjects). The estimated ratio of proportion of treatment failure in subjects receiving FS Grifols relative to Surgicel was 0.370 (95% CI: 0.172, 0.796).

Non-inferiority of FS Grifols Relative to Surgicel in Achieving Hemostasis in Soft Tissue Surgery (Study IG1103)

The analysis of the primary efficacy endpoint indicated that the rate of hemostasis at the TBS by T_4 was 82.8% in the FS Grifols treatment group and 77.8% in the Surgicel treatment group. The estimated ratio of proportion achieving hemostasis at the TBS by T_4 in subjects receiving FS Grifols relative to Surgicel was 1.064 (95% CI: 0.934, 1.213), demonstrating that FS Grifols is non-inferior to Surgicel.

The median TTH was shorter, but not statistically significant, in the FS Grifols treatment group (2.0 minutes) compared to the Surgicel treatment group (3.0 minutes).

The rate of hemostasis of 75.9% by T_3 in the FS Grifols treatment group was statistically and significantly higher (p-value = 0.015) compared to the rate of 60.2% in the Surgicel treatment group. The estimated ratio of proportion achieving hemostasis at the TBS by T_3 in subjects receiving FS Grifols relative to Surgicel was 1.260 (95% CI: 1.048, 1.516), demonstrating that FS Grifols is superior to Surgicel by T_3. The rate of hemostasis at the TBS by the T_2, T_5, T_7, and T_{10} time points was higher in the FS Grifols treatment group, but not statistically superior, as compared to the Surgicel treatment group.

The rate of treatment failure was lower, but not statistically significant in the FS Grifols treatment group (17.2% subjects) compared to the Surgicel treatment group (22.2% subjects). The estimated ratio of proportion of treatment failure in subjects receiving FS Grifols relative to Surgicel was 0.776 (95% CI: 0.456, 1.321).

Similar beneficial results were also obtained and were further strengthened when the data from IG1102 and IG1103 were combined for integrated analysis. The overall results

demonstrated the superiority of FS Grifols to Surgicel in both parenchymous (hepatic) surgery and soft tissue surgery.

Improved Safety Profile

Similar marketed FS products have shown a good safety profile for more than 25 years of use (3,4). FS Grifols preparation has additional features that are designed to improve its safety profile.

FS Grifols exclusively contains non-ruminant origin products. In subjects where preparations containing bovine thrombin had been used, inhibitory antibodies occurred against bovine thrombin and contaminating bovine factor V, with cross-reactivity to human factor V, causing severe bleeding. Antibodies that cross-react with human thrombin may promote thrombosis by impairing the inhibition of thrombin by antithrombin III (5,6,7). Although such cases have not been observed, antibody formation could theoretically occur after use of human FS products. No immunogenicity occurred from the treatment with FS Grifols, Surgicel, or MC in studies IG1101, IG1102, and IG1103.

Rare and serious complications associated with human FS products include cardiovascular collapse after use of FS products containing bovine thrombin on parenchymous organs and severe immune globulin E class-mediated anaphylactic reaction (8,9,10).

FS Grifols does not contain tranexamic acid. Fibrin sealant products used in neurosurgery should not contain tranexamic acid since cerebral edema and seizures have occurred (11).

2.3.2 Risks

Analysis of 5-year data of AEs associated with the use of other FS products (not including FS Grifols) showed that the incidence of AEs was 1 in every 98,933 applications. From a total of 16 suspected AEs, only 6 were related to FS products and were allergic/anaphylactic responses (12).

Because FS Grifols is made from human plasma, it may carry a risk of transmitting infectious agents. The risk of transmitting an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current viral infections, and by incorporation in the production process of specific steps with validated (demonstrated) capacity to inactivate and/or remove potential viral contaminations. Despite these measures, such products may still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. In the three pivotal phase 3 studies (IG1101, IG1102, and IG1103), all enrolled subjects regardless of treatment assignments were monitored for potential transmission of hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and parvovirus (B19V). No treatment-emergent viral infection was detected by viral NAT or viral serology testing in clinical studies IG1101, IG1102, and IG1103.

Anaphylactic/allergic reactions have occurred to aprotinin contained in FS products, especially after re-exposure. In such subjects, antibodies to aprotinin were found (13,14). FS Grifols does not contain aprotinin. However, as with any protein product, allergic type

hypersensitivity reactions theoretically are possible. Signs of hypersensitivity reactions include, but are not limited to, hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis even in cases of strict local application. Although such hypersensitivity reactions were reported in the course of studies IG1101, IG1102 and IG1103, they were considered either not related or unlikely related to FS Grifols treatment.

Thromboembolic events and disseminated intravascular coagulation may occur, and there is also a risk of anaphylactic reaction if human plasma-derived FS is unintentionally applied intravascularly.

A summary of adverse drug reactions (ADRs) can be found in the IB (1).

2.4 Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Period(s)

2.4.1 Administration of Investigational Products

In the 3 pivotal studies, subjects were treated intra-operatively with a single administration of FS Grifols. FS Grifols-treated subjects could have received up to 6 mL of FS Grifols at the TBS by drip application in Study IG1101 and up to12 mL of FS Grifols at the TBS by spray application in study IG1102 and by spraying or dripping in study IG1103. The initial volume of FS Grifols applied to the TBS area was sufficient to entirely cover the intended application area by a thin, even layer. If the hemostatic effect was incomplete after T_{Start} and before 4 minutes (T_4) following T_{Start}, 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.

2.4.2 Justification for Selection of Doses/Timing of Investigational Products

In the 3 pivotal clinical studies, the safety and efficacy of FS Grifols was shown in adult subjects (see Section 2.2). In subjects randomized to the FS Grifols group, study drug was applied to the TBS to sufficiently 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 with the use of an applicator. Before application of FS Grifols to the TBS, the TBS 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).

If the hemostatic effect was incomplete after T_{Start} and before the primary efficacy endpoint assessment time point, T_4, additional amounts of FS Grifols may have been applied at the TBS up to the maximum allowed volume. 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.

2.5 Compliance Statement

This study will be conducted under the conditions described in this protocol and in compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (ICH GCP) and all applicable regulatory requirements.

2.6 Study Population

This clinical study includes pediatric subjects (<18 years old) requiring an elective (non-emergency), open (non-laparoscopic), pelvic, abdominal, or thoracic (non-cardiac) surgical procedure where a TBS is identified, and a topical hemostatic agent is indicated.

In the case of preterm (up to gestational age <37 weeks) and term newborn infants (0 to 27 days) requiring either an elective (non-emergent) or an emergency, open (non-laparoscopic) pelvic, abdominal or thoracic (non-cardiac) surgical procedure wherein a TBS is identified, and a topical hemostatic agent is indicated, will be eligible to participate in the clinical trial.

2.7 Relevant Data and Literature Review

The use of human plasma proteins as tissue sealants dates back to early last century. The concept of using plasma fibrinogen mixed with thrombin to form adhesive was reported over 70 years ago (3). Commercial concentrates rich in clottable fibrinogen became available in Europe in the late 1970s. More recently, commercial FS products were also licensed for use in the United States (US) (2, 4, 15-19). The intended benefits of FS application are to support local hemostasis and sutures, “glue” surfaces of injured tissues in order to obtain adaptation or sealing of surfaces, or improve repair or healing (4, 15-18).

Fibrin Sealant products may be used in a variety of clinical situations and surgical fields, including but not limited to, cardiac and vascular surgery, thoracic surgery, neurosurgery, plastic and reconstruction surgery, gastrointestinal surgery, hepatic and splenic surgery, and dental surgery. Practical applications of FS products in orthopedic surgery, interventional radiology, and minimally invasive endoscopy are growing (2, 4, 15-19).

Fibrin Sealant Grifols is a 2-component FS solution composed of purified sterile frozen solutions of human fibrinogen and human thrombin with calcium chloride. The purification process of both components from human plasma is a procedure based on Cohn’s method; fibrinogen is obtained from Fraction I and thrombin is obtained from the supernatant of Fraction I (1).

Nonclinical studies in animal models supported the safety and efficacy of FS Grifols in liver and vascular surgery (1) and a clinical development plan was designed to assess the safety and efficacy of FS Grifols in the surgical setting as an adjunct to local hemostasis. FS products may differ in their composition, application sets, and technique of use (20-23).

FS Grifols is intended for local application and a local effect; intravascular administration is contraindicated.

3 STUDY OBJECTIVES AND PURPOSE

The objectives of this study are to evaluate the efficacy and safety of FS Grifols as an adjunct to achieve hemostasis during surgery in pediatric subjects.

3.1 Efficacy Objectives

3.1.1 Primary Efficacy Objective

- To evaluate if FS Grifols is non-inferior to EVICEL in terms of the proportion of subjects achieving hemostasis at the TBS by 4 minutes (T_4) from the start of treatment application (T_{Start}) with no occurrence of rebleeding until the completion of the surgical closure by layers of the exposed surgical field containing the TBS ($T_{Closure}$).

3.1.2 Secondary Efficacy Objectives

- To determine the cumulative proportion of subjects achieving hemostasis at the TBS by the defined observation time points of T_7 and T_{10}
- To determine prevalence of treatment failures

3.1.3 Exploratory Efficacy Objectives

- To determine the proportion of subjects achieving at least 1 point decrease in bleeding intensity according to the 5-point validated bleeding severity scale (see Table 7-1) by the defined observation time points of T_4, T_7, and T_{10}
- To determine the mean change from baseline in bleeding intensity according to the 5-point validated bleeding severity scale (see Table 7-1 at the defined observation time points of T_4, T_7, and T_{10}

3.2 Safety Objective

- To evaluate the safety and tolerability of FS Grifols in pediatric subjects undergoing surgery

4 STUDY DESIGN

4.1 Primary Efficacy Endpoint and Secondary Efficacy Endpoints

4.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint in this clinical trial is the proportion of subjects achieving hemostasis at the TBS by T_4, with no occurrence of rebleeding until the completion of the surgical closure by layers of the exposed surgical field containing the TBS ($T_{Closure}$).

Hemostasis is defined as Grade 0 (see Table 7-1) 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.

Rebleeding is defined as Grade ≥1 (see Table 7-1) bleeding from the TBS requiring further hemostatic intervention.

4.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

- Cumulative proportion of subjects achieving hemostasis at the TBS by the defined observation time points of T_7 and T_{10}
- Prevalence of treatment failures
  The following cases will be considered treatment failures:
  - Persistent bleeding at the TBS beyond the 4-minute observation time point
  - Grade 3 or 4 (see Table 7-1) breakthrough bleeding at the TBS that jeopardizes subject safety, according to the investigator's judgment (the surgeon's), at any moment during the 10-minute observation period, and until $T_{Closure}$
  - Use of alternative topical hemostatic agents or maneuvers (other than the study treatment) at the TBS during the 10-minute observation period and until $T_{Closure}$ or use of study treatment at the TBS beyond the assessment of the primary efficacy endpoint at T_4 and until $T_{Closure}$
  - Rebleeding (Grade ≥1) at the TBS after the assessment of the primary efficacy endpoint at T_4 and until $T_{Closure}$

4.2 Study Design and Plan

This is a prospective, randomized, active-controlled, single-blind, parallel group clinical trial to evaluate the efficacy and safety of FS Grifols as an adjunct to hemostasis during surgery in pediatric subjects.

Pediatric subjects (<18 years of age) requiring an elective (non-emergent), open (non-laparoscopic), pelvic, abdominal, or thoracic (non-cardiac) surgical procedure, wherein a

TBS is identified and a topical hemostatic agent is indicated, will be eligible to participate in the clinical trial.

Preterm (up to gestational age <37 weeks) and term newborn infants (0 to 27 days) requiring either an elective (non-emergent) or an emergency, open (non-laparoscopic) pelvic, abdominal or thoracic (non-cardiac) surgical procedure wherein a TBS is identified, and a topical hemostatic agent is indicated, will be eligible to participate in the clinical trial.

The study treatments will be applied on the cut parenchymous surface of a solid organ (i.e., liver) and in soft tissue (i.e., fat, muscle, or connective tissue).

A specific bleeding site will be defined as the TBS when it is determined by the investigator (the surgeon) that control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) is ineffective or impractical and requires an adjunct treatment to achieve hemostasis.

When the TBS is identified, the investigator will record the precise anatomical location of the TBS, rate the intensity of the bleeding at the TBS (Grade 1-4 according to the 5-point validated bleeding severity scale shown in Table 7-1), and record the size of the approximate bleeding surface (small, medium large). For soft tissue surgery only, the investigator will also record the type of soft tissue (i.e., fat, muscle, or connective tissue). In this clinical trial, only subjects with a TBS with bleeding intensity of Grade 1 (mild) or Grade 2 (moderate) will be enrolled (see Table 7-1).

Subjects will be randomly allocated in a 1:1 ratio into 1 of 2 treatment groups: FS Grifols or EVICEL. The first 24 subjects to be enrolled in the study will be adolescents (age range 12 to 17 years). The term “enrolled” implies that the subject was actually randomized to and treated with either the FS Grifols or EVICEL. Enrollment will be monitored by surgery type to ensure approximately 50% of the surgical procedures are hepatic. The overall study schema is presented in Figure 4-1.

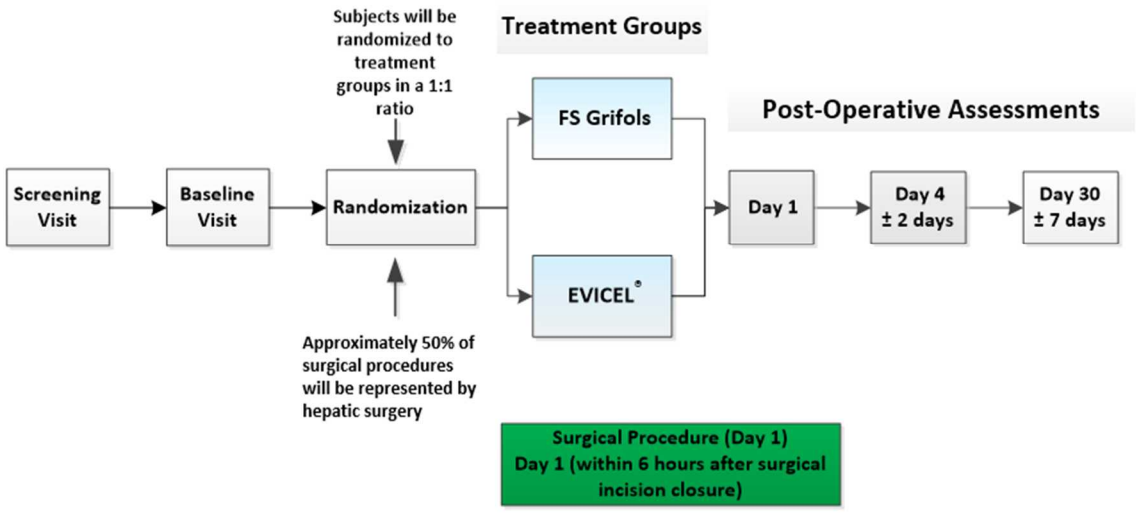

Figure 4-1 Overall Study Schema

4.3 Measures Taken to Minimize/Avoid Bias

4.3.1 Subject Numbering

Within each study site, subjects in the study will receive a consecutive subject number. Subject numbers are generated beginning with the study center number (3 digits, assigned by the sponsor) followed consecutively with a unique number for each subject (4 digits, including leading zeros). For example, if the investigator's center number is 301, subject number will be 3010001, 3010002, 3010003, etc., in consecutive order. Subject numbers, once assigned, will not be reused at any center.

4.3.2 Randomization

Subjects satisfying all pre-operative enrollment criteria will be randomized in 1:1 ratio into the FS Grifols or EVICEL treatment groups. Randomization will be stratified by type of surgery (i.e., parenchymous versus soft tissue surgery) and age groups (i.e., 12-17 years, 2-11 years, 28 days-23 months, and 0-27 days). The investigator site pharmacy will use an Interactive Response Technology (IRT) system to obtain the randomization number and the corresponding assigned treatment (FS Grifols or EVICEL).

At the beginning of the surgical procedure, before any TBS is identified, all materials needed for FS Grifols or EVICEL application will be ready for use. If the subject meets the intra-operative eligibility criteria defined in Section 5.1 and Section 5.2, a randomization number will be recorded in the subject's source documents and electronic Case Report Form (eCRF). If the subject does not meet the intra-operative eligibility criteria, the study drug prepared by the pharmacist will remain unused and discarded according to the respective site standard

procedures. In this case, the IRT system will automatically assign the same treatment to the next subject enrolled in the same stratum.

4.3.3 Blinding

This is a single-blind study. Treatment assignment for subjects participating in the study will be blinded from the sponsor, except for personnel from study drug supply groups. Treatment allocation will only be unblinded as necessary within Grifols Global Pharmacovigilance group for subjects that experience a serious and unexpected ADR, as defined in Section 8.3.7, and reported according to the procedure described in Section 8.3.9.1. Throughout the study, the randomization code will not be broken until data entry is completed, validity of data checked, all associated queries resolved, subject's populations for statistical analysis decided, and database locked.

4.4 Study Treatments

4.4.1 Treatments to Be Administered

4.4.1.1 FS Grifols

FS Grifols is a frozen, sterile, 2-component FS 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. When applied, the solutions generate a cross-linked fibrin clot in a process that mimics the last stage of the human coagulation system.

After thawing, the human fibrinogen and human thrombin solutions are clear or slightly opalescent and colorless or pale yellow. FS Grifols does not contain any preservatives.

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 (WFI).

The human thrombin solution contains:

- Human thrombin: 500 IU/mL solution
- Other ingredients: calcium chloride, human albumin, sodium chloride, glycine, and WFI.

Instituto Grifols, S.A. will provide the FS Grifols kit containing 2 separate packages; 1 package containing 1 syringe each of human fibrinogen and human thrombin sterile frozen solutions assembled in a syringe holder and one package containing the dual applicator device for both drip and spray application. The applicator tip is a dual applicator device intended for use in open surgical procedures allowing both drip application and spray application without gas assistance. The drip and spray tip is a trilumen malleable cannula that

ends in a threaded connector, which allows attachment of a removable airless spray tip. The fibrinogen and thrombin travel through the cannula without making contact until they reach the tip. To drip, the spray tip is unscrewed from the threaded connector at the distal end of the device. As the plungers of the syringe holder are depressed, the fibrinogen and thrombin solutions travel through the device in separate lumens and do not mix until after they exit the threaded connector. In spray mode, the dual applicator mixes the fibrinogen and thrombin in the airless spray tip prior to atomization. If the expression is stopped, the airless spray tip will clog and should be replaced with a one of the 2 spare airless spray tips provided.

4.4.1.2 EVICEL

EVICEL (Omrix Biopharmaceuticals N.V, Diegem, Belgium) is manufactured from pooled human plasma. EVICEL is provided as a single use kit consisting of 2 packages: 1 package containing 1 vial of BAC2 and 1 vial of thrombin. The second package contains a sterile spray application device. The 2 components (BAC2 and thrombin) should be mixed and applied topically as described in the PI (2). EVICEL will be supplied to the individual study sites by Instituto Grifols, S.A.

The BAC2 and thrombin components appear as white to slightly yellowish opaque masses when frozen and as clear to slightly opalescent and colorless to slightly yellowish solutions when thawed. The components contain no preservatives.

BAC2 is a sterile solution consisting mainly of a concentrate of human fibrinogen; the protein from human blood that forms a clot when combined with thrombin. The composition of the BAC2 solution is as follows:

Active ingredient: Concentrate of human fibrinogen (55-85 mg/mL)

Other Ingredients: Arginine hydrochloride, glycine, sodium chloride, sodium citrate, calcium chloride, and WFI.

Thrombin is a sterile solution containing purified human thrombin that activates clotting of the final combined product. Thrombin is a specific protease that transforms the fibrinogen contained in BAC2 into fibrin. The composition of the thrombin solution is as follows:

Active Ingredient: Human thrombin (800-1200 IU/mL)

Other Ingredients: Calcium chloride, human albumin, mannitol, sodium acetate, and WFI.

4.4.2 Labeling of Investigational Products

Investigational products will be labeled according to the requirements of local law and legislation. Label text will be approved according to agreed Grifols procedures, and a copy of the labels will be made available to the study site.

4.4.3 Packaging of Investigational Products

Each single-use 6 mL FS Grifols kit size is composed of 2 type I glass syringes containing sterile frozen solutions of 3 mL human fibrinogen (component 1) and 3 mL human thrombin with calcium chloride (component 2) assembled on 1 sterilized syringe holder with plungers. A plunger bridge connected to the syringe holder allows for simultaneous administration of equal amounts of fibrinogen and thrombin. The FS Grifols syringe holder is packed in a plastic blister. The dual applicator with 2 spare airless spray tips are sealed in a separate blister package.

EVICEL (Omrix Biopharmaceuticals N.V, Diegem, Belgium) is provided as a single use kit consisting of 2 packages: 1 package containing 1 vial of frozen BAC2 and 1 vial of frozen thrombin. The second package contains a sterile spray application device.

EVICEL dosage forms include the following package sizes:

Table 4-1 EVICEL Package Sizes

BAC2 Vial Size (mL)	Thrombin Vial Size (mL)	Package Size (mL)
1.0	1.0	2.0
2.0	2.0	4.0
5.0	5.0	10.0

4.4.4 Storage of Investigational Products

FS Grifols must be stored at ≤ -18ºC (≤ -0.40ºF). FS Grifols has a shelf-life of 2 years when stored at ≤ -18 ºC (≤ -0.40 ºF). It is not to be used after the expiration date stated on the label.

FS Grifols kits will be shipped at frozen ≤-18ºC (≤ -0.40ºF) conditions to each trial site using appropriate containers with a temperature monitoring device. Once at the site, the product will be stored in a freezer at ≤ -18ºC (≤ -0.40ºF).

FS Grifols should not be refrozen once it is thawed.

If the packaging or any of the components of the FS Grifols kit are damaged, the product should not be used but should be quarantined for accountability reconciliation by the clinical monitor before being destroyed.

EVICEL will be stored according to manufacturer' instructions (2).

4.5 Expected Duration of Subject Participation in the Study

The study consists of a Screening Visit, a Baseline Visit, the Surgical Visit, and Postoperative Visits.

The total time of subject's participation in the study is expected to be no longer than 2 months from the Screening Visit to the Post-operative Day 30 (± 7 days) Visit.

4.6 Discontinuation Criteria for Individual Subjects and Study

4.6.1 Discontinuation Criteria for Individual Subjects

See Section 5.3 Subject Withdrawal Criteria

4.6.2 Premature Termination of Study/Closure of Center

The sponsor, institutional review board/ethics committee (IRB/EC), and/or regulatory authorities have the right to close this study or a study center, and the investigator has the right to close a center, at any time, although this should occur only after consultation between involved parties. The IRB/EC must be informed. Should the study/center be closed prematurely, all study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction.

The reasons a study center may be closed include, but are not limited to, the following:

- Lack of enrollment
- Non-compliance with the requirements of the study protocol
- Non-compliance with ICH GCP

4.7 Accountability Procedures for Investigational Products

Investigational products are to be used only for the study in accordance with the directions given in this protocol. The investigator, or designee such as the study pharmacist, is responsible for the distribution of the IP in accordance with directions given in the protocol and pharmacy manual.

The investigator is responsible for maintaining accurate records of the IP for his/her site. Investigational product inventory/dispensing documentation verifying the receipt, dispensing, destruction, or return must be maintained and kept current by the investigator, or designee. The inventory must be made available for inspection by the monitor. Investigational product supplies must be accounted for by the monitor and inventory/dispensing logs must be verified by the monitor prior to IP return or destruction. Written documentation of any used and unused inventory is required. At the end of the study, a copy of the inventory/dispensing log(s) will be retrieved by the monitor and returned to Grifols.

4.8 Maintenance of Treatment Randomization Codes

Access to the actual randomization schedules or codes must be strictly controlled during the course of the study.

5 SELECTION AND WITHDRAWAL OF SUBJECTS

Eligible participants for this clinical study include male or female pediatric subjects (<18 years of age) requiring an elective (non-emergent), open (non-laparoscopic), pelvic, abdominal or thoracic (non-cardiac) surgical procedure, wherein a TBS is identified, and a topical hemostatic agent is indicated. Preterm (up to gestational age <37 weeks) and term newborn infants (0 to 27 days) requiring either an elective (non-emergent) or an emergency, open (non-laparoscopic) pelvic, abdominal or thoracic (non-cardiac) surgical procedure wherein a TBS is identified, and a topical hemostatic agent is indicated.

5.1 Inclusion Criteria

A subject must meet all the following inclusion criteria to be eligible for participation in this study:

Pre-operative:

1. Is less than 18 years of age.
2. Requires an elective (non-emergent), open (non-laparoscopic), pelvic, abdominal, or thoracic (non-cardiac) surgical procedure. Or is a preterm (up to gestational age <37 weeks) or term newborn infant (0 to 27 days) requiring either an elective (non-emergent) or an emergency, open (non-laparoscopic) pelvic, abdominal or thoracic (non-cardiac) surgical procedure.
3. Subject and/or subject's legal guardian is willing to give permission for the subject to participate in the clinical trial and provide written informed consent for the subject. In addition, assent must be obtained from pediatric subjects who possess the intellectual and emotional ability to comprehend the concepts involved in the clinical trial.

Intra-operative:

4. Presence of an appropriate (as defined in inclusion criterion 5) parenchymous or soft tissue TBS identified intra-operatively by the investigator (the surgeon).
5. TBS has Grade 1 (mild) or Grade 2 (moderate) bleeding according to the investigator's (the surgeon's) judgment. The intensity of the bleeding at the TBS will be rated by the investigator using the 5-point validated bleeding severity scale shown in Table 7-1.

5.2 Exclusion Criteria

A subject meeting any of the following exclusion criteria is NOT eligible for participation in the study.

Pre-operative:

1. Subjects admitted for trauma surgery.
2. Subjects unwilling to receive blood products.

3. Subjects with known history of severe (e.g., anaphylactic) reaction to blood products.
4. Subjects with known history of intolerance to any of the components of the IP.
5. Female subjects who are pregnant, breastfeeding or, if of child-bearing potential (i.e., adolescent), unwilling to practice a highly effective method of contraception (e.g., oral, injectable or implanted hormonal methods of contraception, placement of an intrauterine device or intrauterine system, condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilization, or true abstinence) throughout the study.

   True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.).

6. Subjects previously enrolled in clinical trials with FS Grifols.
7. Subjects currently participating, or during the study is planned to participate, in any other investigational device or medicinal product study.

Intra-operative:

8. An appropriate parenchymous or soft tissue TBS (as defined in exclusion criteria 9 and 10) cannot be identified intra-operatively by the investigator (the surgeon).
9. The TBS has Grade 3 (severe) bleeding according to the investigator's (the surgeon's) judgment that cannot be controlled with conventional surgical techniques to Grade 1 or Grade 2 bleeding. The intensity of the bleeding at the TBS will be rated by the investigator using the 5-point validated bleeding severity scale (see Table 7-1).
10. The TBS is in an actively infected surgical field.
11. Occurrence of major intra-operative complications that require resuscitation or deviation from the planned surgical procedure.
12. Application of any topical hemostatic agent on the resection surface of parenchyma or soft tissue prior to application of the IP.

5.3 Subject Withdrawal Criteria

Subjects have the right to withdraw from the study at any time for any reason, either before or after the surgical procedure. The investigator can withdraw a subject from the study at any time.

The investigator will document the reason(s) for withdrawal of each subject in source documents and in the eCRF. All data gathered on the subject prior to termination will be made available to the sponsor.

5.3.1 Screen Failures

Screening evaluations will be used to determine the eligibility of each subject for enrollment. Subjects who fail to meet eligibility criteria during screening, pre-operative, and intra-operative evaluations will be considered screen failures and will not participate in the study.

5.3.2 Removal of Subjects

Subjects may withdraw or be withdrawn from the study for the following reasons:

1. The subject withdraws informed consent at his/her own request or at the request of the legally authorized representatives (e.g., parent or legal guardian).
2. The subject does not meet all inclusion criteria (other than intra-operative) and is deemed a screen failure.
3. The subject does not meet the intra-operative inclusion criteria and is deemed a screen failure.
4. The subject meets any of the exclusion criteria (other than intra-operative) and is deemed a screen failure.
5. The subject meets the intra-operative exclusion criteria and is deemed a screen failure.
6. The subject is not able to adhere to the main protocol requirements (major protocol deviations).
7. The occurrence of an adverse event (AE) which in the investigator's opinion requires the withdrawal of the subject from the study.
8. The subject is lost to follow-up.
9. Subject's death.
10. Any event which in the opinion of the investigator impedes the subject's participation in the study.

For subjects who are screen failures or discontinued from the study early, study completion procedures will be completed as per Section 7.2.1.5.

If the reason for early discontinuation is due to an AE, in so far as was possible, the subject will be followed-up until the event resolves, or is stabilized, and no further change is expected.

In all cases, the reason for withdrawal must be recorded in the eCRF and in the subject's records.

5.3.3 Subject Replacement

Subjects who are randomized and treated with any amount of study drug and withdrawn from the study will not be replaced.

5.3.4 Follow-up of Subjects Withdrawn from Study

Subjects who receive any amount of IP and discontinue early from the study will be requested to return for the Post-operative Day 30 Visit procedures within 7 days of the subject's withdrawal from the study.

6 TREATMENT OF SUBJECTS

See Section 4.4 for the treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), and the route/mode(s) of administration.

6.1 Administration and Timing of Investigational Products for Each Subject

The initial volume of the study treatment to be applied at the TBS should be sufficient to entirely cover the intended application area by a thin, even layer.

For each subject 2 years of age or older randomly assigned to be treated with FS Grifols or EVICEL, the maximum total volume of IP allowed to be applied at the TBS will be 12 mL.

For each subject less than 2 years of age randomly assigned to be treated with FS Grifols or EVICEL, the maximum total volume of IP allowed to be applied at the TBS will be 6 mL.

FS Grifols or EVICEL will be applied via either drip or spray applicator for soft tissue TBS and via spray applicator only for parenchymous tissue TBS.

The IPs are for topical/epilesional use only.

- For subjects ≤ 2 years old, randomized to the FS Grifols treatment group, up to 6 mL of FS Grifols solution will be allowed per subject; and for subjects ≥ 2 years old, up to 12 mL of FS Grifols solution will be allowed per subject . For subjects in the FS Grifols treatment group, the initial volume of FS Grifols to be applied to the TBS should be sufficient to entirely cover the intended application area by a thin, even layer. For every subject in the soft tissue type, FS Grifols will be administered by dripping or spraying onto the TBS surface according to the investigator's judgment. For every subject in the parenchymous tissue type, FS Grifols will be administered by spraying onto the TBS surface. Before any application of FS Grifols to the TBS, 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). If FS Grifols is applied by dripping, the tip of the applicator should be kept as close to the tissue surface as possible without touching the tissue during application. If FS Grifols is applied by spraying, the recommended distance between the spray applicator and the surface of the target area is at least 2 cm. The time of the start of the initial IP application (T_{Start}) and the time of the end of the initial IP application (T_{End}) will be recorded.
- For subjects ≥ 2 years old, randomized to the EVICEL treatment group up to 12 mL of EVICEL solution will be allowed per subject; and for subjects ≤ 2 years old, up to 6 mL

of EVICEL solution will be allowed per subject . For subjects in the EVICEL treatment group, the initial volume of EVICEL to be applied to the TBS should be sufficient to entirely cover the intended application area by a thin, even layer. For every subject in the soft tissue type, EVICEL will be administered by dripping or spraying onto the TBS surface according to the investigator's judgment. For every subject in the parenchymous tissue type, EVICEL will be administered by spraying onto the TBS surface. Spray or drip EVICEL in short bursts (0.1-0.2 ml) onto the tissue to produce a thin, even layer. The amount of EVICEL required depends upon the area of tissue to be treated and the method of application. If EVICEL is applied by dripping, the tip of the applicator should be kept as close to the tissue surface as possible without touching the tissue during application. Individual drops should be applied to the surface area to be treated and the drops should be allowed to separate from each other and from the tip of the applicator. If the applicator tip becomes blocked, the yellow catheter tip should be wiped clean or cut back in 0.5 cm increments. If EVICEL is applied by spraying, the distance between the nozzle and the tissue surface should ideally be between 10 and 15 cm when spraying in open surgery. Spray pressure that is within the recommended guidelines by the device manufacturer should be maintained (e.g., an air pressure of 20-25 psi [measured by airflow]) and insufflation pressure in all such procedures should be monitored (2). The time of the start of the initial IP application (T_{Start}) and the end of the initial IP application (T_{End}) will be recorded.

- If the hemostatic effect is incomplete after T_{Start} and before the primary efficacy endpoint at T_4, additional amounts of IP may be applied at the TBS up to the maximum allowed volume of 12 mL for subjects greater than or equal to 2 years of age and 6 mL for subjects less than 2 years of age 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 IP (e.g., by means of suction, sponges or sterile gauzes). These additional applications of IP should be performed via spray or drip application as per the investigator's judgment for soft tissue type and via spray application for parenchymous tissue type. The time of start (T_{Start2}) and end (T_{End2}) of IP re-application will be recorded. No additional amounts of IP may be applied beyond the primary efficacy endpoint assessment time point at T_4.
- The approximate total amount of IP applied to the TBS and the method(s) of administration (drip or spray) will be documented.
- Subjects in the either treatment 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 IP before the primary efficacy endpoint at T_4, unless there is Grade 3 or 4 (see Table 7-1) 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, EVICEL, or other plasma-derived hemostatic agents are not allowed in this case). In this case, the subject will be considered a treatment failure. The alternative treatment applied will be recorded in subject's source documents and eCRF.
- IP can only be applied to the TBS in this study.

6.2 Prior and Concomitant Therapy

Concomitant medications must be recorded in the eCRF, including the trade and generic names of the medication, the dose, the route of administration, and the duration of the medication (frequency).

Subjects should not receive any alternative hemostatic product or treatment (including application of manual pressure) during the 10-minute observational period, apart from reapplication of FS Grifols or EVICEL before T_4, unless there is Grade 3 or 4 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, EVICEL, or other plasma-derived hemostatic agents are not allowed in this case). In this case, the subject is considered a treatment failure. The alternative treatment applied will be recorded in the subject's source documents and eCRF. FS Grifols or EVICEL cannot be used as hemostatic treatment for any non-TBS.

6.3 Prohibited Concomitant Medications during the Study

Use of an alternative hemostatic product or treatment (including application of manual pressure) during the 10-minute observational period, apart from reapplication of FS Grifols or EVICEL before T_4, is prohibited, unless there is Grade 3 or 4 (see Table 7-1) 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, EVICEL, or other plasma-derived hemostatic agents are not allowed in this case). FS Grifols or EVICEL cannot be used as hemostatic treatment for any non-TBS.

6.4 Treatment Compliance

A measurement of compliance for individual subjects is not applicable for this study as subjects are treated intra-operatively with FS Grifols or EVICEL.

7 ASSESSMENT OF EFFICACY

7.1 Efficacy Variables

This clinical trial evaluates whether FS Grifols is non-inferior to EVICEL in achieving hemostasis during parenchymous or soft tissue surgery in pediatric subjects. This assessment will be mainly done with the primary efficacy endpoint.

7.1.1 Primary Efficacy Variable

The primary efficacy variable is the proportion of subjects achieving hemostasis (binary decision: hemostatic response, Grade 0 = Yes/Grade ≥1 = No) at the TBS by T_4 without occurrence of rebleeding or reapplication of study treatment after T_4 and until $T_{Closure}$, and without Grade 3 or 4 bleeding or use of alternative hemostatic treatment after T_{Start} and until $T_{Closure}$. Hemostasis is defined as Grade 0 bleeding at the TBS according to the investigator's (surgeon's) judgment, so that the surgical closure of the exposed field could begin.

Rebleeding is defined as Grade ≥1 bleeding from the TBS requiring further hemostatic intervention (e.g., manual pressure) after hemostasis was previously achieved at the TBS.

7.1.2 Secondary Efficacy Variable(s)

7.1.2.1 Cumulative Proportion of Subjects Achieving Hemostasis at the Target Bleeding Site by the Time Points of T_7 and T_{10}

The cumulative proportion of subjects achieving hemostasis at the TBS by the time points of T_7 and T_{10} defined as an absence/cessation of bleeding (Grade 0) at the TBS by that time point without occurrence of rebleeding, Grade 3 or 4 bleeding, use of alternative hemostatic treatment, and reapplication of study treatment after T_4 and until $T_{Closure}$.

7.1.2.2 Prevalence of Treatment Failures

The following cases will be considered treatment failures:

- Persistent bleeding at the TBS beyond T_4
- Grade 3 or 4 breakthrough bleeding from the TBS that jeopardizes subject safety according to the investigator's judgment at any moment during the 10-minute observational period and until $T_{Closure}$
- Use of alternative hemostatic treatments or maneuvers (other than the study treatment) at the TBS during the 10-minute observational period and until $T_{Closure}$ or use of study treatment at the TBS beyond T_4 and until $T_{Closure}$
- Rebleeding (Grade ≥1) at the TBS after the assessment of the primary efficacy endpoint at T_4 and until $T_{Closure}$

In the event of Grade 3 or 4 breakthrough bleeding that jeopardizes 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 use any other hemostatic measures at his/her discretion if deemed necessary (use of FS Grifols, EVICEL, or other plasma-derived hemostatic agents are not allowed in this case). In such a case, the subject will be considered a treatment failure. The alternative treatment used will be recorded in the subject's source documents and eCRF.

7.1.3 Exploratory Efficacy Variables

- The proportion of subjects achieving at least 1 point decrease in bleeding intensity according to the 5-point validated bleeding severity scale (see Table 7-1) by the defined observation time points of T_4, T_7, and T_{10}
- The mean change from baseline in bleeding intensity according to the 5-point validated bleeding severity scale (see Table 7-1) at the defined observation time points of T_4, T_7, and T_{10}

7.2 Methods and Timing for Assessing, Recording, and Analyzing Efficacy Parameters

7.2.1 Observations and Measurements

The following is a description of the procedures/assessments to take place at each study visit. See the Schedule of Study Procedures and Events in Appendix 1.

7.2.1.1 Screening Visit (within 21 days prior to Surgical Procedure)

Following signature of the Informed Consent Form (ICF), screening procedures will be performed. Subject number and date of birth will be recorded in the Subject Screening Log. If a subject is ineligible for participation, their demographic data and specific reason for ineligibility will be captured in the subject's source documents and eCRF.

The Screening Visit assessments and activities will include:

- Allocation of subject number
- Adding subject's data into the Screening Log
- Documentation of demographics: year of birth, age at randomization (number of years, number of months), sex, race, and ethnicity
- Documentation of the medical and surgical history for the last 12 months
- Documentation of the lifetime history for the use of topical hemostats and bleeding abnormalities (including inquiry into previous surgery and trauma episodes and the family history)
- Documentation of medications that the subject is taking or has taken within the last 3 months (it includes transfusion of blood or any blood-derived product)
- Review of inclusion/exclusion criteria to confirm subject eligibility
- Type of intervention
- Age group: (Adolescents (12 to 17 years); Children (2 to 11 years); Infants and toddlers (28 days to 23 months) or Preterm (up to gestational age <37 weeks) and term newborn infants (0 to 27 days)

If suitable due to logistic reasons, procedures scheduled at the Screening Visit may be performed during the Baseline Assessments Visit (see Section 7.2.1.2), i.e., within 24 hours prior to the surgical procedure. In this case, the Screening Visit will be combined with the Baseline Assessments Visit. Assessments required during both visits (Screening and Baseline) must be performed.

7.2.1.2 Baseline Assessment Visit (within 24 hours prior to surgical procedure)

Baseline assessments will be performed within 24 hours prior to the scheduled surgery (i.e., the baseline assessments can be performed the same day of the surgery). The following tests and activities will be performed at this pre-operative visit:

- Confirmation of existing and recording of any new events, or changes, in the medical and surgical history of the subject since the Screening Visit. The combined Screening and Baseline Visit requires documentation of the medical and surgical history for the last 12 months.
- Confirmation of existing and recording of any new medications, or changes in medications administered to the subject since the Screening Visit. The combined Screening and Baseline Visit requires documentation of the lifetime history for the use of topical hemostats and bleeding abnormalities. In addition it requires documentation of medications that the subject is taking or has taken within the last 3 months.
- Recording of height and weight.
- Physical assessment.
- Recording of vital signs (i.e., heart rate [HR], respiration rate [RR], systolic [SBP] and diastolic [DBP] blood pressure, and temperature [T]).
- Pregnancy test (human chorionic gonadotrophin [HCG]-based blood or urine assay] for women of childbearing potential (to be performed locally at the investigative site)
  - Women of child-bearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (postmenopausal is defined as amenorrhea for more than 12 consecutive months or women on hormone replacement therapy with documented serum follicle stimulating hormone level <35 mIU/mL). Even in women who are using oral, implanted, or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods to prevent pregnancy or practicing abstinence or where their sexual partner is sterile (e.g., vasectomy), should be considered to be of child-bearing potential.
- Coagulation panel: prothrombin time (PT) and activated partial thromboplastin time (aPTT).
- Hematology: red blood cell (RBC) count, hemoglobin (Hgb), hematocrit (Htc), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), white blood cell (WBC) count and differential, and platelet count.
- Serum clinical chemistry: creatinine, blood urea nitrogen (BUN), total bilirubin (TB), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), glucose, sodium, potassium, chloride, and calcium.
- Assessment of AEs.

- Review of inclusion/exclusion criteria to confirm subject eligibility.
- Randomize subject.

Baseline central laboratory samples (i.e., coagulation, hematology, serum clinical chemistry) may be drawn shortly after anesthesia induction but before start of surgery (i.e., skin incision). All other baseline assessments including local laboratory assessments for determination of subject's eligibility for participation in the study (i.e., pregnancy test) should be completed within 24 hours prior to the surgical procedure and prior to anesthesia induction.

7.2.1.3 Surgical Procedure Day 1

7.2.1.3.1 TREATMENT OF SUBJECTS

The following tests and activities will be performed before surgery begins.

- FS Grifols or EVICEL preparation (see Pharmacy Manual provided separately)
- Confirmation of existing and recording of any new medications (not including gaseous anesthetics), or changes in medications administered to the subject since baseline assessments (including any blood product administered to the subject). Use of anticoagulants and any neutralizing agent should also be recorded in detail including dose and time of administration.
- Recording of vital signs (i.e., HR, RR, SBP, DBP, and T) immediately prior to skin incision to expose the surgical field.
  - At this assessment time, or at any other, when blood pressure parameters, HR and/or T are measured invasively, the anatomic location (e.g., radial artery) of the temporary arterial line used for measurement should be recorded. Regarding the RR measurement, it should be indicated if the subject is under mechanical ventilation or not when the measure is taken.
- Assessment of AEs.

7.2.1.3.2 SURGERY

The surgeon will perform the surgical intervention according to his/her standards as well as the respective institution's standards. Complete details of the conventional surgical techniques used in the surgical procedure will be recorded.

At the time of surgery, the following will be considered:

- When there is generalized bleeding from the cut parenchymous surface of the solid organ (i.e., liver), or from the cut soft tissue (i.e., fat, muscle, or connective tissue), persisting after conventional resection procedure, or dissection, respectively, and primary control of arterial and venous bleeding by sutures, ligations, clips, vascular stapler, point electro-cautery or focal radio-frequency ablation, and it is determined by the investigator (the

surgeon) that the control of bleeding by previously mentioned conventional surgical techniques is ineffective or impractical, and requires an adjunct treatment to achieve hemostasis, this specific bleeding site will be identified and defined as the TBS.

- The intensity of the bleeding at the TBS will be rated by the investigator (surgeon) using the 5-point validated bleeding severity scale shown in Table 7-1 and recorded:

Table 7-1 Validated Bleeding Severity Scale

Grade	Visual Presentation	Anatomic Appearance	Qualitative Description	Visually Estimated rate of Blood Loss (mL/min)
0	No bleeding	No bleeding	No bleeding	≤1.0
1	Ooze or intermittent flow	Capillary-like bleeding	Mild	>1.0-5.0
2	Continuous flow	Venule and arteriolar-like bleeding	Moderate	>5.0-10.0
3	Controllable spurting and/or overwhelming flow	Noncentral venous- and arterial-like bleeding	Severe	>10.0-50.0
4	Unidentified or inaccessible spurting or gush	Central arterial- or venous-like bleeding	Life threatening[a]	>50.0

[a] Systemic resuscitation is required (e.g., volume expanders, vasopressors, blood products, etc).

Source: (24)

If the nature of the bleeding from the parenchymous or soft tissue is Grade 3 (severe), the surgeon may use standard conventional surgical techniques (e.g., cautery, sutures, clips, or ligation) again in order to control the bleeding. If the nature of the bleeding becomes Grade 1 (mild) or Grade 2 (moderate) once those primary hemostatic measures are taken, the subject may be considered eligible for enrollment. If the nature of the bleeding becomes or remains Grade 3 or Grade 4, the subject should not be enrolled into the study and should be considered a screen failure. In this case, the surgeon may use all necessary measures at his/her discretion as deemed necessary (FS Grifols, EVICEL, or other plasma-derived hemostatic agents cannot be used for this purpose). The hemostatic treatment received will be recorded in the subject's source documents and eCRF.

- Upon the identification of a TBS with Grade 1 or 2 (mild or moderate) bleeding, the subject will be deemed eligible for enrollment into the study.
- The approximate size of the TBS will be rated by the investigator (the surgeon) using the following 3-point scale and recorded:
  - Small: TBS ≤10 cm^2.
  - Medium: 10 cm^2 <TBS ≤100 cm^2.

- Large: TBS >100 cm^2.

- The anatomical location of the TBS will be recorded.
- For soft tissue surgery only, the type of soft tissue will be recorded (i.e., fat, muscle, or connective tissue).
- If the subject presents with multiple appropriate bleeding sites, the TBS will be the larger or more clinically relevant site, as judged by the investigator (surgeon).
- If the subject does not have an identifiable TBS, the subject should be withdrawn from the study. The subject will be considered a screen failure as they did not meet the intra-operative criteria, and will be treated according to Section 5.3**.**
- The TBS will be the only site to be evaluated for hemostasis in this study.

At the time of surgery, the following will be performed:

- Verification of intra-operative inclusion and exclusion criteria
- Recording of vital signs (HR, RR [noting if the subject is under mechanical ventilation or not when the measure is taken], SBP and DBP and T) will be measured and recorded at the time of TBS identification and at the following time points:
  - Thirty (30) minutes after T_{Start} (excluding temperature)
  - If the surgical closure by layers of the exposed surgery field containing the TBS is not completed 30 minutes after T_{Start}, then every 30 minutes until $T_{Closure}$ (excluding temperature)
  - At $T_{Completion}$
- Investigational product application: FS Grifols or EVICEL (see Section 6.1)
- Assessment of AEs
- Record $T_{Closure}$
- Record $T_{Completion}$
- Record AEs

7.2.1.3.3 OBSERVATIONAL PERIOD

An observational period of 10 minutes will occur following T_{Start} to determine whether hemostasis has been achieved at the TBS as described in Section 7.2.1.3.2.

- Vital signs (HR, RR [indicate if the subject is or is not under mechanical ventilation when the measure is taken], SBP and DBP, and T) will be recorded at 5 minutes after T_{Start}.
- Confirmation of existing and recording of any new medications, except gaseous anesthetics, or changes in medications administered to the subject since the last assessment (it includes also any blood products administered to the subject). Use of anticoagulants and any neutralizing agent should be also recorded in detail including dose and time of administration.

- Assessment of hemostasis.

  Hemostasis at the TBS will be assessed by the investigator (surgeon) at T_4, T_7, and T_{10}. Hemostasis is defined as an absence/cessation of bleeding (Grade 0) at the TBS according to the investigator's (the surgeon's) judgment, so that the surgical closure of the exposed field could begin.

  In order to facilitate the observation of hemostasis, investigators should remove any excess of accumulated blood around the TBS area by careful aspiration/suction and/or gentle sponging with the edge of a sterile pad, for instance.

  Rebleeding is defined as Grade ≥1 bleeding from the TBS that requires further hemostatic intervention (e.g., manual pressure) after hemostasis is previously achieved at the TBS. If the TBS rebleeds but cessation of rebleeding is again achieved at a later time point, the effective hemostatic time point will be when the cessation of rebleeding happened.

- Assessment of AEs.

7.2.1.4 Post-Operative Day 4 (± 2 days)

A summary of Post-Operative Day 4 (± 2 days) assessments is provided in Appendix 1. The following assessments will be performed:

- Assessment of concomitant medications.
- Physical assessment.
- Recording of vital signs (HR, RR, SBP, DBP, and T).
- Coagulation panel: PT and aPTT.
- Hematology.
- Serum clinical chemistry.
- Assessment of AEs including any potential bleeding related complication.

After surgery, and in the event of the subject's hospital discharge before Post-Operative Day 4, scheduled procedures and assessments should be performed on Post-Operative Day 4 ± 2 days on an outpatient basis as appropriate.

7.2.1.5 Post-Operative Day 30 (± 7 days) – Final Study Visit

A summary of Post-Operative Day 30 (± 7 days) assessments is provided in Appendix 1. The following assessments will be performed:

- Assessment of concomitant medications.
- Physical assessment.

- Assessment of AEs including any potential bleeding related complication.

7.2.2 Description of Laboratory Tests and Procedures

Detailed descriptions of laboratory test procedures are located in the study Laboratory Manual. Table 7-2 provides an example summary of the laboratory tests conducted for this study.

Table 7-2 Name, Description, and Location of Laboratory Tests and Procedures

Test Panel	Description	Location
Hematology	Hgb, Htc, platelets, RBC, MCH, MCHC, MCV, WBC and differential, and platelet count	Central
Chemistry	Sodium, potassium, creatinine, chloride, calcium, BUN, LDH, AST, ALT, ALP, glucose, TB	Central
Coagulation panel	PT, aPTT	Central
Serum or urine pregnancy test	Qualitative serum β-HCG for females of child-bearing potential will be performed at Screening	Local

8 ASSESSMENT OF SAFETY

8.1 Safety Parameters

The safety of FS Grifols in pediatric subjects will be evaluated in this study. Safety endpoints will include:

- Adverse events including SAEs, suspected ADRs/adverse reactions (ARs), and discontinuations due to AEs
- Clinical laboratory panels (i.e., coagulation panel, hematology, serum clinical chemistry)
- Physical examination
- Vital signs

8.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

See Section 7.2.1 for specific timing for assessing, recording, and analyzing safety parameters.

8.2.1 Adverse Events

Adverse events occurring at any time between signing of the subject's ICF and the last day of the subject's participation in the clinical trial will be reported and recorded on the appropriate subject's eCRF entry and paper SAE Report Form (if serious).

It is investigator's responsibility to ensure that all AEs are appropriately recorded.

Adverse events will be elicited by spontaneous reporting by the study individual or by a non-leading inquiry or direct observation by the study staff.

8.2.2 Clinical Laboratory Evaluations

All clinical laboratory data for coagulation panel (PT and aPTT), hematology (RBC count, Hgb, Htc, MCH, MCHC, MCV, WBC count and differential, and platelet count), and serum clinical chemistry (creatinine, BUN, TB, ALP, ALT, AST, LDH, glucose, sodium, potassium, chloride and calcium) will be evaluated by the investigator for each clinical trial subject.

The investigator will be required to classify laboratory results out of the normal range reported by the laboratory as clinically relevant or not according to his/her judgment.

Laboratory results out of the normal range judged by the investigator as clinically relevant will be considered AEs.

8.2.3 Vital Signs

Vital signs will be measured by a medically certified individual or a nurse according to his/her standard clinical practice.

The following vital signs will be assessed:

- Temperature
- Systolic blood pressure and diastolic blood pressure
- Heart rate
- Respiration rate

Vital signs will be routinely monitored by the study staff as detailed in Appendix 1. The investigator will be required to classify vital signs abnormalities as clinically relevant or not according to his/her judgment. Results will be recorded in source documents and in the subject's eCRF. Vital signs abnormalities judged by the investigator as clinically relevant will be considered AEs.

8.2.4 Physical Examinations

A medically certified individual will conduct a physical examination.

Physical examinations will be classified as normal or abnormal, according to the investigator's judgment, and findings will be recorded in source documents and in the subject's eCRF. Abnormal physical findings judged as clinically relevant by the investigator in the context of the subject's medical condition will be considered AEs.

8.3 Procedures for Eliciting Reports of and for Recording and Reporting Adverse Event and Intercurrent Illnesses

8.3.1 Warnings/Precautions

For complete information on FS Grifols and EVICEL refer to the IB and PI, respectively (1,2).

8.3.2 Adverse Event Monitoring

Subjects must be carefully monitored for AEs. This monitoring includes clinical and laboratory tests and physical signs. Adverse events should be assessed in terms of their seriousness, severity, and causal relationship to study treatment.

Adverse events will be elicited by spontaneous reporting by the study individual or by a non-leading inquiry or direct observation by the study staff.

8.3.3 Adverse Event Definitions

8.3.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product or study treatment and which does not necessarily have a causal relationship with this administration. An AE can therefore be any unfavorable and unintended sign (including any abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

8.3.3.2 Suspected Adverse Drug Reactions/Adverse Reactions

All noxious and unintended responses to a medicinal product or study treatment related to any dose should be considered suspected ADRs. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product or study treatment and an AE is at least a reasonable possibility. A suspected ADR with a causal relationship of "definitely" will be labeled as an AR; thus, ARs are a subset of suspected ADRs.

8.3.4 Assessment of Causality of Adverse Event

The investigator is required to provide a causality assessment for each AE reported to the sponsor. The sponsor will consider the investigator's causality assessment and also provide its own assessment.

Causal relationship to the study drug will be established according to medical judgment on whether there is a **reasonable possibility of a causal relationship between the AE and study treatment administration**:

The investigator must determine and classify the AE causality according to the following categories:

Unrelated/Not related: there is not a reasonable possibility of causal relationship between the AE and the study treatment.

Possibly related: there is evidence to suggest a causal relationship between the study treatment and the AE.

Definitively related: there is a reason to conclude that the study treatment caused the AE.

Criteria to assess the causal relationship should take into account of the following conditions:

1. a plausible temporal sequence from the study treatment administration to the AE onset;
6. whether the event follows a known response pattern to the suspected treatment;
7. whether the AE could be reasonably explained by the subject's clinical state, comorbidities, or concomitant medications, as well as
8. the occurrence of improvement on stopping/reducing the treatment (positive dechallenge) and/or reappearance of the event on repeated exposure (positive rechallenge).

For expedited safety reporting purposes, AEs assessed as either "definitively related" or "possibly related" will be considered just RELATED or POTENTIALLY RELATED.

8.3.5 Severity of Adverse Event or Suspected Adverse Drug Reaction

Adverse events and suspected ADRs will be classified depending on their severity according to the following definitions:

Mild: the subject is aware of signs or symptoms causing minimum discomfort but no disruption of usual daily activities consistent with what would be expected in an uneventful postoperative course

Moderate: the AE is sufficiently discomforting to the subject that it interferes with usual daily activities consistent with what would be expected in an uneventful postoperative course (disturbing)

Severe: due to the AE, the subject is unable to perform usual daily activities consistent with what would be expected in an uneventful postoperative course (prevents)

AE and suspected ADR severity gradation must be distinguished from AE and suspected ADR seriousness gradation, which is defined according to event consequence. For example, headache can be mild, moderate, or severe but not necessarily serious in all these cases.

The investigator will be responsible for assessing the AE and suspected ADR intensity during the clinical trial, taking into account current criteria included in this section and according to the investigator's medical judgment.

8.3.6 Expectedness of Adverse Event or Suspected Adverse Drug Reaction

An AE or suspected ADR is considered "unexpected" if the nature, seriousness, severity, or outcome of the reaction(s) is not consistent with the reference safety information (e.g., IB or PI). The expectedness shall be determined by the sponsor according to the reference document (1,2) for any serious suspected ADRs (potentially related SAEs) for expedited safety reporting purposes.

8.3.7 Seriousness of Adverse Event or Suspected Adverse Drug Reaction

An AE or suspected ADR is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE (life-threatening in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- In-patient hospitalization or prolongation of existing hospitalization*
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event (important medical event in the definition of "serious" refers to those events which may not be immediately life-threatening, or result in death, or hospitalization, but from medical and scientific judgment may jeopardize the subject or/and may require medical or surgical intervention to prevent one of the other outcomes listed above).

**Hospitalization is to be considered only for a hospital stay of equal to or more than 24 hours.*

The following hospitalizations should not be reported as SAEs:

- hospitalization or prolongation of hospitalization needed for procedures required by the clinical trial protocol.
- hospitalization or prolongation of hospitalization as part of a routine procedure followed by the center.
- hospitalization for a survey visit, annual physicals, or social reasons.
- Elective or pre-planned hospitalizations for a pre-existing condition that had not worsened from baseline (e.g., elective or scheduled surgery arranged prior to start of the study).

- admissions not associated with an AE (e.g., social hospitalization for purposes of respite care).

This definition permits either the sponsor or the investigator to decide whether an event is "serious". If either the sponsor or the investigator believes that the event is serious, the event must be considered "serious" and evaluated by the sponsor for expedited reporting.

8.3.8 Adverse Event Documentation

All AEs and SAEs occurring after the subject has **signed the ICF through the final study visit (i.e., Post-operative Day 30±7 days)** must be fully recorded in the subject's eCRF, and paper SAE report form (if serious) as well as in the medical record. If no AE has occurred during the study period, this should also be indicated in the eCRF.

It is the responsibility of the investigator to ensure that AEs are appropriately recorded.

At each visit, AEs will be elicited by asking the individual a non-leading question such as "Do you feel different in any way since the last visit?" Moreover, AEs will also be collected through directly observed events or spontaneously volunteered by the subject. Clearly related signs, symptoms, and abnormal diagnostic procedures should preferably be grouped together and recorded as a single diagnosis or syndrome wherever possible.

The following variables must be recorded in the AE eCRF:

- The verbatim term (a diagnosis is preferred)
- Date/time of onset
- Date/time of resolution
- Severity (mild, moderate, severe)
- Causality (unrelated, possibly related, definitely related)*
- Seriousness (yes, no)
- Action taken (with regard to study treatment)
- Other action (to treat the event)
- Outcome and sequel (follow-up on AE)

**Causality assessment will be made only when the AE occurs after the subject has received the study treatment. An AE occurring before subject's exposure to study treatment will be always labeled as "unrelated".*

In addition to the investigator's own description of the AEs (verbatim term), each AE will be encoded according to the Medical Dictionary for Regulatory Activities (MedDRA®).

For example, a laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations) or judged clinically relevant in the context of the subject's medical condition by the investigator, should be reported as an AE. Each event must be described in detail along with start and stop dates, severity, relationship to IP, action taken and outcome. Each event must be adequately supported by documentation as it appears in the subject's medical or case file.

8.3.9 Reporting of Serious Adverse Events

8.3.9.1 Reporting of Serious Adverse Events

Any SAE (see Section 8.3.7) that occurs after **signing the study ICF through the final study visit (i.e., Post-operative Day 30± 7 days)** must be expeditiously reported whether or not considered attributable to the study treatment. Each SAE must be fully recorded in the subject's eCRF and additionally reported in a timely manner using the paper SAE Report Form.

SAEs will be reported using the designated paper SAE Report Form. When the investigator becomes aware of an SAE, she/he must submit a completed, signed and dated paper SAE Report Form (in English) **within 24 hours** to the sponsor by email/fax.

The date of this SAE discovery by the site staff should be documented in the source documents (i.e., medical records).

Each SAE must be followed up until resolution or stabilization. After the initial report, all relevant information for SAE follow-up, and for the outcome, must also be supplied to the sponsor in a timely manner (within 3 days from its identification or within 24 hours for relevant new information) by means of the paper SAE Report Form. In addition, the sponsor or contract research organization may request additional information and/or reports.

All paper SAE Report Forms must be reported to Grifols via email to:

Grifols Global Pharmacovigilance for Reporting SAEs and Pregnancy
Email: [redacted]
FAX: [redacted] (International)

When required, and according to local law and regulations, SAEs must be reported to the IRB/EC and regulatory authorities.

8.3.9.2 Reporting Pregnancy

Pregnancies occurring during the course of the study will not be considered an AE unless a relation to the study drug is suspected. In any case, a Pregnancy Report Form must be completed and sent as soon as possible to the sponsor for any pregnancies that occur in a female subject or partner of a male subject from time of consent through the final study visit

(i.e., end of study). A copy of the form should be filed at the study site for follow-up until the end of the pregnancy. Any pregnancy must be followed by the investigator until delivery or to the end of pregnancy. Any anomalies, complications, abnormal outcomes, or birth defect observed in the child must be reported as an SAE (see email address or fax number in Section 8.3.9.1) within 24 hours of the investigator or study personnel's first knowledge.

8.4 Type and Duration of the Follow-Up of Subjects after Adverse Events

In so far as is possible, all individuals will be followed up until the AE or suspected ADR has been resolved. If an AE/suspected ADR/SAE is present when the subject has completed the study, the course of the event must be followed until the final outcome is known, or the event has been stabilized and no further change is expected and the investigator decides that no further follow-up is necessary.

Any SAE that occurs after the end of the clinical study or after study completion due to early termination will not be actively collected. However, if such cases are reported by an investigator as potentially related to the study treatment, they will be entered into the safety database for expedited purposes. Conversely, if the investigator considers the event not related to the study treatment, then it will be considered a non-case.

9 STATISTICS

9.1 Statistical Methods

Unless otherwise specified, descriptive statistics will include the number of non-missing observations, mean, standard deviation (SD), median, minimum and maximum values for the continuous/quantitative data or absolute and relative frequency counts and percentages for categorical/qualitative data.

Data handling and evaluation procedures will be described in the Statistical Analysis Plan (SAP).

9.1.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment. For quantitative variables, mean, SD, median, and minimum/maximum will be provided. For qualitative variables, the frequency and percentage will be provided.

9.1.2 Efficacy Analysis

The primary efficacy analyses will be performed using the Modified Intent-to-Treat (mITT) population (see Section 9.5 for the definition of the mITT population). Additionally, the primary efficacy endpoint will be also analyzed using the Per-Protocol (PP) population (if different from the mITT population, see Section 9.5 for the definition of the PP population). For sensitivity analysis, the primary efficacy endpoint will be analyzed using the Intent-to-Treat (ITT) population (see Section 9.5 for the definition of the ITT population). For subjects

in both treatment groups in the ITT population who do not meet the intra-operative criteria and do not receive the study treatment, they will be deemed as not achieving hemostasis for the primary efficacy endpoint.

The primary efficacy endpoint of hemostasis at TBS by T_4 will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by type of surgery (i.e., parenchymous versus soft tissue surgery).The ratio of the proportion of subjects meeting the primary efficacy endpoint in the 2 treatment groups (FS Grifols relative to EVICEL) and its 2-sided asymptotic 95% CI will be provided. The non-inferiority will be deemed to have been demonstrated if the lower limit of the 95% CI exceeds 0.8. After the non-inferiority of FS Grifols to EVICEL is established, its superiority may be additionally claimed if the 95% CI for the ratio is entirely above 1.

Secondary efficacy endpoints will be analyzed by similar methods at other individual assessment time points (i.e., T_7 and T_{10}).

Exploratory efficacy endpoints will be descriptively summarized by treatment group. The proportion of subjects achieving at least 1 point decrease in bleeding intensity according to the 5-point validated bleeding severity scale by each of the defined observation time points (i.e., T_4, T_7 and T_{10}) will be analyzed using CMH test stratified by type of surgery (i.e., hepatic versus soft tissue surgery).

Also, an ordered categorical analysis of the hemostatic status at each of the assessment time points (i.e., T_4, T_7 and T_{10}) will be presented. For this, the subjects will be assigned to 1 of 4 categories on the basis of their TTH (0 to ≤4 minutes; >4 to ≤7 minutes; >7 to ≤10 minutes; >10 minutes).

Prevalence of treatment failures will be summarized and analyzed by treatment group.

9.1.3 Safety Analysis

The safety analyses will be based on the Safety population (see Section 9.5 for the definition of the Safety population). The safety analyses will be addressed by listing and tabulation of AEs and includes suspected ADRs, vital signs, physical assessments, and clinical laboratory tests. Data will be described using descriptive analyses.

9.1.3.1 Adverse Events

Adverse events will be coded and classified using MedDRA terms (system organ class and preferred terms).

When a causal relationship of an AE is classified by the investigator as definitively or possibly related, the event will be defined as a suspected ADR. A suspected ADR with a causal relationship of "definitively" will be defined as an AR. The sponsor will consider the investigator's causality assessment and also provide its own assessment. If there is any disagreement in causality assessment between the investigator and the sponsor, separate summary of suspected ADRs/ARs will be provided.

For summary purpose, AEs will be classified as TEAEs or non-treatment-emergent AEs (non-TEAEs) depending on the comparison of AE onset date/time with the start date/time of study treatment with the IP. A TEAE will be defined as an AE which occurs between the start of study treatment and the final visit of the clinical trial. A non-TEAE will be defined as an AE which occurs prior to the start of study treatment. Non-TEAEs and TEAEs will be summarized separately.

The incidence of TEAEs and suspected ADRs/ARs will be summarized by each treatment group, system organ class, preferred term, causal-relationship, intensity (severity) and seriousness (serious vs non-serious) using descriptive statistics. At each level of summarization, a subject will only be counted once per system organ class or preferred term using the most severe AE or the AE with the strongest causal relationship to study treatment.

Subjects with a SAE, AEs leading to death, or who withdraw from the study because of an AE will also be individually listed and summarized.

All AEs will be individually listed.

9.1.3.2 Clinical Laboratory Values

All clinical laboratory data will be summarized descriptively by treatment group and listed for each subject. Change from baseline will be descriptively summarized. Shift tables based on the high/low flags for out of range laboratory results will also be summarized.

The investigator will be required to classify out of the normal range laboratory results reported by the laboratory as clinically significant or not according to his/her judgment.

Out of the normal range laboratory results judged by the investigator as clinically significant in the context of the subject's medical condition will be considered AEs.

9.1.3.3 Vital Signs

Vital signs data and their change from baseline will be summarized descriptively by treatment group and listed for each clinical trial subject.

Clinically significant vital signs abnormalities will be considered as AEs based on the investigator's judgment.

9.1.3.4 Physical Assessment

Physical findings (normal and abnormal) will be listed for each clinical trial subject. Any clinically significant abnormality, as determined by the investigator, developed by an individual during the clinical trial and not already present at baseline will be reported as an AE.

9.2 Determination of Sample Size

The sample size of the study was estimated to provide sufficient power (at least 80%) to demonstrate the hemostatic efficacy of FS Grifols in parenchymous and soft tissue surgery.

Assuming that the true response rate is 80% for the FS Grifols group and 80% for the EVICEL group, it can be shown that a sample size of 172 subjects (86 subjects in the FS Grifols treatment group and 86 subjects in the EVICEL treatment group, with a 1:1 assignment ratio) would give a power of at least 80% to establish non-inferiority, with lower 95% CI for the ratio of the proportion of subjects with hemostasis success by 4 minutes in the 2 treatment groups (FS Grifols relative to EVICEL) above 0.80 (25-27).

The approximate number of subjects planned to be randomized according to age range will be as follows:

- Adolescents (12 to 17 years): up to 100, and not less than 50
- Children (2 to 11 years): up to 100, and not less than 50
- Infants and toddlers (28 days to 23 months): up to100, and not less than 16
- Preterm (up to gestational age <37 weeks) and term newborn infants (0 to 27 days): up to 10

In case any of the age subgroups mentioned above is underrepresented when the target of 172 enrolled (treated) subjects is met, the sponsor may allow over-enrollment of few additional subjects (i.e., not more than 10 additional subjects) beyond this figure in the specific age subgroup.

9.3 Procedure for Accounting for Missing, Unused, and Spurious Data

Unless otherwise noted, if an observation is missing at a specific scheduled visit/time point, the value at that visit should not be imputed and should be reported as “missing”. Hemostasis assessment is an exception. A missing hemostasis assessment at any scheduled time point will be deemed not to have achieved hemostasis at that specific time point only.

9.4 Reporting Deviations from the Statistical Analysis Plan

The detailed statistical analysis methodologies will be documented in the SAP. If there are any deviations from the originally planned analyses in the SAP, they will be fully described and justified in the protocol amendment(s) and/or final Clinical Study Report.

9.5 Subject Populations for Analysis

The ITT population will include all subjects who are randomized, regardless of meeting intra-operative enrollment criteria and regardless of whether the IP was administered to the subject.

The mITT population will include all subjects in the ITT population who meet intra-operative enrollment criteria, and thus treated with any amount of IP.

The PP population will include all subjects in the mITT population who do not have any major protocol deviations (to be determined at a data review meeting prior to unblinding) which could impact the primary efficacy endpoint.

The Safety population will include all subjects who receive any amount of IP.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The data will be recorded and kept current in eCRFs by the study site personnel directly responsible for the information and reviewed for completeness by the monitor. Grifols personnel or designee can review the records.

In accordance with ICH GCP guidelines, the monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency and to verify adherence to the protocol, and the completeness, consistency, and accuracy of data entered. "Source documentation" includes individual subject files, separate from the eCRFs, which should be maintained and include visit dates, laboratory results, concomitant treatment, vital signs, medical history, examinations, AEs, IP dispensing logs, and other notes as appropriate. The investigator agrees to cooperate with the monitor to ensure that any problems noted during the course of these monitoring visits are resolved.

11 QUALITY CONTROL AND QUALITY ASSURANCE

Monitoring and auditing procedures defined/agreed by the sponsor will be followed, in order to comply with ICH GCP guidelines. Each center will be visited at intervals defined in the Clinical Monitoring Plan by a monitor to ensure compliance with the study protocol, ICH GCP, and legal aspects. The on-site verification of the eCRF for completeness and clarity will include cross checking with source documents, and clarification of administrative matters. Query verification of data will be described in the Data Management Plan.

Representatives of regulatory authorities or of Grifols may conduct audits or inspections of the investigator study site. If the investigator is notified of an audit or inspection by a regulatory authority, the investigator agrees to notify the Grifols representative (e.g., Clinical Assessment Monitor, Program Manager, Program Leader) immediately. The investigator agrees to provide to representatives of a regulatory authority or Grifols access to records, facilities, and personnel for the effective conduct of an audit or inspection.

12 ETHICS

12.1 Institutional Review Board/Ethics Committee

Documented approval from appropriate IRBs/ECs will be obtained for all participating centers/countries prior to study start, according to ICH GCP guidelines, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IRBs/ECs approval must be obtained and also forwarded to the sponsor. The IRBs/ECs must supply to the sponsor, upon request, a list of the IRBs/ECs members involved in the vote and

a statement to confirm that the IRBs/ECs is organized and operates according to ICH GCP guidelines and applicable laws and regulations.

12.2 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by ICH GCP guidelines. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an audit by the sponsor representatives and/or an inspection by regulatory authority representatives at any time.

In this clinical trial we capture race per FDA guidance standards. Standard classification for race and ethnicity comes from CDASH standard of CDISC Approved Controlled Terminology that is widely used worldwide for clinical development data capture for regulatory purposes (28). All clinical trial data collection including race are securely stored in electronic data capture (EDC) system which is in compliance with 21 CFR Part 11 and GDPR.

There is no possible race discrimination in the treatment assignation of subjects participating in this clinical trial due to the double blinded nature of this clinical trial in which the allocation of subjects to different treatment groups is at random. The collection of race won't induce any change in the therapeutic decisions in the context of patients participating in the clinical trial.

The investigator must agree to the audit or inspection of study-related records by the sponsor representatives and/or regulatory authority representatives, and must allow direct access to source documents to the sponsor and/or regulatory authority representatives.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard(s) to the study subjects without prior IRB/EC/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IRB/EC/sponsor. Any deviations from the protocol must be fully explained and documented by the investigator.

No medical waivers for protocol inclusion/exclusion criteria will be allowed by the sponsor, and that in case the need for a change to the protocol is identified, it will be submitted as a protocol amendment to the competent regulatory authority and/or EC as applicable per regulations.

12.3 Regulatory Authority Approvals/Authorizations

Regulatory authority approvals/authorizations/ notifications, where required, must be in place and fully documented prior to study start. Study information including contact information for investigator sites responsible for conducting the study will be posted on a publicly accessible clinical registry(ies) as required by local law.

12.4 Subject Information and Consent

Subject information and ICF will be provided to investigator sites. Prior to the beginning of the study, the investigator must have the IRB/EC written approval/favorable opinion of the written ICF and any other written information to be provided to subjects. The written approval of the IRB/EC together with the approved subject information/ICF must be filed in the study files and a copy of the documents must also be provided to sponsor by the investigator site.

Written ICF by the subject or a parent and/or legal guardian along with subject assent must be obtained before any study specific procedure takes place. Participation in the study and date of ICF given by the subject should be documented appropriately in the subject's files. A signed copy of the subject ICF will be provided to the subject or subject's authorized representative.

12.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject code number will be recorded in the eCRF, and if the subject's name appears on any other document (e.g., pathologist report), it must be redacted before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. Subjects will be informed in writing that representatives of the sponsor, IRB/EC, or regulatory authorities may inspect their medical records and personal health information to verify the information collected, and that all personal information made available for an audit or inspection will be handled in strictest confidence and in accordance with local data protection laws.

When the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Handling

The study data will be recorded and kept current in the eCRF by the site study personnel directly responsible for the information. Entries made in the eCRF must be verifiable against source documents. The data in the eCRF will be monitored at the site by Grifols representatives at regular intervals and reviewed for completeness and compared with the source documents. Examples of acceptable source documents include individual subject medical records, prospective information gathered on source documentation worksheets, lab reports and other diagnostics pertinent to this study which are separate from the eCRFs. The listing of types of source documents and their location at the site, which will be defined in the source data agreement, will be filed in Trial Master File.

All AEs and SAEs must be recorded. All SAEs must be recorded on the SAE report form. The SAE report form must be kept in site records with a copy provided to the designated person as detailed in the study file.

13.2 Record Retention

At study completion, all study data will be transferred to Grifols according to ICH GCP guidelines, local laws, regulations, and Grifols requirements. The study file and all source data should be retained until notification is given by the sponsor for destruction.

An investigator is required by ICH GCP guidelines to retain the study files. If an investigator moves, withdraws from an investigation or retires, the responsibility for maintaining the records may be transferred to another person (e.g., other investigator). Grifols must be notified in writing of the person responsible for record retention and the notification will be retained in the sponsor study file and the investigator site file.

14 FINANCING AND INSURANCE

In the event of subject injury as a direct result of either administration of investigational product or any non-standard of care study procedure, the sponsor will pay for the costs of treatment, provided the subject has followed the instructions given by the study doctor and the illness or injury is not due to the natural progression of any conditions existing before the subject participated in the study. Financial compensation for such things as lost wages, disability, or discomfort due to any research-related injury is not available.

Sponsor shall maintain comprehensive general liability insurance or self-insurance in amounts adequate to cover any damage, demand, claim, loss or liability caused or incurred by the sponsor, or as otherwise required by applicable laws and/or regulations.

15 PUBLICATION POLICY

Institution and the investigator agree that the first publication shall be made in conjunction with the presentation of a joint, multi-center publication of the study results from all appropriates sites. If such a multi-center publication is not submitted within 12 months after conclusion of the study at all sites or after Grifols confirms there will be no joint, multi-center publication, then institution and/or investigator shall have the right, at their discretion, to publish, either in writing or orally, the results of the study performed under the protocol, subject to the conditions outlined below:

- The results of the study will be reported in the publicly accessible registry(ies).
- Institution and/or investigator shall furnish Grifols with a copy of any proposed publication at least 30 days in advance of the date of submission for publication.
- Within said 30 day period, Grifols shall:
  - Review such proposed publication for confidential information (other than study results) and for subject information subject to the Health Insurance Portability and Accountability Act of 1996 and other applicable privacy laws;

- Review such proposed publication for the unauthorized use of the name, symbols and/or trademarks of Grifols;
- By written notice to the investigator, identify with specificity the text or graphics in such proposed publication that Grifols contends contains confidential information, protected subject information, or the unauthorized use of Grifols' name, symbols and/or trademarks so that the proposed publication may be edited appropriately to remove such text or graphics before publication; and
- By written request, Grifols may delay proposed publications up to 60 days to allow Grifols to protect its interests in Grifols inventions described in such publications.

- Institution and/or investigator shall give Grifols the option of receiving an acknowledgment for its sponsorship of the study in all such publications or presentation.

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17 APPENDICES

Appendix 1 Schedule of Study Procedures and Events

Phase	Screening Visit[a]	Baseline Visit[a]	Day of Surgery				Post-Operative Visits	
Visit	1	2	3				4	5
Time Period			Day 1					
Procedures and Tests	Day -21 to -1	Day 0	Preoperative	Observational Period	Intraoperative	Postoperative	Day 4 ± 2	Final Study Visit Day 30 ± 7
Informed consent	X							
Inclusion/Exclusion criteria	X	X						
Medical/Surgical history	X	X						
Demographics	X							
Bleeding history	X							
Topical hemostat history	X							
Height and weight		X						
Physical examination		X					X	X
Vital signs		X[b]	X	X[c]	X[d]		X[b]	
Pregnancy test[e]		X						
Randomization		X						
TBS identification					X			
Rate bleeding at TBS[f]					X			
Rate size of TBS					X			
Record anatomical location of TBS					X			
Record type of TBS[g]					X			
Intra-operative inclusion/exclusion criteria					X			
IP preparation			X					
FS Grifols or EVICEL application					X			
Record T_{start}					X			
Hemostatic assessment[h]				X				
Record $T_{Closure}$					X			
Record $T_{Completion}$					X			
Coagulation[j]		X					X	
Hematology[i]		X					X	
Clinical chemistry[k]		X					X	
Prior/Concomitant medications[l]	X	X	X		X	X	X	X
Adverse events		X	X	X	X	X	X	X

Phase	Screening Visit[a]	Baseline Visit[a]	Day of Surgery				Post-Operative Visits	
Visit	1	2	3				4	5
Time Period			Day 1					
Procedures and Tests	Day -21 to -1	Day 0	Preoperative	Observational Period	Intraoperative	Postoperative	Day 4 ± 2	Final Study Visit Day 30 ± 7

IP: investigational product; TBS: target bleeding site; $T_{Closure}$: time of completion of the surgical closure by layers of the exposed surgical field containing the TBS; $T_{Completion}$: time of completion of surgical incision closure – when the last skin closure stitch is put in – of the last exposed file, regardless of if it was the field containing the TBS; T_{Start}: time of the start of initial investigational medicinal product (FS Grifols or EVICEL) application

[a] Procedures scheduled at the Screening Visit may be done during the Baseline Assessments Visit (i.e., within 24 hours prior to the surgical procedure). Assessments required during both visits (Screening and Baseline) must be performed.

[b] Vital signs to include HR, RR, SBP, DBP, and T.

[c] Vital signs to include HR, RR, SBP, DBP, and T immediately prior to skin incision to expose the surgery field and at 5 minutes after T_{Start}.

[d] Vital signs to include HR, RR, SBP, and DBP recorded at 30 minutes after T_{Start}, every 30 minutes until $T_{Closure}$, and at $T_{Completion}$.

[e] Human chorionic gonadotropin-based blood or urine assay for subjects of childbearing potential to be performed locally at the investigative site within 24 hours prior to the surgical procedure. See Section 5.2

[f] 5-point validated bleeding severity scale: Grade 0 (No bleeding), Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (severe), or Grade 4 (life-threatening). Only subjects with Grade 1 (mild) or Grade 2 (moderate) bleeding are eligible for participation. Any subject with Grade 3 (severe) bleeding that cannot be controlled with standard conventional surgical techniques (e.g., cautery, sutures, clips, or ligation) to Grade 1 or 2 or subjects with Grade 4 (life-threatening) bleeding should be withdrawn from the study. See Table 7-1

[g] Type of soft tissue TBS (i.e., fat, muscle, or connective tissue).

[h] Hemostatic assessment of the TBS at 4, 7, and 10 minutes following T_{Start}.

[i] Hematology assessments include: Hgb, Hct, platelets, RBC, MCH, MCHC, MCV, WBC and differential.

[j] Coagulation assessments include PT and aPTT

[k] Clinical chemistry assessments include creatinine, BUN, TB, ALP, ALT, AST, LDH, glucose, sodium, potassium, chloride, and calcium

[l] Prior medications for the last 3 months and concomitant medication during study participation

Appendix 2 Summary of Changes Version 4.0 to Version 5.0

Note: Administrative changes including minor administrative corrections are not included in Protocol Summary of Changes.

Sections	Change From: (Version 4.0) (Strikethrough is added to highlight deleted text.)	Change To: (Version 5.0) (Underline is added to highlight new text.)	Rationale:
Appendices 1 and 2	Removed headers	(no header)	Administrative change to remove incorrect header from the document. Template updated to remove header, this header was left in inadvertently.