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A Prospective, Randomised, Controlled, Study Evaluating the Safety and Effectiveness of EVARREST® Sealant Matrix in Controlling Mild or Moderate Hepatic Parenchyma or Soft Tissue Bleeding During Open Abdominal, Retroperitoneal, Pelvic and Thoracic (non-cardiac) Surgery in Paediatric Patients

The EVARREST® Paediatric Mild/Moderate Liver and Soft Tissue Bleeding Study

Protocol Number: 400-12-004

Original Protocol:	06 November 2013
Amendment 1:	04 December 2014
Amendment 2:	17 March 2016
Amendment 3:	13 December 2016
Amendment 4:	05 March 2018
Administrative Change 5:	29 April 2020

Sponsor:

ETHICON, Inc.
P.O. Box 151
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Somerville, NJ 08876-0151

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Protocol Approved by:

[redacted]

Compliance Statement
This study will be conducted in accordance with specific provisions of the associated IRB/IECs, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable national and regional regulatory requirement(s).

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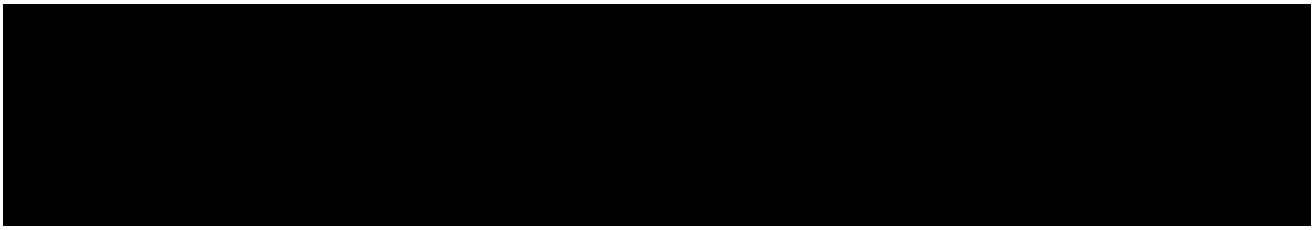

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Principal Investigator:

I have read this protocol and agree to conduct this clinical investigation in accordance with the design and specific provisions outlined herein. I understand the protocol, and I understand I am solely responsible to ensure the investigation is conducted in accordance with Good Clinical Practices (GCP), applicable country regulations the Declaration of Helsinki, the signed clinical study contract with Sponsor and with the protocol outlined herein. I will conduct this study as outlined therein and will make reasonable effort to complete the study within the time period designated by the Sponsor.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who will assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the product and the conduct of the study.

I will fulfill the requirements of my Institutional Review Board (IRB)/Ethics Committee (EC), or other oversight committee, to ensure complete and continual oversight of this clinical investigation. I will use an Informed Consent Document approved by the Sponsor and my reviewing IRB/EC (where required).

I agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events, product related adverse events, or procedure related adverse events as defined in this protocol to the Sponsor, and comply with all adverse event reporting requirements of my reviewing IRB/EC. I agree to permit the Sponsor, its authorized representatives, my reviewing IRB/EC, and any regulatory authority/body access to all records relating to the clinical investigation.

The below signature confirms I have read and understood this protocol and its associated amendments or attachments and will accept respective revisions or amendments provided by the Sponsor.

_____ _____

Investigator Signature Date

_____

Investigator Name (printed)

_____

Site Identification Number

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A Prospective, Randomised, Controlled, Study Evaluating the Safety and Effectiveness of EVARREST Sealant Matrix in Controlling Mild or Moderate Hepatic Parenchyma or Soft Tissue Bleeding During Open, Abdominal, Retroperitoneal, Pelvic and Thoracic (non-cardiac) Surgery in Paediatric Patients

SYNOPSIS

OBJECTIVES: To evaluate the safety and haemostatic effectiveness of EVARREST Sealant Matrix (EVARREST Fibrin Sealant Patch) (EVARREST) in controlling mild or moderate soft tissue & parenchymal bleeding during open hepatic, abdominal, pelvic, retroperitoneal, and thoracic (non-cardiac) surgery in paediatric patients.

STUDY DESIGN: This is an open label, prospective, randomised, multicentre, controlled, clinical study comparing EVARREST to SURGICEL (oxidized regenerated cellulose (ORC)) (Control) as an adjunct to haemostasis when conventional methods of controlling mild or moderate bleeding are ineffective or impractical during surgery in paediatric patients.

At least 40 qualified paediatric subjects with an appropriate mild or moderate bleeding Target Bleeding Site (TBS) will be randomised in a 1:1 allocation ratio to either EVARREST or SURGICEL (control). Absolute time to haemostasis will be assessed as well as haemostasis at 4 and 10 minutes from randomisation.

Enrolment will be staggered by age (as required by the European Medicines Agency (EMA) Paediatric Committee). The first 36 subjects enrolled will be aged ≥1 years to <18 years of age. Enrolment of a subsequent group will include 4 subjects from 1 month (≥ 28 days from birth) to <1 year of age will follow. Ongoing safety assessment will ensure adequate safety monitoring occur during the staged enrolment.

Subjects will be followed post-operatively through hospital discharge and at 30 days (+/-14 days) post-surgery.

TBS DEFINITION: The Target Bleeding Site (TBS) will be defined as the first accessible mild or moderate bleeding site identified in the hepatic parenchyma or soft tissue, where conventional methods of controlling bleeding are ineffective or impractical, and is amenable to manual compression. The TBS must be a site where occlusion of the injured tissue surface blood vessels is required to achieve haemostasis.

The TBS must be an area that can have firm pressure applied and maintained continuously until 4 minutes after randomisation, and to which EVARREST can be applied with a margin of 1-2cm. (Refer to Investigator's Brochure).

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

BLEEDING SEVERITY:

Mild Bleeding: a TBS with a small area of capillary, arteriole or venule oozing

Moderate Bleeding: a TBS with a larger area of capillary, arteriole, or venule oozing that presents a significant challenge because of the larger area involved, increasing the volume of blood loss,
Or
A TBS with bleeding that is more pronounced than oozing, that could also come from a small artery or vein, but is not massive.

Severe Bleeding (EXCLUDED FROM THIS PROTOCOL): (arterial, venous, or mixed) that is rapidly flowing, pulsatile or spurting that in the surgeon's judgment requires rapid control to prevent hemodynamic consequences (e.g. hypovolemia, tachycardia, or hypotension) and could involve major volume loss which if not treated rapidly could be life threatening. EVARREST or SURGICEL should not be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial bleeding.

PROCEDURE:

The TBS will be identified during the dissection related to the primary operative procedure. This will be the site assessed for haemostatic effectiveness.

Once the TBS is identified, the surgeon will immediately randomise the subject into the study. The randomly assigned treatment (EVARREST or SURGICEL) will be applied immediately at the actively bleeding TBS. The size of the treatment article applied should be sufficient for coverage of the entire TBS, and should overlap the bleeding source with a margin of 1-2 cm.

Randomised Subjects

After placement of the assigned study treatment (EVARREST or SURGICEL)**,** firm manual continual manual compression will be applied over the entire bleeding area until 4 minutes from randomisation. The surgeon may use a surgical sponge (laparotomy pad or surgical gauze) to assist in providing adequate pressure over the entire surface area.

Haemostasis is defined as no detectable bleeding at the TBS. Absolute time to haemostasis, defined as the absolute time elapsed from randomisation to the last moment in time at which detectable bleeding at the TBS is observed, will be recorded.
Haemostasis will be assessed at 4 minutes from randomisation by carefully releasing manual compression and removing the surgical sponge (if used). Haemostasis will also be assessed at 10 minutes from randomisation and absolute time to haemostasis will be recorded.

For patients assigned to EVARREST, the EVARREST should not be removed once bleeding has been stopped.

For all subjects, if bleeding requiring treatment occurs after the 4 minute assessment the surgeon can revert to their standard of care for treatment.

Additional Treatment Impact on the Success/Failure of Endpoints

- Any additional treatment at the TBS after the 4 minute endpoint will be considered a failure for the 4 minute secondary endpoint.
- Any additional treatment after the 10 minute time point will be considered a failure for the 10 minutes secondary endpoint.

Any EVARREST re-treatment must be performed according to the Investigator's Brochure.

All subjects will have haemostasis assessed at 10 minutes after randomisation and have absolute time to haemostasis recorded regardless of any additional treatments.

EVARREST can only be used on a single TBS to be evaluated. If additional soft tissue or hepatic parenchymal bleeding sites are identified, the surgeon should treat according to their standard of care.

TEST PRODUCT: EVARREST Sealant Matrix/ EVARREST Fibrin Sealant Patch

STUDY POPULATION: Paediatric subjects, undergoing non-emergent abdominal, retroperitoneal, pelvic, hepatic or thoracic (non-cardiac) surgery procedures, wherein an appropriate TBS is identified. For this study paediatric subjects for this study are defined as; Infants and toddlers (28 days (1 month) from birth to 23 months), Children (2 to 11 years) and Adolescent (12 to less than 18 years).

New born infants (0-27 days from birth) are excluded from this study. Pre-term births are excluded from this protocol until the subject reaches 28 days from 37 weeks of pregnancy as determined by the investigator.

PRIMARY ENDPOINT: Absolute time to haemostasis defined as the absolute time elapsed from randomisation to the last moment in time at which detectable bleeding at the TBS is observed.

SECONDARY ENDPOINTS:

- Proportion of subjects achieving haemostatic success at 4 minutes following randomisation and no bleeding requiring treatment at the TBS occurs any time prior to final fascial closure
- Proportion of subjects achieving haemostatic success at 10 minutes following randomisation and no bleeding requiring treatment at the TBS occurs any time prior to final fascial closure
- Proportion of subjects with no re-bleeding at the TBS
- Incidence of adverse events that are potentially related to bleeding at the TBS;
- Incidence of adverse events that are potentially related to thrombotic events;
- Incidence of re-treatment at the TBS;
- Incidence of adverse events
- Summarization of Haemoglobin, Haematocrit, Platelets laboratory results, volume of blood loss, & volume of blood and blood products transfusions

SAFETY: Adverse events will be collected from time of randomisation, throughout the follow-up period. Intra-operative bleeding at the TBS after 10 minutes will be an adverse event.
The following data will also be collected: laboratory tests (including Haemoglobin, Haematocrit, Platelets), volume of blood loss and volume of blood product transfused.

STATISTICAL ANALYSIS: Sample size of 40 subjects is considered adequate to summarize data descriptively. The continuous data will be summarized by number of subjects, mean, median and standard deviation (SD). The categorical data will be summarized by frequency along with associated percentages. Two-sided 95% confidence intervals (CIs) for median absolute time to haemostasis will be reported separately for EVARREST and SURGICEL groups. In addition, for success/failure secondary endpoints (4 and 10 minutes haemostasis endpoints), two-sided 95% CI will be reported for P_F, P_C and for ratio P_F /P_C where P_F is the proportion of success in EVARREST subjects and P_C is the proportion of success in control subjects. The lower limits of these 95% CI will be utilized for statistical inferences.

SAMPLE SIZE: At least 40 randomised subjects.

Surgical Procedures: Open surgical procedures with challenging mild or moderate hepatic parenchyma or soft tissue target bleeding sites.

The surgical procedures must be **open** procedures, to allow for appropriate EVARREST application. When patients are undergoing abdominal and thoracic (non-cardiac) procedures, open is defined as the opening of the peritoneum or pleura. The following surgical procedures are permitted to be included in this study:

- Hepatic
- Intra-Abdominal
- Intra-Thoracic (Non-Cardiac)
- Retroperitoneal
- Pelvic (Extra-peritoneal space)

Laparoscopic, thoracoscopic and other endoscopic procedures are excluded from this study.

Soft Tissue includes but may not be limited to the following tissue types:

- Muscle
- Lymph node beds
- Lymphatic Tissue
- Fat
- Loose Areolar Connective Tissue

The study will target to have approximately a minimum of 25% of procedures with the target bleeding site in the hepatic parenchyma and approximately a minimum of 25% of procedures with the target bleeding sites in soft tissue. Enrolment will be monitored by the sponsor and the Investigators will be notified by the sponsor once those targets have been met.

Inclusion Criteria

Pre-operative:

1. Paediatric subjects aged ≥28 days (≥ 1 month) to <18 years, requiring non-emergent open hepatic, abdominal, retroperitoneal, pelvic or thoracic (non-cardiac) surgical procedures;
    i) The first 36 subjects to be enrolled will be subjects aged ≥1 years to <18 years.
    ii) The next 4 subjects to be enrolled will be subjects aged ≥28 days to <1 year.
2. The subject's parent/legal guardian must be willing to give permission for the subject to participate in the trial, and provide written Informed Consent for the subject. In addition, assent must be obtained from paediatric subjects who possess the intellectual and emotional ability to comprehend the concepts involved in the trial. If the paediatric subject is not able to provide assent (due to age, maturity and/or inability to intellectually and/or emotionally comprehend the trial), the parent/legal guardian's written Informed Consent for the subject will be acceptable for the subject to be included in the study.

Intra-operative

3. Presence of an appropriate mild or moderate bleeding soft tissue or hepatic parenchyma Target Bleeding Site (TBS) identified intra-operatively by the surgeon;
4. Ability to firmly press trial treatment at TBS until 4 minutes after randomisation;

Exclusion Criteria

Pre-operative

1. Subjects with known intolerance to blood products or to one of the components of the study product or is unwilling to receive blood products;
2. Female subjects, who are of childbearing age (i.e. adolescent), who are pregnant or nursing;
3. Subject is currently participating or plans to participate in any other investigational device or drug without prior approval from the Sponsor;
4. Subjects who are known, current alcohol and/or drug abusers
5. Subjects admitted for trauma surgery
6. Subjects with any pre or intra-operative findings identified by the surgeon that may preclude conduct of the study procedure.

Intra-operative

7. Subject with TBS in an actively infected field (Class III Contaminated or Class IV Dirty or Infected)[1]
8. TBS is from large defects in arteries or veins where the injured vascular wall requires repair with maintenance of vessel patency and which would result in persistent exposure of the EVARREST or SURGICEL to blood flow and pressure during healing and absorption of the product;
9. TBS with major arterial bleeding requiring suture or mechanical ligation;
10. Bleeding site is in, around, or in proximity to foramina in bone, or areas of bony confine.

[1] Appendix 1

SCHEDULE OF EVENTS

Procedures	**Screening** (within 21 days prior to procedure) [5]	**Baseline** (within 24 hours prior to procedure)	**Surgical Procedure**	**Post-Surgery to Hospital Discharge**	**30-Day Follow Up** (+/- 14 days)
Inclusion/ Exclusion	**X**	**X**	**X**		
Informed Consent / Assent (as applicable)	**X**				
Demographics	**X**				
Medical and Surgical History	**X**	**X**[2]			
Concomitant Medications		**X**	**X**	**X**	**X**
Physical Exam (including height and weight)	**X**			**X**	**X**
Full Blood Count with Differential	**X**[3]	**X**[3]		**X**	
Coagulation (PT, aPTT, INR)	**X**[3]	**X**[3]		**X**	
Pregnancy Tests (if applicable)		**X**[3]			
Randomisation			**X**		
Treatment Application and Haemostasis assessment			**X**		
Determination of Haemostasis at TBS			**X**		
Operative/Surgical information[4]			**X**	**X**	
Assessment of bleeding or thrombotic events			**X**	**X**	**X**
Adverse Events			**X**	**X**	**X**

[2] Review for changes in medical history from screening visit and preform pregnancy test (if applicable)
[3] At least one FBC with differential and coagulation parameter are needed pre-procedure. If pre-operative blood tests are repeated, the blood test closest to the date prior to surgery will be used.
[4] Including length of stay, blood loss and transfusion information.
[5] May be combined with Baseline visit

1. INTRODUCTION

Bleeding during surgical procedures may manifest in many forms. It can be discrete or diffuse from a large surface area. It can be from large or small vessels; arterial (high pressure) or venous (low pressure) of high or low volume. It may be easily accessible or it may originate from difficult to access sites. The bleeding tissues may be firm or friable.

Conventional methods to achieve haemostasis include use of surgical techniques, sutures, ligatures or clips, and energy-based coagulation or cauterisation. When these conventional measures are ineffective or impractical, adjunctive haemostasis techniques and products are typically utilized, including topical absorbable haemostats such as oxidized regenerated cellulose, gelatin, or collagen and active haemostats such as topical thrombin or fibrin sealants.

Fibrin sealants are typically dual component systems consisting of virus-inactivated, human plasma-derived thrombin and fibrinogen. The two components are mixed during application to a target site and upon combination mimic the final step in the coagulation pathway to form a stable, physiological fibrin clot that assists in healing[i]. The fibrinogen component may also contain anti-fibrinolytic agents. Fibrin sealants have proven to be valuable adjuncts for haemostasis in a variety of surgical and endoscopic procedures. They have been successfully used as biodegradable tissue adhesives for haemostasis, wound healing, or tissue sealing purposes in cardiovascular, thoracic, neurologic, gastrointestinal, urologic, gynaecologic, hepatic and plastic and reconstructive surgical procedures[ii,iii,iv,v,vi]. They have also been evaluated in bleeding from soft tissue tumour beds following surgical resection[vii]. Fibrin sealants have been shown to reduce post-operative complications, including blood loss and reduce the need for repeated procedures by promoting wound healing[viii].

The requisite preparation time for lyophilised products can be impractical and furthermore the use of fibrin sealants can complicate the application of pressure to the bleeding site, in that applied pressure can disrupt the sealant bond or cause the sealant to adhere to gloves or gauze. Application of fibrin sealants to actively bleeding sites can result in the sealant lifting or floating off the target site[ix], particularly in high volume or high pressure bleeding.

EVARREST Sealant Matrix/EVARREST Fibrin Sealant Patch (EVARREST) is a topical absorbable haemostat and will be evaluated in this study to measure its safety and effectiveness in controlling mild/moderate bleeding from hepatic parenchyma or soft tissue as required by the Paediatric Investigational Plan.

The Product

EVARREST is a sterile bio-absorbable combination product consisting of two constituent parts— a flexible backing and a coating of two biological components (Human Fibrinogen and Human Thrombin). The product has been developed for the management and rapid control of bleeding, including active, challenging bleeding.

The primary mechanism of action of EVARREST follows the principles of normal physiological fibrin clot formation. Upon contact with a bleeding wound surface, the biological components (Human Fibrinogen and Human Thrombin) on the matrix hydrate and the subsequent fibrinogen-thrombin reaction initiates the last step of blood clot formation in a normal and well-understood biochemical reaction. Haemostasis occurs when fibrinogen is converted into fibrin monomers, which spontaneously polymerize to a fibrin clot, forming a sealing layer that adheres to the tissue surface and integrates into the matrix. The matrix component provides physical support and a large surface area for the biological components, imparts inherent mechanical integrity to the product and supports clot formation. Natural healing occurs as the

product is absorbed by the body, which is expected to occur within approximately 8 weeks, as demonstrated in rodent and swine animal models.

The patch component of EVARREST consists of an oxidized regenerated cellulose (ORC) layer underlying a layer of polyglactin 910 (PG910) non-woven fibers. The PG910 layer contains the embedded biological components. The patch component provides a large surface area for the biological components and imparts inherent mechanical integrity to the product. The flexibility of EVARREST accommodates the physiological movements of tissues and organs.

Safety concerns potentially linked to the fibrinogen and thrombin components when used in fibrin sealants include the risks of viral transmission and anaphylactic and/or hypotensive reactions. Two independent virus inactivation/removal steps are included in the production process of each biological component of fibrin patch. These procedures ensure a high level of viral safety. As these biological components are of human origin, the risk of anaphylactic reaction should be reduced compared to fibrin sealants containing material of bovine origin.

EVARREST has been evaluated in three early phase clinical studies and five pivotal clinical studies:

1. Phase I study to evaluate the safety of the product when used adjunctively in partial nephrectomy procedures. EVARREST was used in this study as an adjunct to haemostasis (after attempts to control bleeding with conventional surgical techniques had been made).
2. Phase II study using EVARREST actively (not adjunctively) in partial nephrectomy procedures.
3. Pivotal study in 141 subjects with mild to moderate bleeding in retroperitoneal, intra-abdominal, pelvic and thoracic (non-cardiac) soft tissue conducted in US.
4. A Phase III non-IND pivotal clinical trial in 91 subjects with severe bleeding in retroperitoneal, intra-abdominal, pelvic and thoracic (non-cardiac) soft tissue conducted in Europe (UK and Germany), Australia and New Zealand.
5. A Phase III non-IND pivotal clinical trial in 104 adult subjects undergoing hepatic surgery conducted in Europe (UK, Germany, The Netherlands), Australia and New Zealand
6. A Phase II clinical trial in 42 adult subjects undergoing cardiovascular surgery conducted in the US.
7. A Phase III IND pivotal clinical trial in 102 adult subjects undergoing hepatic surgery conducted in the US, UK, Australia and New Zealand.
8. A Phase III clinical trial in 156 adult subjects undergoing cardiovascular (aortic) surgery conducted in the US, Europe (UK and Belgium), Japan and Australia.

Integrating the six randomized studies (3-8 above), of 298 randomised subjects treated with EVARREST, 89.9% achieved haemostasis at 3 or 4 minutes of randomisation and 97% achieved haemostasis within 10 minutes of randomisation. By comparison, of 267 control subjects 49.4% achieved haemostasis at 3 or 4 minutes of randomisation and 78.3% achieved haemostasis at 10 minutes.
A Phase 2 clinical study indicated that EVARREST is an effective haemostat in the clinical scenario of aortic reconstruction surgery, in systemically anticoagulated subjects on cardiopulmonary bypass, within a range of hypothermia. In the clinical setting of the study, EVARREST had a higher success rate than both TachoSil® (an Absorbable Fibrin Sealant Patch approved for use in cardiovascular surgery) and current standard of care methods in achieving immediate and durable haemostasis at the anastomotic suture line during cardiovascular surgery. No safety signals were identified during the study.

In addition, A Phase III clinical study provided additional evidence that EVARREST is safe and effective when administered with manual compression during cardiovascular surgery, wherein subjects underwent major aortic reconstruction. EVARREST was shown to be superior to TachoSil with a success rate significantly higher compared to the success rate in the TachoSil group across all efficacy time points.

The safety results showed that the incidence of clinically meaningful adverse events is evenly distributed between treatment groups and were of a nature to be expected following these surgical procedures.

2. STUDY OBJECTIVES

The objective of this study is to evaluate the safety and haemostatic effectiveness of the EVARREST versus control (SURGICEL ORC) as an adjunct to controlling mild to moderate soft hepatic parenchyma or soft tissue bleeding during open hepatic, abdominal, pelvic, retroperitoneal, and thoracic (non-cardiac) surgery in paediatric population.

The primary endpoint will be the absolute time to haemostasis, defined as the absolute time elapsed from randomisation to the last moment in time at which detectable bleeding at the TBS is observed.

The secondary endpoints of this study include:

- Proportion of subjects achieving haemostatic success at 4 minutes following randomisation and no bleeding requiring treatment at the TBS occurs any time prior to final fascial closure
- Proportion of subjects achieving haemostatic success at 10 minutes following randomisation and no bleeding requiring treatment at the TBS occurs any time prior to final fascial closure
- Portion of subjects with no re-bleeding at the TBS.
- Incidence of adverse events that are potentially related to bleeding at the TBS;
- Incidence of adverse events that are potentially related to thrombotic events;
- Incidence of re-treatment at the TBS;
- Incidence of adverse events
- Summarization of Haemoglobin, Haematocrit, Platelets laboratory results, estimated intraoperative blood loss and number of blood products transfusions

3. OVERVIEW OF STUDY DESIGN

This is an open-label, randomised, multicentre controlled, study evaluating the safety and effectiveness of the EVARREST compared with SURGICEL in controlling mild or moderate bleeding in hepatic parenchyma or soft tissue for which standard methods of achieving haemostasis are ineffective or impractical

Eligible subjects will be randomised in a 1:1 allocation ratio to either EVARREST or SURGICEL treatment. Subjects will be followed post-operatively through discharge and at 30 days (+/-14 days) post-surgery.

Enrolment will be staggered by age. The first group enrolled will include subjects ≥1 years to <18 years of age and the subsequent group will include subjects from 1 month (≥ 28 days from birth) to <1 years of age. Ongoing safety assessment will ensure adequate safety monitoring occur during the staged enrolment.

4. STUDY POPULATION

4.1 General Considerations

The Investigator is expected to invite all subjects expected to meet the study entry criteria to participate in the study.

The TBS will be the only region evaluated for the primary endpoint and all secondary effectiveness endpoints. Please refer to section 7.1.3. for definition of the TBS.

The study will target to have approximately a minimum of 25% of procedures have the target bleeding site in the hepatic parenchyma and approximately a minimum of 25% of the target bleeding sites in soft tissue. Enrolment will be monitored by the sponsor and the Investigators will be notified by the sponsor once those targets have been met.

4.2 Inclusion Criteria

Pre-operative:

1. Paediatric subjects aged ≥28 days (≥1 month) to <18 years, requiring non-emergent open hepatic, abdominal, retroperitoneal, pelvic or thoracic (non-cardiac) surgical procedures;
    i) The first 36 subjects to be enrolled will be subjects aged ≥1 years to <18 years.
    ii) The next 4 subjects to be enrolled will be subjects aged ≥28 days to <1 year.
2. The subject's parent/legal guardian must be willing to give permission for the subject to participate in the trial, and provide written Informed Consent for the subject. In addition, assent must be obtained from paediatric subjects who possess the intellectual and emotional ability to comprehend the concepts involved in the trial. If the paediatric subject is not able to provide assent (due to age, maturity and/or inability to intellectually and/or emotionally comprehend the trial), the parent/legal guardian's written Informed Consent for the subject will be acceptable for the subject to be included in the study.

Intra-operative

3. Presence of an appropriate mild or moderate bleeding soft tissue or hepatic parenchyma Target Bleeding Site (TBS) identified intra-operatively by the surgeon;
4. Ability to firmly press trial treatment at TBS until 4 minutes after randomisation;

4.3 Exclusion Criteria

Pre-operative

1. Subjects with known intolerance to blood products or to one of the components of the study product or is unwilling to receive blood products;
2. Female subjects, who are of childbearing age (i.e. adolescent), who are pregnant or nursing;
3. Subject is currently participating or plan to participate in any other investigational device or drug without prior approval from the Sponsor;

4. Subjects who are known, current alcohol and/or drug abusers

5. Subjects admitted for trauma surgery

6. Subjects with any pre or intra-operative findings identified by the surgeon that may preclude conduct of the study procedure.

Intra-operative

7. Subject with TBS in an actively infected field (Class III Contaminated or Class IV Dirty or Infected)[5]
8. TBS is from large defects in arteries or veins where the injured vascular wall requires repair with maintenance of vessel patency and which would result in persistent exposure of the EVARREST or SURGICEL to blood flow and pressure during healing and absorption of the product;
9. TBS with major arterial bleeding requiring suture or mechanical ligation;
10. Bleeding site is in, around, or in proximity to foramina in bone, or areas of bony confine.

5. RANDOMISATION

5.1 Overview

Randomisation will be used to avoid bias in the assignment of treatment to each subject, to increase the likelihood that attributes of the subject are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

5.2 Procedures

ETHICON will provide each site with computer-generated randomisation envelopes, each bearing the subject randomisation number, and containing the treatment allocation.

Treatment will be assigned randomly to each subject on a 1:1 basis to either EVARREST or SURGICEL treatment.

In the event that a potential subject fails intra-operative criteria (i.e. no TBS identified, or an intra-operative exclusion), and is not randomised to the study, the unused randomisation envelope should be returned to the series, and used for the next subject.

Given the difference between the EVARREST and SURGICEL treatment groups, it will not be possible for the surgeon to be blinded to the treatment. However, to avoid any bias in the conduct of the surgical procedure, randomisation should only take place after completion of the following steps:

1. EVARREST and SURGICEL will be prepared and available in the sterile field in the operating room, ready for administration for each patient.
2. The investigator must perform the surgical procedure according to his/her standard of care.

[5] Appendix 1

3. Once the investigator encounters an appropriate hepatic parenchyma or soft tissue TBS related to the primary operative procedure, randomisation should immediately take place. The randomisation envelope will be opened simultaneously with starting the stopwatch.

If the subject is randomised to SURGICEL then the unused EVARREST treatment product MUST immediately be removed from the sterile field and placed for destruction. After the procedure accountability of the product should be documented.

If additional soft tissue bleeding sites requiring a topical haemostatic product are identified after the treatment of the initial target bleeding site, these bleeding sites should be treated according to the surgeon's standard of care.

6 INVESTIGATIONAL PRODUCT AND CONTROL GROUP

6.1 EVARREST Sealant Matrix / Fibrin Sealant Patch (Treatment Group)

6.1.1 Formulation

EVARREST Sealant Matrix / Fibrin Sealant Patch is a sterile bio-absorbable combination product consisting of two constituent parts— a flexible matrix and a coating of two biological components (Human Fibrinogen and Human Thrombin) embedded in a flexible composite patch component. The active side is white-to-yellowish in color and powdery in appearance; the non-active side has an embossed wave pattern.

The patch component of EVARREST consists of an oxidised regenerated cellulose (ORC) layer underlying a layer of polyglactin 910 (PG910) non-woven fibers. The PG910 layer contains the embedded biological components. The patch component provides a large surface area for the biological components and imparts inherent mechanical integrity to the product. The flexibility of EVARREST accommodates the physiological movements of tissues and organs.

Each unit of EVARREST used for this clinical trial will be 4x4 inches (10.2 x 10.2 centimeters) or 2x4 inches (5.1 x 10.2 centimeters) in size. For additional details, please refer to the Investigator's Brochure.

6.1.2 Labelling and Packaging

EVARREST is packaged in a polyester tray and lid assembly within an outer pouch composed of polyester laminated aluminium foil with an inner heat seal coating. The tray/lid assembly maintains product integrity during storage and transport. The outer aluminium pouch serves as a barrier to moisture and microbial contamination.

The aluminium pouches are packed into padded cardboard envelopes as secondary packaging.

The cardboard envelopes may be labelled with the following information as applicable:

- Name and address of manufacturer
- Protocol number
- Lot/Batch number
- Expiry date
- EudraCT number
- Storage conditions
- Statement that the product is limited for clinical trial use only

6.1.3 Shipping, Handling and Storage Conditions

Shipping conditions should be 2º to 25 ºC.

Unopened packages of EVARREST should be stored at 2º to 25 ºC.

Once opened, the product can remain in the sterile field throughout the surgical procedure but must be kept dry to avoid pre-activation. Unused, open product should be appropriately discarded.

Distribution of the EVARREST to the clinical sites will be performed by a qualified distribution centre with proper inventory and quality control capabilities once all the necessary documentation and approvals are obtained.

6.1.4 Preparation

EVARREST comes ready to use in sterile packages and must be handled accordingly. Only undamaged packages should be used. Once the aluminium pouch is opened, re-sterilisation is not possible. EVARREST does not require any preparation. The following procedure for opening and applying the product should be followed to ensure that the sterility of EVARREST is maintained. Note that EVARREST must be kept dry at all times prior to application to avoid pre-activation.

Please refer to the Instructions for Use for further details.

Non-sterile nurse / Study Personnel
Remove the foil pouch from the carton. Carefully peel open the foil pouch taking care to not touch the inside of the foil or the white sterile tray containing the EVARREST. Present the white tray to the scrub nurse.

Sterile nurse/field
Remove the sterile tray from inside the foil pouch. Within the sterile field, hold the tray securely in the palm of the hand, ensuring that the side with the holes is facing upwards. Using the tabs on the side of the tray, remove the top of the tray with the other hand and discard.

The lower portion of the tray contains the EVARREST with active side facing downwards. The active side is powdery and white to yellowish in colour, whilst the non-active side has an embossed wave pattern. EVARREST does not stick to gloves, forceps or any surgical instruments.

The opened EVARREST can remain in the sterile field to be available for use throughout the procedure but must be kept dry and should be discarded appropriately at the end of the procedure.

EVARREST can be carefully cut to the size and shape required with sterile scissors, avoiding excessive handling.

6.1.5 Dose, Route and Duration of Administration

For each subject, EVARREST will be available in the sterile field and ready for administration prior to randomisation. EVARREST is intended for topical use only. See application procedures in Section 7.1.3. Additional information can also be found in the Investigator's Brochure.

6.2 Investigational Product Dispensation and Accountability

A dispensing log will be kept by the designated study personnel. This log will contain information on the date of administration, subject ID and quantity of EVARREST dispensed, details of any remaining product, and subsequent destruction. The study monitor will verify these logs during the course of the study

6.3 SURGICEL Oxidised Regenerated Cellulose (Control Group)

For this study, SURGICEL treatment will be initiated with 4 minutes of continuous manual compression following randomisation with or without gauze or sponge.

All haemostasis evaluations for the EVARREST treatment group will also be required for the SURGICEL treatment group.

6.4 Concomitant Medications

6.4.1 Topical Haemostats

The use of any other topical haemostats or fibrin sealant/fibrin sealant patch will be permitted and must be used according to the surgeon's usual practice. Details of all topical haemostats used for the subject throughout the procedure will be recorded on the Concomitant Medication CRF.

6.4.2 Documentation of Concomitant Medications

Indication and start-stop dates of concomitant medications administered from 24 hours prior to surgery up to the follow up contact or evaluation will be recorded. This will include medications used chronically (even if temporarily halted for surgery) and those medications administered as a prophylactic before, during and after surgery.

Anaesthetics used for surgery and over the counter (OTC) drugs will not be recorded as concomitant medication (with the exception of prophylactic aspirin, which should be documented). Concomitant medications used to treat Adverse Events (even if the concomitant medication is an OTC drug or nutritional supplement) must also be documented.

7 STUDY EVALUATIONS

7.1 Study Procedures

The schedule of events included in the synopsis summarizes the frequency and timing of the study procedures. Data collected for the subject during the study will be recorded in the subject's medical records, and study worksheets/source documents, as appropriate, and recorded into the eCRF.

7.1.1 Screening (Within 21 Days Prior to Surgical Procedure)

Prospective subjects will be screened within 21 days prior to surgery.
The following tests and activities will be performed at the screening visit unless existing data from within 21 days prior to surgery is available, in which case the test/activity will not be repeated. The timing of these activities may occur based on routine hospital practice but may be done up to the day of, but prior to, surgical procedure.

- Informed Consent & Assent process as applicable.
- Allocation of screening number.
- Documentation of demography (age, gender, race/ethnic origin).
- Physical examination as per normal procedure.
- Documentation of relevant medical and surgical history.

- Laboratory evaluations – these may be collected at any time within 21 days prior to surgery. Only one pre-operative laboratory evaluation is needed. The laboratory results closest to the date prior to surgery will be used.
  - Full blood count (FBC) with differential
  - Coagulation parameters to include Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), International Normalised Ratio (INR) and platelet count

- Review of Inclusion / Exclusion criteria to confirm subject pre-operative eligibility. In the event that a subject is not eligible, the reason will be documented on the worksheet/screening log.

7.1.2 Baseline Assessments (Within 24 Hours Prior to Procedure)

The following activities will be performed within 24 hours prior to the procedure. The timing of these activities may occur based on routine hospital practice. The Screening Visit activities may be combined with this visit.

- Review of inclusion / exclusion criteria to confirm subject pre-operative eligibility. In the event that a subject is not eligible, the reason will be documented on the worksheet/screening log.

- Documentation of all concomitant medications as stated in Section 6.4

- Documentation of any changes in medical history from the screening visit (if done on a separate visit from Baseline).

- Document subject weight and calculate maximum EVARREST units that could be used during the procedure

- Serum or urine pregnancy test (for female subjects of childbearing age)

- At least one FBC with differential, coagulation parameter testing and pregnancy test (if applicable) are needed pre-procedure. If pre-operative blood tests are repeated, only the test results closest to the date prior to surgery will be collected.

The maximum size of EVARREST to be implanted is 6.9 square cm per kilogram of body weight. Where subject's body weight allows additional pads to be placed, a maximum of four units (each unit is 4 x 4 inches (10.2 x 10.2 centimeters) of EVARREST may be implanted (left in place at the bleeding site) per subject assigned to be treated with EVARREST.

If the unit size used is 2x4 inches (5.1 x 10.2 centimeters), a maximum of eight units may be implanted (left in place at the bleeding site) per subject assigned to be treated with EVARREST (where subject's body weight allows).

Note: At least one FBC with differential, coagulation parameter testing and pregnancy test (if applicable) are needed pre-procedure. If pre-operative blood tests are repeated, only the test results closest to the date prior to surgery will be collected.

7.1.3 Surgical Procedure

The surgeon will use his / her standard surgical techniques for the surgical procedure.

Target Bleeding Site Identification

For this investigation, the target bleeding site (TBS) will be identified during the soft tissue or hepatic dissection related to the primary operative procedure. (For example, the TBS might be the retroperitoneal bed during or following nephrectomy, the area of lymph node dissection during peri-aortic node dissection, the pelvic wall during low anterior resection of the colon or in the hepatic parenchyma after a hepatic resection.)

The surgical procedure must be an open procedure to allow for appropriate EVARREST application. When patients are undergoing abdominal and thoracic (non-cardiac) procedures, open is defined as the opening of the peritoneal or pleural/thoracic cavity. The following surgical procedures are permitted to be included in this study:

- Hepatic
- Intra-Abdominal
- Intra-Thoracic (Non-Cardiac)
- Retroperitoneal
- Pelvic (Extra-peritoneal space)

Laparoscopic, thoracoscopic and other endoscopic procedures are excluded from this study.

Soft Tissue includes but may not be limited to the following tissue types:

- Muscle
- Lymphatic Tissue/lymph node beds
- Fatty tissue
- Loose Areolar Connective Tissue

For this study, the TBS will be defined as the FIRST actively bleeding site identified during the soft tissue or hepatic dissection related to the primary operative procedure with challenging mild to moderate bleeding, where conventional methods of control (i.e. suture, ligature, cautery) have been deemed ineffective or impractical, and require an alternative method to achieve haemostasis. The TBS must be a site where occlusion of the injured tissue surface blood vessels is required to achieve haemostasis. This excludes large defects in large arteries or veins where the injured vascular wall requires repair with maintenance of vessel patency and which would result in persistent exposure of the EVARREST to blood flow and pressure during healing and absorption of the product. ***EVARREST should not be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial bleeding.***

The TBS area must be possible to cover with an appropriate overlap with a margin of 1-2 cm, using, a single 4 x 4 inch (10.2 cm x 10.2 cm) EVARREST or two 2 x 4 inch (5.1 cm x 10.2 cm) units of EVARREST. If two 2 x 4 inch (5.1 cm x 10.2 cm) units of EVARREST are used, there must be overlap with a margin of 1-2 cm between the 2 units of EVARREST.

As a frame of reference, the following scale of bleeding intensity will be utilised. Only target bleeding sites with mild or moderate bleeding as defined by this scale will be included:

Mild Bleeding: A TBS with a small area of capillary, arteriole or venule oozing.

Moderate Bleeding:

1. A TBS with a larger area of capillary, arteriole, or venule oozing that presents a significant challenge because of the larger area involved, increasing the volume of blood loss.

Or

2. A TBS with bleeding that is more pronounced than oozing, that could also come from a small artery or vein, but is not massive, pulsatile, and flowing.

Severe Bleeding (EXCLUDED BY THIS PROTOCOL):

Bleeding (arterial, venous, or mixed) that is rapidly flowing, pulsatile or spurting that in the surgeon's judgment requires rapid control to prevent hemodynamic consequences (e.g. hypovolemia, tachycardia, or hypotension) and could involve major volume loss which if not treated rapidly could be life threatening. EVARREST should not be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial bleeding.

The TBS will be identified, and will be the only specific site or region to be evaluated for time to haemostasis in this clinical study. The following activities will be performed, and information will be collected, during the surgical procedure:

- Review of inclusion and exclusion criteria to confirm intra-operative. In the event that a subject is no longer eligible, the reason for the screen failure will be documented in the source documentation and screening log
- Haemostatic methods used at TBS prior to EVARREST application (none (other methods are impractical), suture, ligation, cautery, other)
- Primary Operative Procedure information: Abdominal resection, retroperitoneal tumour resection, hepatic resection or other (specify)
- TBS location information: hepatic, abdominal, pelvic, retroperitoneal, thoracic (non-cardiac or other location (specify)
- Type of bleeding (mild or moderate)
- Size of TBS (length, width, area)
- TBS tissue type: hepatic parenchyma, loose areolar connective tissue, fat, lymphatic tissue/lymph node beds, muscle or other (specify)
- Liver only TBS assessment (See 7.1.3.3)
- Documentation of concomitant medications as outlined in Section 6.4
- Total number of units used

Pre-Randomisation Procedures:

- EVARREST and SURGICEL will be prepared and available in the sterile field in the operating room, ready for administration for each subject.

- When the surgeon encounters the first appropriate TBS with mild or moderate bleeding in the hepatic parenchyma or soft tissue related to the primary operative procedure where conventional methods of control (i.e. suture, ligature, cautery) are ineffective or impractical, the subject can be considered for randomisation.

Randomisation:

- Once intra-operative eligibility is confirmed, and the TBS identified, the randomisation envelope will be opened while simultaneously starting the stopwatch will be immediately started, and recording the time on the wall clock (T_0).

For Subjects Randomised to EVARREST

The maximum size of EVARREST to be implanted is 6.9 square cm per kilogram of body weight. Where subject's body weight allows additional pads to be placed, a maximum of four units of the 4 x 4 inches (10.2 x 10.2 centimeters) EVARREST or a maximum of eight units of the 2 x 4 inches (5.1 x 10.2 centimeters) EVARREST may be implanted (left in place at the bleeding site) per subject assigned to be treated with EVARREST.

The size of the EVARREST applied should be sufficient for coverage of the entire TBS, and should overlap the TBS with a margin of 1-2 cm.

The surgeon will immediately apply firm continual manual compression over the entire bleeding area until 4 minutes from randomisation. The surgeon may use a surgical sponge (laparotomy pad or surgical gauze) to assist in providing adequate even pressure over the entire surface area.

The absolute time to haemostasis will be recorded, which is defined as the time elapsed from randomisation to the last moment in time at which detectable bleeding at the TBS is observed, i.e., complete haemostasis at the TBS.

Haemostasis will also be assessed at 4 minutes and 10 minutes and at initiation of final closure, post-randomisation for all subjects.

EVARREST should not be removed once bleeding has been stopped.

If breakthrough bleeding occurs at the TBS at any time after application, the surgeon may re-treat with EVARREST if clinically appropriate, or revert to their standard of care. Any EVARREST re-treatment must be performed according to the Investigator's Brochure.

EVARREST Re-treatment

- If the surgeon finds the EVARREST was not applied properly (if there are folds, creases or crimps in the patch) the EVARREST pad should be removed and a new EVARREST pad applied as per the Investigator's Brochure. No matter the point of application, haemostasis must be assessed at 4 and 10 minutes from randomisation.
- If bleeding is due to insufficient coverage of the bleeding area, additional patches may be applied. Ensure that the edges overlap (by approximately 0.5 to 1 inch or 1 to 2 cm) with the existing patch.
- If bleeding is due to incomplete adherence to the tissue (where bleeding persists under the dressing), remove the patch and use a new one.
- If bleeding still occurs during or after the specified duration of compression, remove the used EVARREST and inspect the bleeding site. If no other primary hemostatic measures (i.e., standard surgical techniques) appear to be required, repeat the application procedure above with a new EVARREST.

EVARREST can only be used on a single TBS to be evaluated. If additional soft tissue/hepatic bleeding sites are identified, the surgeon should treat according to their standard of care.

For Subjects Randomised to SURGICEL

The control treatment group will be initiated with application of SURGICEL as per its Instructions for Use.

The surgeon will immediately apply firm continual manual compression over the entire bleeding area until 4 minutes from the time of randomisation.

The absolute time to haemostasis will be recorded, which is defined as the time elapsed from randomisation to the last moment in time at which there is detectable bleeding at the TBS is observed, i.e., complete haemostasis at the TBS.

Haemostasis will also be assessed at 4 minutes and 10 minutes and at initiation of final closure, post-randomisation for all subjects.
Additional SURGICEL may be used at the target bleeding site prior to the 4 minute time point if the surgeon finds the SURGICEL was improperly applied.

If haemostasis in the SURGICEL group is not achieved, or if bleeding requiring re-treatment at the TBS occurs anytime after the 4-minute assessment, the surgeon must control bleeding according to their standard of care.

HAEMOSTASIS ASSESSMENT (TIME TABLE):

T_0	Start time when randomisation envelope is opened
T_{APP}	Time when haemostatic product is initially applied with manual compression
T_4	TBS Bleeding assessment 4 minutes following randomisation. Note: Manual compression must be maintained from application until this initial assessment.
T_{10}	TBS Bleeding assessment 10 minutes following randomisation.
T_{ABS}	Absolute time to haemostasis; as defined as the absolute time elapsed from randomisation to the last moment in time at which there is detectable bleeding at the TBS

7.1.3.1 Adverse events from start of randomisation, including any complications potentially related to bleeding and/or thrombotic events.

7.1.3.2 Additional procedural and hospital stay information will also be recorded including surgery procedural times, blood product usage, blood transfusions, ICU time, estimated blood lost, cell saver use, surgical procedure/reason for surgery and alternative/additional methods used to achieve haemostasis (if applicable).

7.1.3.3 Additional surgical details will be captured for a liver only TBS, including estimated total transected plane area; estimated transected plane area treated (0-25%, 26-50%, 51-75%, 76-100%); reason for, type and location of liver resection; hepatic parenchymal classification/type; and surgeon description of bleeding site at the TBS (area, density, arterial/venous/mixed, and characterisation of intensity of flow).

7.1.4 Post-Surgery until Hospital Discharge

Prior to discharge, the following blood samples must be drawn and data will be recorded:

- Blood samples will be taken for Full Blood Count (FBC) with Differential and Coagulation parameters (PT, aPTT, INR).
- Physical examination as per the institution's normal procedure.
- Changes in concomitant medications.
- Date of hospital discharge (for overall Length of Stay).
- Adverse events, including any complications potentially related to bleeding and/or thrombotic events.

7.1.5 30-day Follow-Up Visit (+/- 14 days)

The following information will be recorded either at the clinical follow-up visit approximately 30 days following surgery:

- Changes in concomitant medications, including use of any blood products following hospital discharge.
- Physical examination as per the institution's normal procedure.
- Adverse events, including any complications potentially related to bleeding and/or thrombotic events.

7.2 Procedures for Handling Biological Samples

7.2.1 Laboratory Tests

All laboratory investigations for FBC and Coagulation parameters will be performed at the local hospital laboratory. The volume of blood to be taken will be determined according to the standard practices of each hospital. The normal reference ranges and laboratory accreditation certificates must be provided to ETHICON. Local labs will be performing the tests in a blinded fashion as the local labs will not be aware of the randomised treatment.

7.3 Premature Withdrawal of Subjects for the Study

All randomised subjects should be encouraged to remain in the study until they have completed the 30-day follow-up visit. Subjects and/or their parent/legal guardian may discontinue participation in the study at any time and for any reason. However, if the subject decides to discontinue participation in the study, the reason must be documented when possible. Reasons for early withdrawal include, but are not limited to:

- Consent withdrawn by the subject or parent/legal guardian;
- Subject refusal to complete study visits and/or procedures;
- Lost to follow-up: a recorded delivery letter will be sent to the subject at their last known address, after a minimum of three attempts to reach the subject by telephone have failed. If communication via certified letter is unsuccessful, the subject will be considered lost to follow-up;
- Adverse events.

Subjects who discontinue from the study prematurely will not be replaced.

8 STATISTICAL METHODS

The Data Management and Biostatistics groups of Clinical Development at ETHICON will be responsible for the overall analysis of data from this protocol. The detailed Statistical Analysis Plan (SAP) will be based on and will supplement the statistical design and analysis described in this section.

8.1 Sample Size Determination

No formal sample size determination was performed for this study, however a total of 40 randomised subjects are considered adequate to provide sufficient information to evaluate data descriptively.

8.2 Data Analysis

The categorical data will be summarized descriptively by frequencies along with associated percentages for each group. The continuous variables will be summarized descriptively by number of subjects, mean, standard deviation, minimum, and maximum for each group. If applicable, a 5% significance level will be used for any statistical tests. Two-sided 95% confidence intervals will be quoted.

8.2.1 Analysis Sets

There will be three analysis sets defined:

- Full analysis set (FAS or intent-to treat) consists of all randomised subjects. Subjects who do not complete the procedure with the use of EVARREST or SURGICEL after randomisation will be included in the FAS analysis.
- Evaluable analysis set (or per protocol) consists of all FAS subjects who have no major protocol deviations affecting the primary effectiveness endpoint and have data available for this primary effectiveness endpoint.
- Safety analysis set will consist of all subjects who received treatment.
- If any subjects are mis-randomised, the FAS and Evaluable analysis sets will summarize data as randomised, and the safety set will summarize as treated. If more than 2 subjects are mis-randomised, then the FAS and Evaluable analysis sets will also summarize data as treated.

The primary endpoint analysis will be based on the Full analysis set. The evaluable analysis will be considered supportive.

Major protocol deviations will be determined prior to database lock.

8.3 Effectiveness

8.3.1 Effectiveness Variables

The following primary endpoint will be analysed using the FAS/ITT and Evaluable set:

- Absolute time to haemostasis defined as the absolute time elapsed from randomisation to the last moment in time at which detectable bleeding at the TBS is observed.

The following secondary endpoints will be analysed using the FAS/ITT set only:

- Proportion of subjects achieving haemostatic success at 4 minutes following randomisation and no bleeding requiring treatment at the TBS occurs any time prior to final fascial closure
- Proportion of subjects achieving haemostatic success at 10 minutes following randomisation and no bleeding requiring treatment at the TBS occurs any time prior to final fascial closure
- Proportion of subjects with no re-bleeding at the TBS

The following additional analysis will be performed for the FAS and Evaluable sets: Absolute time to haemostasis will also be analysed descriptively separately for subjects who achieved haemostasis with and without additional randomised treatments being required.

8.3.2 Methods of Analysis

Descriptive statistical analysis will be conducted overall, based on treatment and by paediatric groups (1 month (≥ 28 days from birth) to <1 year and 1≤18 years). Primary endpoint data will also be summarized into Infants and toddlers (28 days to 23 months), Children (2 to 11 years) and Adolescent (12 to <18 years).

Two-sided 95% confidence intervals (CIs) for median absolute time to haemostasis will be reported separately for EVARREST and SURGICEL groups. In addition, for success/failure secondary endpoints (4 and 10 minutes haemostasis endpoints), two-sided 95% CI will be reported for P_F, P_C and for ratio P_F / P_C where P_F is the proportion of success in EVARREST subjects and P_C is the proportion of success in control subjects. The lower limits of these 95% CI will be utilized for statistical inferences.

8.4 Safety

8.4.1 Safety Variables / Criteria

The following will be summarized using the Safety set:

- Incidence of adverse events that are potentially related to bleeding at the TBS;
- Incidence of adverse events that are potentially related to thrombotic events;
- Incidence of re-treatment at the TBS;
- Incidence of adverse events.
- Laboratory tests (including Haemoglobin, Haematocrit, Platelets)
- Estimated intra-operative blood loss
- Volume of blood product transfused

8.4.2 Methods of Analysis

Adverse events will be summarized descriptively by the treatment received, using Medical Dictionary for Regulatory Activities (MedDRA) terminology**.**

Laboratory values (including coagulation parameters) will be reported in International System (SI) units. Values and changes from baseline will be listed and summarized. Clinically significant changes will be reported as part of the AE summary.

AEs (MedDRA terminology) will also be summarized into Infants and toddlers (28 days to 23 months), Children (2 to 11 years) and Adolescent (12 to <18 years).

8.5 Interim Analyses

None.

8.6 Handling of Missing Data

It is not anticipated that there will be any data missing for treated subjects for the primary endpoint, but if there is, missing data will not be imputed for the primary analysis.
Analyses of secondary endpoints will consider missing data as failures.

9 SAFETY DEFINITIONS

9.1 Adverse event

An adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) can be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a drug, without any judgment about causality. Since post-operative pain is an expected outcome of this type of surgery, for purposes of this study, only exacerbations of expected post-operative pain based on the Investigator's judgment should be reported as an AE.

9.1.1 Suspected adverse reaction

A suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means there is evidence to suggest a causal

relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction.

9.1.2 Adverse reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

9.2 Serious Adverse Event

A serious adverse event (SAE) or suspected adverse reaction is any untoward medical occurrence that, in the view of either the investigator or sponsor, it:

- Results in death;
- Is considered to be life-threatening;
- Requires inpatient hospitalisation or prolongation of existing hospitalization;
- Results in persistent or significant disability, incapacity or substantial disruption of the ability to conduct normal life functions;
- Results in a congenital anomaly or birth defect;
- Is an important medical event that may not result in death, be life-threatening, or require hospitalisation but may be considered serious when, based upon appropriate medical judgment, they may jeopardise the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2.1 Life threatening

Life threatening refers to an adverse event or suspected adverse reaction in which, in the view of the investigator or sponsor, the subject was at immediate risk of death at the time of the event; it does not include an event that might have caused death if it were more severe.

Any event requiring inpatient hospitalisation (or prolongation of hospitalization) that occurs during the course of a subject‘s participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

- Social reasons in absence of an adverse event;
- Surgery or procedure planned before entry into the study (must be documented in the CRF)

9.2.2 Unexpected

An adverse event or suspected adverse reaction is considered unexpected if it is not listed in the Investigator’s Brochure or is not listed at the specificity or severity that has been observed; or, though they are mentioned as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, they are not specifically mentioned as occurring with the particular drug under investigation.

9.3 Suspected unexpected serious adverse reaction (SUSAR)

A suspected unexpected serious adverse reaction (SUSAR) is a suspected adverse reaction that is both serious and unexpected.

9.4 Relationship

Relationship to the investigational product:

The relationship of the investigational product to an adverse event must be determined using the following classification:

None:	No relationship with investigational product.
Possible:	Reasonable possibility that the event was caused by the investigational product.
Related:	The event was certainly or probably caused by the investigational product.

Relationship to the surgical procedure:

None:	No relationship to the surgical procedure.
Possible:	Reasonable possibility that the event was caused by the surgical procedure.
Related:	The event was certainly or probably caused by the surgical procedure.

9.5 Severity

The following definitions should be used to determine the severity rating of all AEs:

Mild:	Awareness of signs or symptoms, but these are easily tolerated and are transient and mildly irritating only. There is no loss of time from normal activities and symptoms do not require medication or a medical evaluation.
Moderate:	Discomfort enough to cause interference with usual activities or require therapeutic intervention, such as concomitant medication.
Severe:	Incapacity with inability to work or do usual activities.

9.6 Collection of Adverse Events

AEs will be recorded as they are reported, whether spontaneously volunteered or in response to questioning about well-being. AEs will be collected from the start of randomisation at the baseline visit, throughout the hospital admission, and until completion of the 30-day follow-up visit.

Details of all AEs occurring during the study must be recorded on the AE form with the following information:

- Description of the event
- Dates of onset and resolution
- Severity
- Action taken
- Outcome
- Relationship to investigational product
- Whether the AE is serious or not

All AEs will be documented in the subject's source documents (e.g. medical records) and eCRF. All AEs will be followed until completion of the 30-day follow-up visit or until a stable resolution, whichever is sooner.

Expectedness of an SAE will be defined based on whether the specificity or severity of which is not consistent with the current Investigator's Brochure.

Other: The investigator may also need to consider whether an event is attributable to the investigational product, based on insufficiencies or inadequacies in the instructions or as a result of user error.
The investigator must contact the Sponsor should this occur.

9.7 Adverse Event Reporting

It is a requirement that the Investigator promptly reports all SAEs (irrespective of relationship) as soon as possible, but no later than 24 hours after becoming aware of the event occurring.

Suspected, unexpected serious adverse drug reactions (SUSARs) will be reported to all relevant competent authorities, and IRBs /Ethics Committees within the required timeframes of seven calendar days for SUSARs that are fatal or life-threatening, and fifteen calendar days for all other SUSARs.

All other Adverse Events (AEs) must be reported (entered) into the [redacted] clinical trial database (electronic case report form (eCRF) within two weeks from the date the site becomes aware of the AE.

10 REGULATORY OBLIGATIONS

10.1 Informed Consent

Prior to participation, the study procedures and any known or likely risks will be explained to the subjects and/or their parent/legal guardian by the investigator or other medically qualified co-investigator. An Informed Consent Form will also be provided containing all the required information. Any questions will be answered and the patient and/or their parent/legal guardian will then be given sufficient time to consider their participation in the study before signing a consent form. Subjects and/or their parent/legal guardian should receive a copy of the Informed Consent Form. In addition, assent must be obtained from paediatric subjects who possess the intellectual and emotional ability to comprehend the concepts involved in the trial. If the paediatric subject is not able to provide assent (due to age, maturity and/or inability to intellectually and/or emotionally comprehend the trial), the parent/legal guardian's written Informed Consent for the subject will be acceptable for the subject to be included in the study.

The Investigator (or designee) will explain that the subjects and their parent/legal guardian are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify.

Each subject and/or their parent/legal guardian will be informed that the subject's source medical records may be checked by representatives from the Sponsor or from a regulatory agency, in accordance with applicable regulations. However, they should be made aware that all information will be treated with confidentiality, and a study ID code or number will identify them.

10.2 Institution Approval / Ethics Committees

The investigator must submit the Protocol and the Consent/Assent Form to the appropriate Institution department/EC according to local requirements. Approval from the Institution/EC must be obtained prior to starting any study-related procedure.

10.3 Data Management

10.3.1 Data Collection

The Investigator must maintain required records on all study subjects. Data for this study will be recorded in the subject's medical records, study-specific worksheets and on electronic CRFs provided by Sponsor in accordance with the parameters set forth in ICH Topic E6 for GCP (1.5.96) Guidelines - Responsibilities

of Sponsor, Monitor and Investigator. All data on the eCRFs should be recorded with appropriate source documentation.

Each EDC eCRF will be completed by the PI or PI's designee. Every effort should be made to respond to all monitoring and/or data management questions on each eCRF as completion of the data is required by the protocol. A unique ID number will identify each subject. The unique ID number will be visible on each eCRF. At no time should the subject name appear on the eCRFs. Complete data is needed in order to provide statistical analysis for each subject. All data should be recorded accurately and completely. The Investigator is responsible for reviewing and approving each completed eCRF. Assurance of overall review and approval will be documented by the Investigator electronically signing each subject's electronic casebook.

10.3.2 Data Correction

Required data corrections to eCRFs will be prompted via automated electronic edit checks and/or queries manually created by sponsor reviewers. The change(s), individual making the change(s), and time the change(s) were made to the eCRFs will be automatically captured in the audit trail within [redacted] Documentation.

Investigators must keep accurate separate records (other than the CRFs) of all subjects' visits, being sure to include all pertinent study related information. A statement should be made indicating that the subjects have been enrolled in Protocol and have provided written Informed Consent. Any and all side effects and adverse events must be thoroughly documented. Results of any diagnostic tests conducted during the study should also be included in the source documentation. Telephone conversations with the subjects concerning the study must also be recorded.

The Investigator is responsible for maintaining a Subject Identification Log, which will include all subjects who provided Informed Consent (i.e. to include randomised subjects and screening failures). This confidential subject identification code provides the link between named subject source records in the subject file and anonymous CRF data provided to ETHICON.

The Investigator must retain all study related documentation until at least two years after the final marketing application is approved, or at least two years have elapsed since the formal discontinuation of the clinical study. Study documents should not be destroyed without prior written agreement between the Investigator and ETHICON. The sponsor must be notified if the Investigator wishes to assign the study records to another party, or move them to another location.

10.4 Sponsor Obligations

10.4.1 Monitoring

The Sponsor monitor or designee will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the trial. The monitor will visit as soon as possible following enrolment of the first subject and at regular intervals during the study as deemed necessary. It will be the monitor's responsibility to inspect the source documents at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries. The study monitor will have access to laboratory test reports and any other source records and data needed to verify the entries on the eCRFs, unless restricted by local laws. The Investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.4.2 Regulatory Requirements

This study will be conducted in accordance with specific provisions of the associated IRB/IECs, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and the applicable national and regional regulatory requirements.

10.4.3 Liability and Insurance Conditions

In case of any damage or injury occurring to a subject in association with the trial medication or participation in the study, ETHICON has provided insurance cover. A copy of this policy is on file at ETHICON.

11 INVESTIGATOR OBLIGATIONS

11.1 Audit and Inspection

The Investigator will make source data and documents for this study available to an appropriately qualified quality assurance auditor mandated by ETHICON, or to regulatory authority inspectors, after appropriate notification.

11.2 Confidentiality of Subject Records

The Investigator will ensure that the subjects' anonymity will be maintained. On eCRFs or other study documents submitted to ETHICON, subjects will not be identified by their names, but by an identification code *that may consist of a combination of the, site, and randomisation or enrolment number*. Documents not for submission to ETHICON i.e. the Subject Identification Log and original subjects' consent forms will be maintained in the Investigator Site File.

11.3 Record Retention

The Investigator will maintain all source documents that support the data collected from each subject, and all trial documents as specified by applicable regulatory requirement(s). The Investigator will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least 2 years after the last approval of a marketing application worldwide, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with ETHICON. It is the responsibility of ETHICON to inform the Investigator as to when these documents no longer need to be retained. If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. ETHICON must be notified in writing of the name and address of the new custodian.

12 CHANGES TO THE PROTOCOL

12.1 Protocol Amendments

All protocol amendments are required to be submitted for information / consideration to the regulatory authorities, IRBs and ECs.

12.2 Clinical Trial Termination

Both the Investigator and ETHICON reserve the right to terminate the study at any time. Should this be necessary, the procedures will be arranged on an individual study basis after review and consultation with both parties. In terminating the study, ETHICON and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests and safety.

12.3 Use of Information and Publication

All information concerning study data, ETHICON's operations, patent application, formulas, manufacturing processes, basic scientific data, and formulation information, supplied by the Sponsor or Sponsor designee to the investigator and not previously published, is considered confidential and remains

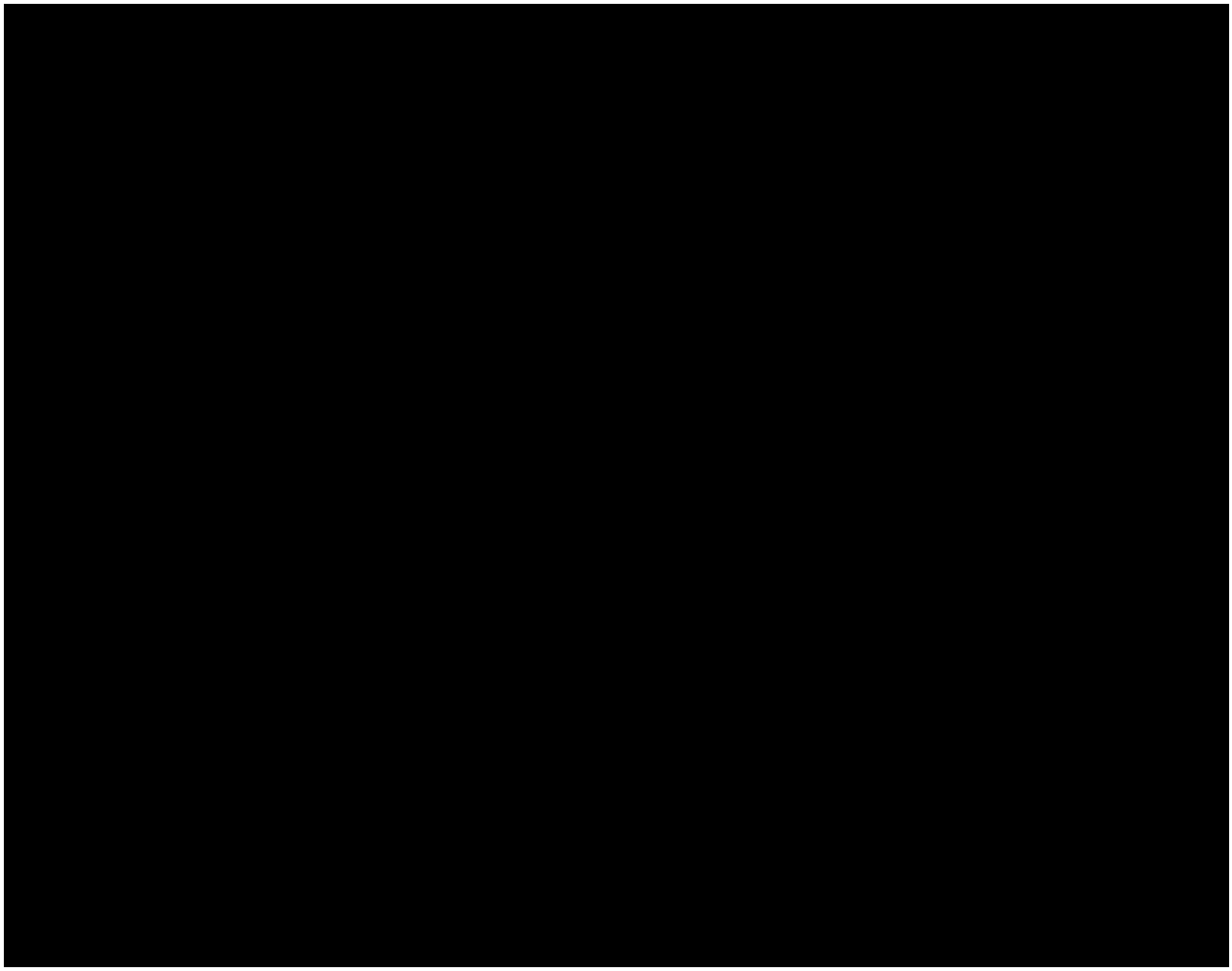
the sole property of ETHICON. The Investigator agrees to use this information only to accomplish this study and will not use it for other purposes without the sponsor's written consent.

The Investigator understands that the information developed in the clinical study will be used by ETHICON in connection with the continued development of the EVARREST product, and thus may be disclosed as required to other clinical investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the sponsor with all data obtained in the study.

Any publication or other public presentation of results from this study requires prior review by ETHICON. Draft abstracts, manuscripts, and materials for presentation at scientific meetings must be sent to the sponsor at least 30 working days prior to abstract or other relevant submission deadlines. Authorship of publications resulting from this study will be based on generally accepted criteria for major medical journals.

The investigator understands not to use the name of ETHICON, EVARREST, or any its employees, in any publicity, news release or other public announcement, written or oral, whether to the public, press or otherwise, relating to this protocol, to any amendment hereto, or to the performance hereunder, without the prior consent of ETHICON.

13 ETHICON CONTACT DETAILS



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Appendix 1: U.S. Center for Disease Control (CDC) Guideline for Prevention of SSI Surgical Wound Classification

CLASS I/CLEAN:

An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital and urinary tracts are not entered. Clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow non-penetrating (blunt) trauma should be included in this category if they meet these criteria.

CLASS II/CLEAN-CONTAMINATED:

An operative wound in which the respiratory, alimentary, genital and urinary tract is entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.

CLASS III/CONTAMINATED:

Open, fresh, accidental wounds, operations with major breaks in sterile technique or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered.

CLASS IV/DIRTY OR INFECTED:

Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.