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

The EVARREST® Pediatric Single Arm Mild or Moderate Liver and Soft Tissue Bleeding Study

Protocol Number: BIOS-16-001

Original Protocol:	22 June 2016
Administrative Change 1:	13 December 2016
Amendment 1:	26 October 2017
Amendment 2:	05 February 2018
Amendment 3:	12 December 2019
Amendment 4:	12 May 2020
Amendment 5:	23 July 2021
Amendment 6:	02 November 2023

Sponsor:

ETHICON Inc.
1000 US Highway 202 S
Raritan, NJ 08869, United States

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Sponsor Approval:

PPD
Senior Director of Clinical

Date

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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Nigel Hall, MRCPCH, FRCS (Paed), FRCS (Eng), PhD Date
Coordinating Investigator

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Principal Investigator Agreement:

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 efforts 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 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.

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, Study Evaluating the Safety and Effectiveness of EVARREST Fibrin Sealant Patch in Controlling Mild or Moderate Hepatic Parenchyma or Soft Tissue Bleeding During Open, Abdominal, Retroperitoneal, Pelvic and Thoracic (non-cardiac) Surgery in Pediatric Patients

SYNOPSIS

OBJECTIVES: The objective of this study is to evaluate the safety and hemostatic effectiveness of 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 pediatric patients.

STUDY DESIGN: This is an open label, prospective, multicenter, single arm clinical study evaluating EVARREST as an adjunct to hemostasis when conventional methods (i.e. suture, ligature, cautery) of controlling mild or moderate bleeding are ineffective or impractical during surgery in pediatric patients.

For this study, approximately 12 sites in US and UK will be utilized for consecutive screening and enrollment.

At least thirty-five (35) pediatric subjects with an appropriate mild or moderate bleeding TBS will be enrolled in this study. The age of the subjects enrolled in the study will be from 1 month to <18 years. This will include a minimum of 4 subjects aged 1 month (≥ 28 days from birth) to <1 year.

All 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 hemostasis.

The TBS must be an area that can have firm pressure applied and maintained continuously until 4 minutes after TBS identification, and to which EVARREST can be applied with a margin of 0.5-1 inch (1-2 cm). (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.

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 should not be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial bleeding.

PROCEDURE:

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. This site will then be assessed for hemostatic effectiveness after product application as described below.

Once the TBS is identified, the surgeon will immediately apply EVARREST 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 0.5-1 inch (1-2 cm).

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

Hemostasis is defined as no detectable bleeding at the TBS. Absolute time to hemostasis, defined as the absolute time elapsed from TBS identification to the last moment in time at which detectable bleeding at the TBS is observed, will be recorded.

Hemostasis will be assessed at 4 minutes from TBS identification by carefully releasing manual compression and removing the surgical sponge (if used). Hemostasis will also be assessed at 10 minutes from TBS identification and absolute time to hemostasis will be recorded.

EVARREST should not be removed after bleeding has been stopped.

If bleeding requiring treatment occurs after the 4 minute assessment the surgeon can retreat the TBS with EVARREST or revert to their standard of care.

<u>Additional Treatment Impact on the Success/Failure of Endpoints</u>

- 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.

Hemostasis will be assessed at 4 minutes and 10 minutes after TBS identification

and absolute time to hemostasis is 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 Fibrin Sealant Patch

STUDY POPULATION: Pediatric subjects, undergoing non-emergent abdominal, retroperitoneal, pelvic, hepatic or thoracic (non-cardiac) surgery procedures, wherein an appropriate TBS is identified. For this study, pediatric subjects are defined as:

Infants and toddlers (28 days (1 month) from birth to 23 months), children (2 to 11 years) and adolescents (12 to less than 18 years). A minimum of 4 subjects aged 1 month (≥ 28 days from birth) to <1 year will be enrolled in this study.

Newborn 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 hemostasis defined as the absolute time elapsed from TBS identification to the last moment in time at which detectable bleeding at the TBS is observed.

SECONDARY ENDPOINTS:

- Proportion of subjects achieving hemostatic success at 4 minutes following TBS identification and no bleeding requiring treatment at the TBS any time prior to final fascial closure
- Proportion of subjects achieving hemostatic success at 10 minutes following TBS identification and no bleeding requiring treatment at the TBS 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 any adverse events
- Summarization of hemoglobin, hematocrit, platelets, laboratory results, estimated intraoperative blood loss and number of blood products transfusions

SAFETY:

Adverse events will be collected from time of TBS identification, throughout the follow-up period. Intra-operative bleeding at the TBS after 10 minutes will be considered an adverse event.

The following data will also be collected: laboratory tests (including hemoglobin, hematocrit, platelets), estimated intraoperative blood loss and number of blood products transfused.

STATISTICAL ANALYSIS:

Sample size of 35 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. A two-sided 95% confidence interval (CI) for median absolute time to hemostasis will be reported. In addition, for success/failure secondary endpoints (4 and 10 minutes hemostasis endpoints), two- sided 95% CI will be reported for P_F, where P_F is the proportion of success in EVARREST subjects. The lower limits of these 95% CI will be utilized for statistical inferences.

SAMPLE SIZE:

At least 35 qualified subjects with an identified TBS.

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 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
- Other tissue types (specify) excluding visceral organs except liver

The study will target to have a minimum of 20 procedures with the target bleeding site in the hepatic parenchyma and the remaining procedures with the target bleeding sites in soft tissue. Enrollment 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. Pediatric subjects aged ≥28 days (≥ 1 month) to <18 years, requiring non-emergent open hepatic, abdominal, retroperitoneal, pelvic or thoracic (non-cardiac) surgical procedures;
   i) A minimum of 4 subjects to be enrolled 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 pediatric subjects who possess the intellectual and emotional ability to comprehend the concepts involved in the trial. If the pediatric 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 TBS identified intra-operatively by the surgeon;
4. Ability to firmly press trial treatment at TBS until 4 minutes after TBS identification;

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 study during this study period 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.
7. Subjects that have received a COVID-19 vaccine either 4 weeks prior to surgery or scheduled to receive COVID-19 vaccine within the 30-day follow-up period.

Intra-operative

8. Subject with TBS in an actively infected field (Class III Contaminated or Class IV Dirty or Infected)[1]
9. 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 EVARREST to blood flow and pressure during healing and absorption of the product;
10. TBS with major arterial bleeding requiring suture or mechanical ligation;
11. 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)[4]	**Baseline** (within 24 hours prior to procedure)	**Surgical Procedure**	**Post-Surgery to Hospital Discharge**	**30-Day Follow Up** (+/- 14 days)[5]
Inclusion/ Exclusion	**X**	**X**	**X**		
Informed Consent / Assent (as applicable)	**X**				
Demographics	**X**				
Medical and Surgical History	**X**	**X**[1]			
Concomitant Medications		**X**	**X**	**X**	**X**
Physical Exam (including height and weight)	**X**			**X**	
Complete Blood Count with Differential	**X**[2]	**X**[2]		**X**	
Coagulation (PT, aPTT, INR)	**X**[2]	**X**[2]		**X**	
Pregnancy Tests (if applicable)		**X**			
Treatment Application and Hemostasis assessment			**X**		
Determination of Hemostasis at TBS			**X**		
Operative/Surgical information[3]			**X**	**X**	
Assessment of bleeding or thrombotic events			**X**	**X**	**X**
Adverse Events			**X**	**X**	**X**

[1] Review for changes in medical history from screening visit and preform pregnancy test (if applicable)
[2] At least one CBC 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.
[3] Including length of stay, blood loss and transfusion information.
[4] May be combined with Baseline visit
[5] May be conducted via telephone if clinic visit not possible

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 firmor friable.

Conventional methods to achieve hemostasis include use of surgical techniques, sutures, ligatures or clips, and energy-based coagulation or cauterization. When these conventional measures are ineffective or impractical, adjunctive hemostasis techniques and products are typically utilized, including topical absorbable hemostats such as oxidized regenerated cellulose, gelatin, or collagen and active hemostats 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 hemostasis in a variety of surgical and endoscopic procedures. They have been successfully used as biodegradable tissue adhesives for hemostasis, wound healing, or tissue sealing purposes in cardiovascular, thoracic, neurologic, gastrointestinal, urologic, gynecologic, hepatic and plastic and reconstructive surgical procedures[ii,iii,iv,v,vi]. They have also been evaluated in bleeding from soft tissue tumor 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 lyophilized 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].

EVARREST Sealant Matrix/EVARREST Fibrin Sealant Patch (EVARREST) is a topical absorbable hemostat 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 Pediatric Research Equity Act (PREA) as a deferred pediatric study and as a Post marketing Requirement to Biologics Licensing Agreement (BLA) BL125392.

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. Hemostasis 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, CCI [redacted]

CCI [redacted]

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. CCI [redacted]

EVARREST has been evaluated in the following 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 hemostasis (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.
9. A post-market, non-investigational study in 150 subjects with soft tissue bleeding during intra-abdominal, retroperitoneal, pelvic and non-cardiac thoracic surgery conducted in a single center in US.
10. A Phase III clinical trial in 40 pediatric subjects with mild or moderate soft tissue or hepatic parenchymal organ conducted in UK and Belgium.

Integrating the six randomized studies (3-8 above), of 298 randomized subjects treated with EVARREST 89.9% achieved hemostasis at 3 or 4 minutes of randomization and 97% achieved hemostasis at 10 minutes of randomization. By comparison, of 267 control subjects 49.4% achieved hemostasis at 3 or 4 minutes of randomization and 78.3% achieved hemostasis at 10 minutes.

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

A Phase 2 clinical study indicated that EVARREST is an effective hemostat 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 hemostasis 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 non-investigational, randomized study (9 above), evaluated the clinical utility of EVARREST against standard of care (manual compression, with or without topical absorbable hemostat) in soft tissue bleeding during intra-abdominal, retroperitoneal, pelvic and non-cardiac thoracic surgery. One hundred and fifty (150) subjects; 75 randomized to EVARREST and 75 randomized to Standard of Care were enrolled. No safety concerns were identified in this study. Any differences between the groups were considered to be clinically insignificant.

EVARREST Fibrin Sealant Patch has also been evaluated for safety and efficacy in a pediatric population (10 above). EVARREST was demonstrated to be a safe and effective adjunctive hemostat in controlling mild to moderate soft tissue and hepatic bleeding in pediatric subjects undergoing hepatic, abdominal, pelvic, retroperitoneal, and thoracic (non-cardiac) surgery. A total of 40 subjects were recruited in the UK and randomized to EVARREST (20 subjects) or SURGICEL® (20 subjects). The primary effectiveness endpoint was absolute time to hemostasis (the absolute time elapsed from randomization to the last moment in time at which detectable bleeding at the TBS was observed) and the secondary effectiveness endpoints was the proportion of subjects achieving hemostatic success at 4- and 10-minutes following randomization with no bleeding requiring treatment at the TBS any time prior to final facial closure, and proportion of subjects with no re-bleeding at the TBS.

The analysis (all randomized subjects) for the primary effectiveness endpoint demonstrated that the median absolute time taken to achieve hemostasis in both groups was 4.0 minutes (95% CI of median: [4.0, 4.0 minutes] in EVARREST group; [4.0, 7.6 minutes] in SURGICEL® group). The primary effectiveness endpoint was also analyzed by age group (28 days to <24 months, 2 to 11 years, and 12 to <18 years), and the median absolute time to hemostasis was 4.0 minutes among all the age groups in both EVARREST and SURGICEL® groups. The percentage of subjects with hemostasis at 4 minutes following randomization was higher in EVARREST group (80.0%, 16/20 subjects, 95% CI: 56.3-94.3%) compared to SURGICEL® group (60.0%, 12/20 subjects, 95% CI: 36.1-80.9%); the ratio of proportions (EVARREST/SURGICEL®) was 1.33 (95% CI: [0.87, 2.16]). A higher percentage of subjects achieving hemostasis at 10 minutes following randomization was also observed in the EVARREST group (95.0%, 19/20 subjects, 95% CI: [75.1%, 99.9%]) compared to the SURGICEL® group (90.0%, 18/20 subjects, 95% CI: [68.3%, 98.8%]). In addition, the surgeon reverted to standard of care for 3 subjects in the SURGICEL group achieving hemostasis at the 10-minute time point assessment.

No new safety signals were identified in this study. The AE and SAE profiles in this study are those that would be anticipated following major surgical procedures in the population treated. No clinically meaningful differences between treatment groups were observed, and all SAEs that occurred were single events.

EVARREST Fibrin Sealant Patch was first approved in the US in 2012 (BLA # 1603) and is currently indicated for use with manual compression as an adjunct to hemostasis in adult patients undergoing surgery, when control of bleeding by standard surgical methods of hemostasis (e.g., suture, ligature, cautery) is ineffective orimpractical.

2. STUDY OBJECTIVES

The objective of this study is to evaluate the safety and hemostatic effectiveness of 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 pediatric patients.

The primary endpoint will be the absolute time to hemostasis, defined as the absolute time elapsed from TBS identification 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 hemostatic success at 4 minutes following TBS identification and no bleeding requiring treatment at the TBS any time prior to final fascial closure
- Proportion of subjects achieving hemostatic success at 10 minutes following TBS identification and no bleeding requiring treatment at the TBS 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 hemoglobin, hematocrit, platelets, laboratory results, estimated intraoperative blood loss and number of blood products transfused

3. OVERVIEW OF STUDY DESIGN

This is an open-label, multicenter, single-arm study evaluating the safety and effectiveness of EVARREST in controlling mild or moderate bleeding in hepatic parenchyma or soft tissue for which standard methods of achieving hemostasis are ineffective or impractical.

For this study, approximately 12 sites in US and UK will be utilized for consecutive screening and enrollment.

Eligible subjects will be treated with EVARREST. Subjects will be followed post-operatively through discharge and at 30 days (+/-14 days) post-surgery.

At least thirty-five (35) pediatric subjects with an appropriate mild or moderate bleeding TBS will be enrolled in this study. The age of the subjects enrolled in the study will be from 1 month to <18 years. This will include a minimum of 4 subjects aged 1 month (≥ 28 days from birth) to <1 year.

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.

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 study will target to have a minimum of 20 procedures with the target bleeding site in the hepatic parenchyma and the remaining procedures with the target bleeding sites in soft tissue. Enrollment 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. Pediatric subjects aged ≥28 days (≥1 month) to <18 years, requiring non-emergent open hepatic, abdominal, retroperitoneal, pelvic or thoracic (non-cardiac) surgical procedures;

i) A minimum of 4 subjects to be enrolled will be 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 pediatric subjects who possess the intellectual and emotional ability to comprehend the concepts involved in the trial. If the pediatric 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 TBS identification.

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, 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 study 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.
7. Subjects that have received a COVID-19 vaccine either 4 weeks prior to surgery or scheduled to receive COVID-19 vaccine within the 30-day follow-up period.

Intra-operative

8. Subject with TBS in an actively infected field (Class III Contaminated or Class IV Dirty or Infected) [1]
9. 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 EVARREST to blood flow and pressure during healing and absorption of the product;

[1] Appendix 1

10. TBS with major arterial bleeding requiring suture or mechanical ligation;

11. Bleeding site is in, around, or in proximity to foramina in bone, or areas of bony confine.

5. RANDOMIZATION

This study will be a single-arm study and therefore randomization is not required for this study protocol.

6. INVESTIGATIONAL PRODUCT

6.1. EVARREST Fibrin Sealant Patch

6.1.1. Formulation

EVARREST Fibrin Sealant Patch is a sterile, bio-absorbable combination product consisting of two constituent parts— a flexible matrix and a coating of biological components (human plasma-derived fibrinogen and 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 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.

Each unit of EVARREST used for this clinical trial will be 2x4 inches (5.1 x 10.2 centimeters) in size. Additional inactive ingredients are: arginine hydrochloride, calcium chloride, glycine, human albumin, mannitol, sodium acetate, sodium chloride, and sodium citrate. EVARREST does not contain any preservative. For additional details, please refer to the Investigator's Brochure (IB).

6.1.2. Labelling and Packaging

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

The aluminum 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 study contact/sponsor
- Protocol number
- Lot/Batch number
- Expiry date
- Storage conditions
- Reference to Package Leaflet for instructions of preparation and use in the Investigator's Brochure
- "Caution: New Drug—Limited by Federal (or United States) Law to Investigational Use"

- "For Clinical Trial Use Only"
- Patient ID

6.1.3. Shipping, Handling and Storage Conditions

Shipping conditions should be 2º to 25 ºC.

Store unopened packages of EVARREST at 2 to 25°C. EVARREST does not require refrigeration. Do not freeze. Do not use if package is opened or damaged.

Once opened, keep EVARREST dry to avoid pre-activation of the biological components prior to use, so that it can remain in the sterile field throughout the surgery. Unused, open product should be appropriately discarded.

Distribution of EVARREST to the clinical sites will be performed by a qualified distribution center 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 aluminum pouch is opened, re-sterilization 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. Remove the white sterile tray from the pouch and place onto the sterile field.

Sterile nurse / 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 the active side facing downwards. The active side is powdery and white to yellowish in color, 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 TBS identification. 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 (if applicable). Additional information can also be found in the Investigator's Brochure.

6.3. Concomitant Medications

6.3.1. 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.

Anesthetics 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. Prior to any study specific related procedures and within 21 days prior to the surgical procedure, the following activities and tests will be performed at the screening visit. 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 (including height and weight) 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.
  - Complete blood count with differential
  - Coagulation parameters to include Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), International Normalized 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 and may overlap with some of the screening visit activities (see section 7.1.1).

- Review of inclusion / exclusion criteria to confirm subject pre-operative eligibility. In the event that a subject is no longer eligible, the reason for the screen failure will be documented on the source documentation and screening log.
- Documentation of all concomitant medications as stated in Section 6.3
- Documentation of any changes in medical history since 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 CBC 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 eight units (each unit size used is 2x4 inches (5.1 x 10.2 centimeters)), may be implanted (left in place at the bleeding site) per subject assigned to be treated with EVARREST.

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
- Lymph node beds
- Lymphatic Tissue/lymph node beds
- Fatty tissue

- Loose Areolar Connective Tissue
- Other tissue types (specify) excluding visceral organs except liver

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 hemostasis. The TBS must be a site where occlusion of the injured tissue surface blood vessels is required to achieve hemostasis. 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 0.5-1 inch (1-2 cm), using, a single or two 2 x 4 inch (5.1 cm x 10.2 cm) units of EVARREST and it must be possible to control all bleeding with manual compression. 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 utilized. 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 hemostasis 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
- Hemostatic methods used at TBS prior to EVARREST application *(none (other methods are impractical), suture, ligation, cautery, other)*

- Primary Operative Procedure information: *Abdominal resection, retroperitoneal tumor 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 6.3
- Total number of units used

Pre-Treatment Procedures:

- EVARREST 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 treatment with EVARREST.

Treatment (TBS Identification):

Once intra-operative eligibility is confirmed, and the TBS identified, the stopwatch will be immediately started, the time on the wall clock will be recorded (T_0) and EVARREST will be applied to the TBS.

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 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 0.5-1 inch (1-2 cm).

The surgeon will immediately apply firm continual manual compression over the entire bleeding area until 4 minutes from time of TBS identification. 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 hemostasis will be recorded, which is defined as the time elapsed from TBS identification to the last moment in time at which detectable bleeding at the TBS is observed, i.e., complete hemostasis at the TBS.

Hemostasis will also be assessed at 4 minutes and 10 minutes and at initiation of final closure post-TBS identification for all subjects.

EVARREST should not be removed once bleeding has been stopped.

Under any circumstances, all subjects will have hemostasis assessed again 10 minutes after TBS identification and absolute time to hemostasis recorded.

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 patch may be removed in its entirety and a new EVARREST applied as per the Investigator's Brochure. No matter the point of application, hemostasis must be assessed at 4 and 10 minutes from TBS identification.
- 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 the single TBS to be evaluated. If additional soft tissue/hepatic bleeding sites are identified, the surgeon should treat according to their standard of care.

HEMOSTASIS ASSESSMENT (TIMETABLE):

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

7.1.3.1 Adverse events from start of TBS identification, 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 (Intraoperative Cell Savage System) use, surgical procedure/reason for surgery and alternative/additional methods used to achieve hemostasis (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 characterization 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 Complete Blood Count (CBC) with Differential and Coagulation parameters (PT, aPTT and 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 or via telephone if an in-person hospital visit is impractical:

- Changes in concomitant medications, including use of any blood products following hospital discharge.
- 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 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 will be provided to the Sponsor.

7.3. Premature Withdrawal of Subjects for the Study

All 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; or
- Other, specify

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 35 subjects with identified TBS 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. The continuous variables will be summarized descriptively by the number of subjects, mean, standard deviation, minimum, and maximum for each group.

8.2.1. Analysis Sets

The following four analysis sets defined:

- All Enrolled Set (AES) consists of all subjects who provided informed consent or assent form for this study.
- Full analysis set (FAS or intent-to treat) consists of all enrolled and eligible subjects for whom TBS was identified. Subjects who do not complete the procedure after TBS identification 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 endpoint.
- Safety analysis set will consist of all subjects who received treatment.

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 analyzed using the FAS and Evaluable set:

- Absolute time to hemostasis defined as the absolute time elapsed from TBS identification to the last moment in time at which there is detectable bleeding at the TBS.

The following secondary endpoints will be analyzed using the FAS set only:

- Proportion of subjects achieving hemostatic success at 4 minutes following TBS identification and no bleeding requiring treatment at the TBS occurs any time prior to final fascial closure
- Proportion of subjects achieving hemostatic success at 10 minutes following TBS identification 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 hemostasis will also be analyzed descriptively separately for subjects who achieved hemostasis with and without additional treatments being required.

8.3.2. Methods of Analysis

Descriptive statistical analysis will be conducted overall and by pediatric 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 Adolescents (12 to <18 years).

Two-sided 95% confidence interval (CI) for median absolute time to hemostasis will be reported. In addition, for success/failure secondary endpoints (4 and 10 minutes hemostasis endpoints), two-sided 95% Clopper-Pearson CI will be reported for P_F, where P_F is the proportion of success in EVARREST treated subjects.

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 hemoglobin, hematocrit, platelets)
- Estimated intra-operative blood loss
- Volume of blood product transfused

8.4.2. Methods of Analysis

Adverse events will be summarized descriptively, using Medical Dictionary for Regulatory Activities (MedDRA) terminology**.** Separate summaries will be provided for study product-related and procedure-related AEs. Serious AEs will be summarized in a similar manner.

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 unfavorable 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 hospitalization 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 hospitalization but may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3. 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 hospitalization (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)

9.3.1. 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.

9.4. Suspected Unexpected Serious Adverse Reaction (SUSAR)

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

9.5. 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.

9.6. 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.

9.7. 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 TBS identification, 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.

9.8. Adverse Event Reporting

It is a requirement that the Investigator promptly reports all SAEs (irrespective of relationship to the study product) to PAREXEL, the safety monitoring CRO, as soon as possible, but no later than 24 hours after becoming aware of the event occurring. The SAE should also be entered into the electronic case report form (eCRF) on the CCI clinical trial database. SAE reports must be communicated as follows:

For US sites:

Fax: +1-1 781 434 5957
Email: NorthAmerica_Medical@parexel.com

PAREXEL International 1
Federal Street
Billerica, MA 01821 United
States
Phone: +1-781 434 5010

For UK Sites:

Fax number +49 30 315 118 7777
Email: Medical_Berlin@parexel.com

In the event that the site is unable to complete the SAE form to report the event within 24 hours of their knowledge of the event, the investigators may report the SAE over the telephone via the SAE answering service, and then provide the completed SAE form via fax or email.

Phone: +49 30 30685 274
Fax number +49 30 315 118 7777

Suspected, unexpected serious adverse drug reactions (SUSARs) will be reported to all relevant competent authorities, PIs, 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 CCI 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 pediatric subjects who possess the intellectual and emotional ability to comprehend the concepts involved in the trial. If the pediatric 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 GCP 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 CCI .

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 documented.

The Investigator is responsible for maintaining a Subject Identification Log, which will include all subjects who provided Informed Consent (i.e. to include treated 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 enrollment 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 (GCP) and the applicable national and regional regulatory

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 insurance coverage. A copy of this policy is on file at ETHICON.

11. INVESTIGATOR OBLIGATIONS

This study will be conducted in accordance with, 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.

11.1. Financial Disclosure

The investigator is responsible for updating the Sponsor if there are any changes that would affect their Financial Disclosure during the conduct of the study.

11.2. 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.

11.3. 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 enrollment 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.

11.4. 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. Documentation of approval is required before implementation of amendments.

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, Sponsor 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 Johnson & Johnson (J&J), Ethicon, ETHICON™ Biosurgery, Fibrin Pad (EVARREST®), EVARREST® Fibrin Sealant Patch, EVARREST® Sealant Matrix 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

ETHICON **Clinical and Medical Affairs**		
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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.