SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Absorbable Hemostatic Agent
Device Trade Name:	ETHIZIA™
Device Procode:	SGV
Applicant's Name and Address:	Ethicon, Inc. 1000 Route 202 Raritan, NJ 08869
Date(s) of Panel Recommendation:	None
PMA Number:	P240035
Date of FDA Notice of Approval:	December 15, 2025

II. INDICATIONS FOR USE

ETHIZIA™ is indicated for use in adult patients with a body weight of ≥25kg as an adjunct to hemostasis in open liver surgery for minimal, mild, or moderate bleeding sites when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical.

III. CONTRAINDICATIONS

- ETHIZIA is not indicated for use on severe (i.e., pulsatile) bleedings (defined by Surface Bleeding Severity Scale 4-5).
- ETHIZIA is not intended for intravascular use. Do not attempt to force ETHIZIA into blood vessels, and only apply ETHIZIA after standard surgical techniques have been used to close the vessel. ETHIZIA should not be used in infected wounds.
- ETHIZIA should not be used in patients with a known hypersensitivity to the component materials, including porcine proteins and FD&C Blue #1.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ETHIZIA labeling.

V. DEVICE DESCRIPTION

ETHIZIA is a sterile, resorbable hemostatic patch that should be applied on a visible bleeding site. It presents as a blue, soft, flexible, porcine gelatin (1 ± 0.2 grams per ETHIZIA) fiber-based gelatin carrier impregnated with NHS-POx / NU-POx granulate (1 ± 0.2 grams per ETHIZIA). Blue color (202 – 686 µg per ETHIZIA) is an aid to visualize ETHIZIA when applied onto a bleeding location. ETHIZIA measures 10 by 5 cm and can be applied on both sides. As ETHIZIA is a homogenously impregnated fibrous material, it is also suited to being torn into smaller pieces for application on irregularly shaped structures and areas that are difficult to access. Figure 1 shows a representative image of ETHIZIA. ETHIZIA product specifications are listed in Table 1.

The product is not removed at the end of surgery but is resorbed in 4-6 weeks.

Degradation of ETHIZIA depends upon several factors including the amount used, the anatomical location, and degree of saturation with blood or other fluids.

Figure 1. ETHIZIA

Table 1 – ETHIZIA Specifications	
Parameter	**Specification**
Appearance	Fibrous, coherent patch, homogeneously colored (blue)
Shape	Rectangular
Dimensions	Length: 100 ± 5 mm
	Width: 50 ± 5 mm
	Thickness: 5 ± 3 mm
Weight	1.6 – 2.5 grams
Composition	Porcine gelatin (1 ± 0.2 grams per ETHIZIA)
	NHS POx/NU-POx granulate (1 ± 0.2 grams per ETHIZIA)
	FD&C Blue No. 1 (202 – 686 µg per ETHIZIA
Ratio Blue NHS-POx/NU-POx	Blue NHS-POx/NU-POx (75:25 (w/w) to 85:15 (w/w)
Loading (% of granulates in final finished device)	36-61%
Sterility assurance level (SAL)	10^{-6}

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of uncontrolled bleeding. Hemostasis involves the interaction of blood vessels, platelets, and the coagulation cascade to form a localized mechanical seal. A variety of adjunctive methods exist to achieve hemostasis. During a major hemorrhage, direct pressure or clamps may result in hemostasis. Minor bleeding can be controlled and stopped by ligation, pharmacological agents (topical thrombin and tissue sealants), laser cautery (heat, electric current, or a caustic substance) or topical agents such as oxidized cellulose, collagen, and gelatin sponges. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

ETHIZIA is CE Marked and was introduced into commercial distribution in Europe, the Middle East, Africa, and Asia in 2024, and the product is currently marketed in the countries listed in Table 2 below.

Table 2. CE-Marked Version of ETHIZIA Marketed Countries	
Europe	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Latvia, Luxembourg, Netherlands, Norway, Poland, Spain, Sweden, Switzerland, United Kingdom
Middle East and Africa	Bahrain, Israel, Kuwait, Qatar, Saudi Arabia, United Arab Emirates
Asia	Hong Kong

The ETHIZIA Hemostatic Patch has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device. ETHIZIA has not been marketed in the United States.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of ETHIZIA:

- Allergic reaction
- Anemia
- Biloma
- Blockage of artery or vein/ischemia of organs
- Closing of intestinal tract
- Damage of organs and vessels

- External compression of tubular structures such as arteries, bile ducts, veins, bowel
- Gastrointestinal hemorrhage
- Haemobilia
- Hematoma
- Hemostat migration, folding or fragmentation resulting in bowel erosion or obstruction
- Imaging artifact (resulting in unnecessary invasive diagnostic procedures or reoperation)
- Infection/ Postoperative abscess
- Intra-abdominal fluid collection
- Masking residual cancer at margin of resection resulting in higher local recurrence rates and decreased disease-free survival
- New surgery
- Pain
- Post procedural bile leak
- Pseudo abscess
- Pseudo mass formation
- Pulsatile hematoma
- Pyrexia
- Rash
- (Re)Bleeding
- Toxic response
- Thromboembolic event

For the specific adverse events that occurred in the clinical studies of ETHIZIA, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

Multiple non-clinical studies to support the safety and effectiveness of ETHIZIA, including design verification and validation, pre-clinical animal studies, biocompatibility, shelf life, packaging testing and sterilization, and endotoxin validation and testing was conducted.

A. Laboratory Studies

Bench Testing

Characterization testing of ETHIZIA was completed consistent with the requirements set forth in USP <29> Absorbable Gelatin Sponge and consistent with other FDA approved hemostats. An overview of the non-clinical testing is provided in Table 3 that demonstrates that ETHIZIA meets the design specifications.

Table 3. Summary of Bench Testing – Chemical and Physical Properties			
Test	**Purpose**	**Acceptance Criteria**	**Results**
N-hydroxysuccinimide (NHS) Degree of Functionalization (NHS-DF) - Nuclear Magnetic Resonance Spectroscopy (USP <761>)	To determine the quality and stability of ETHIZIA during production, release and storage.	85 - 115 mole% at release	PASS Avg mole%: 94%
Molecular Weight Distribution or Polydispersity Index (PDI) of Granulate – Size exclusion chromatography (USP <621>)	To determine the process capability and detecting variations in stability and/or pre-crosslinking of ETHIZIA.	≤ 2.0 at release	PASS Avg PDI: 1.5
Residual Solvents - GC-Head Space (ICH Impurities: Guideline for Residual Solvents Q3C)	To determine the residual contents of the eight (8) solvents that are used during various processes of manufacturing ETHIZIA.	Not more than acceptable levels in specifications	PASS (All solvents)
Water Content - Karl Fischer Coulometric Analysis (USP <921>)	To determine the water content (wt. %) in batches of ETHIZIA.	≤ 4.0 wt.%	PASS Avg: 3.4 wt.%
Elemental Impurities - ICP-MS (USP <232>)	To determine the presence and concentration of heavy metals / elemental impurities in batches of ETHIZIA.	Not more than acceptable levels in specifications	PASS
Residue on Ignition - Sulfated Ash (USP <281>)	To determine the amount of non-volatilized residual substance remaining from ETHIZIA after igniting the sample which was treated sulfuric acid.	Not more than 2.0%	PASS Avg: 0.04 wt.%
Amount of FD&C Blue No.1 - UV-Vis (USP <851>)	To quantify the amount of FD&C Blue No. 1 in different predefined parts of ETHIZIA, to verify uniform distribution of the dye-containing granulate in ETHIZIA and ensure that the specification for FD&C Blue No. 1 in ETHIZIA is not surpassed.	120-270 ppm (parts per million)	PASS Avg 195.5 ppm

Table 3. Summary of Bench Testing – Chemical and Physical Properties			
Test	**Purpose**	**Acceptance Criteria**	**Results**
Granulate Content - Gravimetric testing	To determine the amount of granulate impregnated in the gelatin carrier of ETHIZIA during the production process.	0.8-1.2g per patch	PASS Avg: 0.97 grams ±0.08
Granulate Content - Size exclusion chromatography (USP <621>)	To determine the amount of granulate impregnated in the gelatin carrier of ETHIZIA in the final finished device.	36-61 wt.%	PASS Avg: 48% ± 4.23
Ratio Blue NHS-POx/NU-POx Nuclear Magnetic Resonance Spectroscopy (USP <761>)	To verify the composition of the granulate.	Blue NHS-POx/NU-POx (75:25 (w/w) to 85:15 (w/w)	PASS Avg 79:21 w/w
Appearance - Visual	To verify that the carrier has been loaded with active polymers and to ensure production of visually acceptable products.	Fibrous, coherent, blue patch	PASS
Dimensions – Dimensional testing	To determine if the dimensions of ETHIZIA meet the pre-defined criteria.	Length: 100 ± 5 mm Width: 50 ± 5 mm Thickness: 2 - 4 mm	PASS
Flexibility – Physical/Visual	To determine the flexibility of the ETHIZIA as an indicator of performance (appropriate application) in various surgical settings to conform to the shape and anatomy of an organ.	Ability to be bent or rolled around a 10 mm in diameter shaft without mechanical failure.	PASS
Friability-Visual/Gravimetric	To determine the loss of granulate from the ETHIZIA upon introduction of vibrational stress.	Material loss less than 1% following mechanical stressing	PASS Avg: 0.05%
Swelling Degree - Gravimetric	To determine ETHIZIA's swelling capacity during the uptake of fluids could be harmful for other surrounding organs/tissues when applied in the human body.	Full saturation of sample is required to determine a maximum swelling degree. <200 wt.%	PASS Avg: 119%
Weight - Gravimetric	To determine the final weight of ETHIZIA.	1.6 – 2.5 g	PASS Avg: 1.89 g

Biocompatibility Testing

ETHIZIA is categorized as an implant device with long-term contact (> 30 days) with blood according to Table A.1 in Attachment A of FDA's 2023 Biocompatibility guidance document *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process*. Table 4 summarizes biocompatibility testing performed on ETHIZIA.

Table 4. Summary of Biocompatibility Testing

Endpoint	Applicable ISO 10993 Standard	Result
Physical and Chemical Information	ISO 10993-1: Evaluating and Testing with a Risk Management Process	PASS Negligible toxicological risk
Cytotoxicity	ISO 10993-5: Tests for *in vitro* cytotoxicity (MTS Cytotoxicity Assay)	Acceptable [1]
Sensitization– Kligman Guinea Pig Maximization Study	ISO 10993-10: Tests for irritation and skin sensitization	PASS Non-sensitizer
Intracutaneous Irritation – Rabbit intracutaneous irritation Study	ISO 10993-10: Tests for irritation and skin sensitization	PASS Non-irritant
Material Mediated Pyrogenicity - Rabbit Pyrogenicity Study	ISO 10993-11 Tests for systemic toxicity	PASS Non-pyrogenic
Acute Systemic Toxicity	ISO 10993-11: Tests for systemic toxicity	PASS Non-toxic
Hemocompatibility Coagulation – Partial Thromboplastin Time (PTT)	ISO 10993-4: Selection of tests for interactions with blood	PASS Non activator
Hemocompatibility - SC5b-9 Complement Activation Assay	ISO 10993-4: Selection of tests for interactions with blood	Acceptable [2]
Hemocompatibility- *In vitro* hemolysis	ASTM -F756-17: Standard Practice for Assessment of Hemolytic Properties of Materials ISO 10993-4: Selection of tests for interactions with blood	Acceptable [2]
Genotoxicity – Mouse Lymphoma Assay	ISO 10993-3: Tests for genotoxicity, carcinogenicity, and reproductive toxicity	PASS Non-genotoxic
Genotoxicity- Mouse Peripheral Blood Micronucleus Study	ISO 10993-3: Tests for genotoxicity, carcinogenicity, and reproductive toxicity	PASS Non-genotoxic

Table 4. Summary of Biocompatibility Testing		
Endpoint	**Applicable ISO 10993 Standard**	**Result**
Genotoxicity - Bacterial Reverse Mutation Study	ISO 10993-3: Tests for genotoxicity, carcinogenicity, and reproductive toxicity	PASS Non-genotoxic
Carcinogenicity	Risk of carcinogenicity from non-genotoxic carcinogens was evaluated by toxicological risk assessment on the extractables and leachables from the device which concluded a low risk for adverse carcinogenic effects with a worst-case exposure to three devices used simultaneously.	
Systemic Toxicity (Sub-chronic and Chronic) & Local tissue effects (Implantation)	ISO subcutaneous implantation Study (4, 13 weeks) for systemic toxicity and local tissue effects.	PASS The test article was classified as a slight irritant in comparison with the control article and the negative control article at 4-weeks. The test article elicited minimal or no reaction when compared to the control article and negative control article at 13-weeks. There was no evidence of systemic toxicity at 4-weeks and 13-weeks.

[1] Undiluted test extracts prepared from ETHIZIA showed cytotoxicity potential *in vitro*. Based on testing on device components, the observed cytotoxicity is most likely mediated by free N-Hydroxysuccinimide (NHS) degradant which is released upon aqueous activation of the electrophilic EL-POx polymer in ETHIZIA. The *in vitro* cytotoxicity may be further exacerbated due to poor buffering ability of the *in vitro* test system. In contrast, in a clinical use setting, the availability of free NHS is expected to be significantly lower as upon application, ETHIZIA cross-links into a hydrogel which degrades releasing free NHS along with other decomposition products over the course of 4-6 weeks. Further, clinically relevant animal studies did not show any evidence of negative tissue responses to ETHIZIA. Taken together with the conclusions from the chemical characterization and toxicological risk assessment, the cytotoxicity observed *in vitro* is considered to be an acceptable worst-case representation.

[2] The test article was considered to be a potential activator of the complement system. In addition, the test article was found to be hemolytic in *in vitro* hemolysis assay by direct contact method. However, systemic toxicity studies, clinically-relevant animal studies, and clinical data did not demonstrate any abnormalities related to hematological response to the device. In addition, ETHIZIA is not intended for intravascular use. For these reasons, the hemocompatibility results were considered to be an acceptable worst-case representation.

B. Animal Studies

An overview of the non-clinical animal studies is provided in Table 5.

Table 5. Summary of Non-Clinical Animal Studies		
Study	**Treatments Applied**	**Results**
GLP hemostatic effectiveness trials		
Evaluation of ETHIZIA following functional application on bleeding organs in a swine model -Organ: liver -Lesion type: biopsy punch -Procedure type: open	24 pigs 208 applications • 80 ETHIZIA • 80 Surgifoam + Thrombin (Topical RECOTHROM Thrombin (Baxter) was used in combination with every application of Surgifoam) • 48 Hemopatch	ETHIZIA successfully demonstrated non-inferiority to both the Surgifoam+Thrombin and Hemopatch hemostasis devices when comparing time to hemostasis and re-bleed events at implant and termination in each of the 72 hour, 4 week and 8 week cohorts. There were no safety concerns of ETHIZIA as compared to controls.
GLP subcutaneous implant studies		
3-day, 7-day, and 14-day subcutaneous implantation study in rabbits	10 rabbits 100 applications • 35 ETHIZIA implanted sites • 32 Surgifoam® + Thrombin implanted sites (Control 1) • 33 Gelatin carrier implanted sites (Control 2)	At 3-Day time point, the in-life grading of the swelling was slight-to-moderate for 24 out of the 35 implanted ETHIZIA sites, slight for 12 out of the 32 Surgifoam+Thrombin implanted sites, and slight-to-moderate for 16 out of the 33 gelatin carrier implanted sites. At 7-Day time point, less than half of the implant sites for each of the three treatment groups had slight swellings (and one site was graded moderate for Surgifoam+Thrombin). No swelling was graded for any of the implant sites for ETHIZIA at 10-Day and 14-Day timepoints of the study (only 2 sites of Surgifoam+Thrombin and 1 site of Gelatin carrier were graded slight at 10-Day).

Table 5. Summary of Non-Clinical Animal Studies		
Study	**Treatments Applied**	**Results**
Non-GLP studies		
ETHIZIA partly heparinized *in vivo* porcine model[1, 2] -Organ: liver, spleen and kidney -Lesion type: abrasion, resection, metastasectomy -Procedure type: open	2 pigs 36 ETHIZIA applications	Hemostasis was achieved after the intended application time (n=30 for 30sec, n=2 for 60sec and n=2 for 180sec) in 94% of all bleedings, and 94% hemostasis achieved within 3 minutes.
ETHIZIA partly heparinized *in vivo* porcine model[1, 2] -Organ: liver, spleen and kidney -Lesion type: abrasion, resection, metastasectomy -Procedure type: open	2 pigs 35 applications • 28 ETHIZIA • 7 TachoSil	ETHIZIA resulted in high rates of hemostasis (83%) in a non-heparinized and heparinized liver, spleen and kidney model of minimal to severe bleedings.
In vivo heparinized porcine model[1] -Organ: liver -Lesion type: abrasion -Procedure type: open	2 pigs 22 ETHIZIA applications	100% hemostasis at 5 minutes (all in 30 seconds).
In vivo non-heparinized and heparinized porcine model[1] -Organ: liver -Lesion type: abrasion -Procedure type: open	2 pigs 32 ETHIZIA applications	100% hemostasis at 3 minutes (all in 30 seconds)
[1]The performance of ETHIZIA in anticoagulated patients has not been studied. [2]The safety and effectiveness of ETHIZIA has not been established for use in anatomic locations other than the liver.		

C. Additional Studies

Shelf-life and Packaging Validation

The sterile barrier system and packaging were validated per ISO 11607-1:2019, "*Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier Systems and packaging Systems*" and ISO 116072:2019, "*Packaging for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes*".

Packaging testing included simulated conditioning and transport, visual inspection, pouch seal integrity, and seal strength after real-time aging. Shelf life testing further included ETHIZIA performance testing to ensure ETHIZIA met specifications after real time

aging. Results demonstrated that ETHIZIA device and packaging meets required specifications for the stated shelf life of 2 years when stored according to manufacturer's specifications between 5°C and 25°C and in presence of the included desiccant.

Sterilization

ETHIZIA is terminally sterilized using Electron Beam (E-Beam) irradiation in accordance with ISO 11137-1 *Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices.*

All sterilization testing conducted for ETHIZIA demonstrate that this device meets a sterility assurance level (SAL) of 10^{-6} for the subject device. Bioburden and pyrogen testing were performed and results demonstrate that all test samples met the predetermined acceptance criteria.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study (IDE G210325) to establish a reasonable assurance of safety and effectiveness of ETHIZIA as an adjunct to hemostasis in open liver surgery for minimal, mild or moderate bleeding sites when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical. G210325 is a prospective, randomized (2:1), multicenter, multi-national pivotal IDE clinical investigation for subjects undergoing open elective liver resection surgery in the US, and Europe. A total of 131 eligible subjects were randomized to ETHIZIA (n=87) or TachoSil® Fibrin Sealant Patch (TachoSil) (n=44) at 9 clinical sites in the US and Europe.

Supplemental clinical data was provided from a prospective, single arm, multicenter, pre-market, first-in-human (FIH) clinical investigation for subjects undergoing open elective liver resection surgery. This study included a total of 47 subjects treated with ETHIZIA at 3 clinical sites in the Netherlands.

Data from these clinical studies were the basis for the PMA approval decision. A summary of the clinical studies is presented below.

Pivotal Clinical Study IDE G210325:

A. Study Design

Patients were treated between August 4, 2022 and May 10, 2024. The database for this PMA reflected data collected through June 18, 2024 and included 131 patients. There were 9 investigational sites.

The study was a pre-market, prospective, randomized, multicenter, multi-national pivotal clinical investigation evaluating the safety and effectiveness of ETHIZIA versus TachoSil for hemostasis during open liver surgery. The primary objective of

this investigation was to demonstrate non-inferiority in the achievement of hemostasis of the first target bleeding site at 3 minutes without rebleeding at 10 minutes when traditional means of achieving hemostasis such as suture, ligature, cautery were ineffective or impractical in subjects receiving ETHIZIA compared to subjects receiving TachoSil. In this investigation hemostasis was defined as a grade of 0 (None/Dry) on the Severity Bleeding Severity Scale (SBSS) at the time of the surgery by the study investigator.

The study was conducted in compliance with United States Food and Drug Administration (FDA) regulations 21 CFR Parts 50, 54, 56, and 812, and International Council for Harmonization (ICH) E6 Good Clinical Practices (GCP). The sponsor collaborated with a Contract Research Organization (CRO) for study management, data management, site activation, site monitoring and data verification, medical writing, Independent Data monitoring committee (IDMC) and Independent Adjudication committee (IAC) facilitation.

An IDMC comprised of independent medical experts and an expert biostatistician operated throughout the course of the study to minimize study bias by review of blinded data regarding trial conduct, patient selection, and safety and effectiveness endpoints.

An IAC of independent physicians reviewed all serious adverse events (SAEs) and adverse events of special interest (e.g., bleeding-related events, thromboembolic events, biloma, and allergic reaction) occurring during the 3-month follow-up after surgery for relatedness to the device and expectedness of the event based on the clinical scenario comprising of patient and procedural characteristics.

TachoSil, an absorbable collagen sponge, coated on one side with fibrinogen and thrombin, was used as the control. The clinical trial choice of comparator control product was based on the following considerations:

- The control is a legally marketed alternative with similar indications for use.
- A standard-of-care hemostatic patch to obtain the highest standards of clinical evidence when compared to the investigational device.
- Both products being ready-to-use, which limits blood loss during surgery and increases the comparability in safety and performance.
- Both products have similar risk-benefit ratio for patches because of position and structure of the patch on the target bleeding site in relation to the patient anatomy.

Subjects were randomized intraoperatively in a 2:1 ratio to ETHIZIA (study group) or TachoSil (control group). The pivotal study enrolled 131 subjects, 87 patients randomized to ETHIZIA and 44 patients randomized to TachoSil. Subjects were treated and enrolled between August 2022 and May 2023. There were 9 investigational sites enrolling patients: 5 study sites located in the United States and 4 study sites OUS, 1 located in Germany and 3 located in the Netherlands. Subjects were blinded to the treatment group to which they were randomized. However, due to

the physical differences in the investigational and control devices, blinding of the surgeon was not possible. To minimize investigator bias during this clinical investigation, a validated bleeding scale was used to assess the severity of bleeding before randomization and to evaluate hemostasis after patch use. The baseline bleeding severity was assessed prior to randomization, at which time the investigator was not aware of the treatment assignment. Further, the training and testing required for all investigators to use a validated bleeding severity scale for the assessment of successful hemostasis which reduced subjectivity for the effectiveness assessments.

The study hypothesis was that the probability of cases achieving hemostasis at 3 minutes using ETHIZIA is non-inferior to TachoSil.

1. Clinical Inclusion and Exclusion Criteria:

   Enrollment in the Pivotal Study was limited to patients who met the following inclusion criteria:

   - Subject was scheduled to undergo elective open surgery on the liver;
   - Subject was willing and able to give written informed consent for the clinical investigation participation;
   - Subject was 22 years of age or older at the time of enrollment; and
   - Subject had been informed of the nature of the clinical investigation.

   In addition, subjects must have met the following intraoperative inclusion criteria:

   - Subject in whom the Investigator was able to identify a target bleeding site at the liver resection plane for which any applicable conventional means for hemostasis (e.g., suture, ligature or cautery) were ineffective or impractical and the choice was made to use a hemostatic agent to stop the bleeding; and
   - Subject had a target bleeding site with a Surface Bleeding Severity Score (SBSS) of 1, 2, or 3. Hemostasis was defined by a grade of 0 (None/Dry) on the SBSS. The SBSS provides a validated score for assessment of bleeding at the target site, and consists of 6 subscales (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe; not immediately life-threatening, 5=extreme; immediately life threatening).

   Patients were not permitted to enroll in the Pivotal Study if they met any of the following exclusion criteria:

   - The target bleeding site was from a large defect in an artery or vein that requires vascular reconstruction with maintenance of vessel patency;

- Subject was scheduled to undergo surgery on other organs than the liver and its associated biliary and vascular system;
- Subject was scheduled to undergo a staged liver surgery procedure (e.g., Associating Liver Partition and Portal vein ligation for Staged hepatectomy [ALPPS])
- Subject was taking multiple antithrombotic therapies in therapeutic dosage up to the time of surgery, but allowing exclusive use of acetylsalicylic acid;
- Subject had platelet count <100 x 10^9/L, an activated partial thrombin time of >100s, or international normalized ratio >2.5;
- Subject had a total bilirubin level of ≥2.5 mg/dL;
- Subject was pregnant, planning to become pregnant or actively breastfeeding from screening through the 12-week follow-up visit;
- Subject had a known hypersensitivity to brilliant blue (FD&C Blue #1), porcine (pig) gelatin, or horse proteins;
- Subject who had religious objections to receiving products with components of animal (pig/horse) or human origin;
- Subject had an active or suspected infection at the bleeding site;
- Subject in whom the investigational device would be used at the site of a synthetic graft or patch implant;
- Subject had a life expectancy of less than 3 months;
- Subject had a documented severe congenital or acquired immunodeficiency;
- Subject had or planned to receive any organ transplantation
- Subject was currently participating or has participated in another clinical investigation within the past 30 days that could affect the endpoints of the study, such as trials related to the surgical procedure, and on anti-coagulation;
- Subject was not appropriate for inclusion in the clinical investigation, per the medical opinion of the Investigator; and
- Subject had any incidental (pre- and peri-operative) findings deemed by the Investigator to potentially jeopardize the safety or welfare of the subject.

2. Follow-up Schedule:

All patients were scheduled to return for a follow-up visit at week 6 (± 2 weeks), which included a laboratory and ultrasound imaging assessment. A telephone assessment took place at week 12 (± 2 weeks). Adverse events and complications were recorded at all visits.

Study procedures are summarized in Table 6 below. Preoperatively, information was collected on baseline demographics (age, sex, race and ethnicity), medical history (allergies, smoking status, cardiac disorders, systemic hypertension, renal dysfunction, diabetes, hereditary blood disorders,

blood transfusions in the last 3 months, previous abdominal surgery, liver disease, portal hypertension, malignancies and prior therapies, indication for surgery, other critical medical condition or previous surgery, and American Society of Anesthesiologists classification), physical examination, relevant concomitant medications, and laboratory test data. Laboratory tests included hematology (complete blood count), coagulation (prothrombin time or PT, activated partial thromboplastin time or aPTT, International Normalized ratio or INR), and chemistry tests (bilirubin, calcium, potassium, sodium, chloride, albumin, creatinine, aspartate transaminase or AST, alanine transaminase or ALT, gamma glutamyl transferase or GGT, and pregnancy test, if applicable. Inclusion/exclusion criteria were confirmed preoperatively.
Postoperatively, the objective parameters measured during the study included hemostatic performance data (including primary and secondary study endpoints), surgical procedural data (surgery date, procedure length, number of devices used, blood loss in ml, surface bleeding severity scale or SBSS of target bleeding site, use of adjunct hemostatic agents/techniques, amount of material needed versus bleeding surfaces, user satisfaction (per investigator, per procedure), hospitalization information (duration of stay in intensive care unit, total hospitalization period, blood transfusion in ml), intraoperative device and/ procedure related adverse events, intraoperative device deficiencies, and laboratory test data (same as preoperative tests).

Table 6: Schedule of Assessments

Assessments	**Screening (< 6 weeks before surgery)**	**Admission before surgery[1]**	**Treatment**	**Hospital-ization after surgery**	**Week 6 (± 2 weeks)**	**Week 12 (± 2 weeks)**	**Up to 5-year follow-up**
Informed consent	X						
Inclusion / Exclusion criteria	X	X	X				
Baseline demographics	X						
Medical history	X						
Medication	X	X		X	X	X	
Physical examination	X	X		X	X		
Laboratory tests	X[2]	X[2]		X	X		
Procedural Data			X				
User questionnaire			X				
Adverse events assessment			X	X	X	X	
Imaging					X[3]		

Table 6: Schedule of Assessments							
Assessments	**Screening (< 6 weeks before surgery)**	**Admission before surgery[1]**	**Treatment**	**Hospital-ization after surgery**	**Week 6 (± 2 weeks)**	**Week 12 (± 2 weeks)**	**Up to 5-year follow-up**
Cancer recurrence / progression						X	6±1 months, 9±1 months, 12±2 months, 18±3 months, 24±3 months, 30±3 months 36±3 months 42±3 months 48±3 months 54±3 months 60±3 months

[1] In situations where the patient was screened during the admission before surgery, this was considered to be the screening visit and no additional visit at admission before surgery was performed.
[2] At least once before surgery during one of the assessments, with the latest data being the final presurgical data used in analyses.
[3] Ultrasound imaging was mandatory at the Week 6 (±2 weeks) follow-up point. If other imaging, for example Computed Tomography (CT), was performed in this follow-up window per standard of care for the evaluation of adverse events, these were considered to replace the requirements of ultrasound imaging.

Patients undergoing liver resection for liver malignancy or metastases would be observationally followed for 5 years to review local cancer recurrence, disease-free survival, and overall survival. This observational follow-up would not be in direct contact with the patient, but through electronic health records and/or contact with the patient's treating physician.

The key timepoints and assessments are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints:

The primary effectiveness endpoint was defined as the percentage of cases achieving hemostasis at 3 minutes without rebleeding at the 10-minute time point, at the first target bleeding site. There could be multiple bleeding sites that required hemostatic device application for one subject, the first bleeding site that (1) a hemostatic device was applied to stop bleeding, and (2) had an SBSS of 1, 2, 3, was defined as the first target bleeding site (at subject level) and was used for the analyses on primary effectiveness endpoint and key secondary endpoint. Other bleeding sites being treated by the hemostatic device were referred to as target bleeding sites. Results for hemostasis across all treated target bleeding sites are summarized on Tables 15 and 16.

The secondary effectiveness endpoints of this clinical investigation consisted of:

- Time to hemostasis (seconds), censored at 600 seconds if hemostasis not achieved at 10 minutes);
- Time to hemostasis (no censoring);
- Treatment failure, defined as no hemostasis at 10 minutes;
- Rebleeding after 10 minutes but before subject closure; and
- Percentage of hemostasis at 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 360, 420, 480, 540, and 600 seconds

The key secondary effectiveness endpoint was the time to hemostasis (seconds) censored at 10 minutes for the cases that do not achieve hemostasis by 10 minutes. Achievement of hemostasis was assessed every 30 seconds starting after the initial 30 seconds of application for ETHIZIA, and every 30 seconds after the initial 3 minutes for TachoSil, up to the 5-minute time point, and every 60 seconds between 5 and 10 minutes.

The safety of ETHIZIA was assessed by the incidence, severity, and relation to hemostatic device of all Adverse Events (AEs). The AEs for the ETHIZIA treatment group were compared to those for the TachoSil treatment group. All AEs were collected, with adverse events of special interest (AESI) being:

- Bleeding-related events, including rebleeding of the bleeding site(s) treated with hemostatic patch at any point in time (within 10 minutes of application, prior to subject closure, and postoperative), and including hematoma;
- Thromboembolic events;
- Biloma; and
- Allergic reaction.

Exploratory endpoints in the study consisted of:

- Procedure duration (minutes);
- Estimated blood loss (mL) during surgery;
- Number and type of blood transfusions during hospitalization;
- Duration of ICU stay;
- Total hospitalization stay;
- Postoperative drainage volume, characteristics, and duration;
- Need for and cause of reoperation;
- Imaging of the liver resection at 6 weeks post-surgery to detect:
    1. Fluid collection and its size (mL) and aspect,
    2. Pseudoaneurysm,
    3. Patch encapsulation, and
    4. Rolling up of the device on the resection plane;
- Amount of hemostatic material needed vs bleeding surface;
- User satisfaction (questionnaire) for ETHIZIA Hemostatic Patch;
- Physician treatment preference assessment (questionnaire);

5-Year Exploratory Endpoints:

- Local recurrence of liver cancer at the resection site;
- Cancer-free survival;
- Overall survival

4. Statistical Analysis Plan:

For the primary effectiveness endpoint, the study hypotheses were:
H0: PG-PT$\leq$ -10% vs. H1: PG-PT> -10%, where PG and PT were the probability of subject's first bleeding site achieving hemostasis at 3 minutes in the ETHIZIA and TachoSil arm, respectively.

Non-inferiority with respect to the primary effectiveness endpoint was evaluated using the Farrington-Manning test. The estimated rate and the 95% exact (Clopper-Pearson) confidence interval for each group, and their difference in rate between the treatment group and the corresponding 95% Newcombe confidence interval were reported.

If non-inferiority was established, then superiority of the primary endpoint and the first key secondary endpoint were to be tested in the order using a hierarchical testing procedure for labeling claim. The key secondary endpoint, the time to hemostasis (censored at 10 minutes) was analyzed using a one-sided Wilcoxon-Mann-Whitney test.

Other endpoints were summarized descriptively.

5. Sample Size Calculation:

Sample size was estimated based on non-inferiority test, comparing ETHIZIA and TachoSil arms on the primary effectiveness endpoint. The calculation was conducted under the following assumptions: 80% of patients achieve hemostasis at 3 minutes in the TachoSil group, 92% of patients achieve hemostasis in the ETHIZIA group, a non-inferiority margin of 10%, and an overall one-sided type 1 error rate of 0.025. A total sample size of 130 subjects was estimated to achieve 90% power for the study.

6. Analysis Populations:

The Intent-to-Treat population (ITT) included all subjects who were randomized, irrespective of any deviation from the protocol or premature discontinuation.
The Per-Protocol population (PP) was the cohort for the primary endpoint analysis and included all subjects in the ITT population who received the randomized treatment with ETHIZIA or TachoSil devices, and had an assessment of primary endpoint, and had no major protocol deviations.

The list of major protocol deviations potentially leading to PP population exclusion includes at least the following deviations:

- Violations of inclusion or exclusion criteria.
- Use of a patch in the instance of SBSS 0, 4, or 5.
- Use errors deeming the product ineffective.
- Use of disallowed medication (that may influence the interpretation of efficacy results).

The Safety Population included all randomized subjects who received treatment with ETHIZIA or TachoSil. The treatment group assignment was defined by the treatment actually received.

Evaluable subjects were subjects that did not meet any of the following withdrawal criteria:

- change in SBSS to ineligible (SBSS of 0, 4, or 5) between randomization and application of the hemostatic patch; or
- death of the subject in the time between patch application and patch use.

The primary analysis for the primary endpoint and the key secondary endpoint were performed for the PP population as well as the ITT population. Consistent results from the analysis of ITT and PP datasets were necessary to conclude non-inferiority of ETHIZIA to TachoSil. All other secondary endpoints, and exploratory analyses, were summarized descriptively by treatment group, and no statistical analysis was performed.

The Safety Population was used for safety analysis.

7. Interim Analysis:

   The trial was planned to have one interim analysis for the purposes of stopping the trial early for success or futility and for sample size re-estimation. The interim analysis was to be performed once 70% (n = 91) of the planned evaluable subjects were treated. To account for multiple testing and control the overall type I error rate of the trial at a 1-sided level of 0.025, the Lan-DeMets approach with an O'Brien-Fleming alpha-spending function was used with the significance level of 0.00738 (one-sided) for the interim analysis, and 0.02275 for final analysis to claim study success. For sample size re-estimation, the interim decision rule was defined based on conditional power (when the p value is greater than 0.00738) to ensure overall type 1 error control.

   Interim analysis was conducted, and results were reviewed by the independent data monitoring committee (IDMC). Despite the interim results, the committee recommended that the trial should proceed without modifications to allow for the collection of additional safety information, given the relatively small sample size at that stage of the study. No claim was made based on the interim analysis.

B. Accountability of PMA Cohort:

At the time of database lock, of 131 patients enrolled in the PMA study, 92 % (120) patients are available for analysis at the completion of the study, at the 12-Weekpost-operative visit (*final visit evaluated for safety and effectiveness as the basis for the PMA submission*).

Subject disposition of this clinical study are summarized in Table 7. A total of 195 subjects were screened and 132 subjects met preoperative eligibility criteria. One (1) subject that was randomized was subsequently withdrawn from the study intraoperatively due to not meeting intraoperative inclusion criteria (i.e., severity of bleeding changed), resulting in 131 enrolled subjects (87 ETHIZIA; 44 TachoSil). One (1) subject randomized to TachoSil did not receive it as it was not available in the operating room and instead, the investigator used a different hemostatic agent not included in the study. This was recorded as a protocol deviation and the subject was maintained in the trial for protocol-defined follow-up. The subject was lost to follow-up prior to completion of the 12-week visit. Thus, overall, of the 132 randomized subjects, 130 subjects met the inclusion and exclusion criteria and were treated with either ETHIZIA or TachoSil (87 ETHIZIA, 43 TachoSil).

A total of 120 subjects (79 ETHIZIA; 41 TachoSil) completed the trial 12-week follow-up period; 12 subjects (9 ETHIZIA; 3 TachoSil) discontinued from the trial prematurely, 5 of which were lost to follow-up (3 ETHIZIA; 2 TachoSil), 1 subject withdrew due to 'Other' (randomized to ETHIZIA but not treated with ETHIZIA as described above) (Table 7), and 6 subjects died during the follow-up period; the deaths were unrelated to the study treatment (5 ETHIZIA; 1 TachoSil).

Table 7. Subject Disposition (Randomized Subjects)

Category	TachoSil (N=44) n (%)	ETHIZIA (N=88) n (%)	Overall (N=132) n (%)
Subjects randomized	44 (100)[1]	88 (100)	132 (100)
Subjects treated	43 (97.7) [1]	87 (98.9)	131 (99.2)
Subjects completed the trial (up to 12-week follow-up visit)	41 (93.2)	79 (89.8)	120 (90.9)
Subjects who withdrew from the trial prematurely	3 (6.8)	9 (10.2)	12 (9.1)
Withdrawal of consent	0	0	0
Investigator's and sponsor's decision	0	0	0
Non-compliance to protocol	0	0	0
Lost to follow-up	2 (4.5)	3 (3.4)	5 (3.8)
Adverse event	0	0	0
Death	1 (2.3)	5 (5.7)	6 (4.5)
Other[2]	0	1 (1.1)	1 (0.8)

Abbreviations: N, number of subjects in the population; n, number of subjects with the specified outcome; SBSS, Surface Bleeding Severity Scale.
Note: The presented frequencies and the denominators used to calculate percentages are based on the number of subjects in the population (N).
[1] One subject was randomized to TachoSil but received a different hemostatic agent not included in the study.
[2] Other = due to protocol withdrawal criteria: change in SBSS between point of randomization and patch application.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an open liver resection clinical trial performed in the US.

The average age for all subjects was 61.7 years and there were more females in the ETHIZIA treatment group (ETHIZIA: 37/87, 42.5%; TachoSil: 12/43, 27.9%) and a higher percentage of Hispanic or Latino subjects in the ETHIZIA treatment group (ETHIZIA: 11/87, 12.6%;TachoSil: 2/43, 4.7%) (Table 8). There was some variability in demographics between sites but owing to the small numbers of subjects at some sites, it was not meaningful to compare demographics across sites. The study

population was considered typical for an open liver resection clinical trial evaluating the safety and effectiveness of a hemostatic agent. In sites located outside of the US, the percentage of Asian subjects was lower than in sites within the US but other demographic variables were similar.

The majority of subjects self-identified as White (107/130, 82.3%) and the remaining subjects self-identified as Asian (12/130, 9.2%), Black or African American (1/130, 0.8%), American Indian or Alaska Native (1/130, 0.8%), and Other (9/130, 6.9%). There were no clinically relevant differences for any of the physical measurements (height, weight, BMI) between treatment arms.

Table 8. Subject Demographics (Safety Population)

Measure		**TachoSil (N=43) n (%)**	**ETHIZIA (N=87) n (%)**	**Overall[1] (N=130) n (%)**
Age	Mean (SD)	61.3 (13.88)	61.9 (14.99)	61.7 (14.58)
	Median	63.0	67.0	65.5
	Min, Max	26, 82	23, 84	23, 84
Sex	Male	31 (72.1)	50 (57.5)	81 (62.3)
	Female	12 (27.9)	37 (42.5)	49 (37.7)
Race	White	38 (88.4)	69 (79.3)	107 (82.3)
	Black or African American	0	1 (1.1)	1 (0.8)
	Asian	5 (11.6)	7 (8.0)	12 (9.2)
	American Indian or Alaska Native	0	1 (1.1)	1 (0.8)
	Native Hawaiian or Other Pacific Islander	0	0	0
	Other	0	9 (10.3)	9 (6.9)
Ethnicity	Hispanic or Latino	2 (4.7)	11 (12.6)	13 (10.0)
	Not Hispanic	40 (93.0)	75 (86.2)	115 (88.5)
	Other	1 (2.3)	1 (1.1)	2 (1.5)
Measure		**TachoSil (N=43) n (%)**	**ETHIZIA (N=86) n (%)**	**Overall[1] (N=129) n (%)**
Height (cm)	Mean (SD)	175.1 (9.43)	170.8 (10.40)	172.2 (10.25)
	Median	173.0	170.2	172.0
	Min, Max	162.0, 196.0	147.0, 197.0	147.0, 197.0
Weight (kg)	Mean (SD)	84.4 (20.64)	78.9 (15.67)	80.7 (17.60)
	Median	79.6	80.3	80.0
	Min, Max	52.0, 155.0	49.4, 125.0	49.4, 155.0
BMI (kg/m^2)	Mean (SD)	27.3 (5.10)	27.1 (5.27)	27.2 (5.20)
	Median	26.9	26.3	26.6
	Min, Max	18.6, 42.8	18.3, 42.3	18.3, 42.8

Table 8. Subject Demographics (Safety Population)			
Measure	**TachoSil (N=43) n (%)**	**ETHIZIA (N=87) n (%)**	**Overall[1] (N=130) n (%)**
Abbreviations: BMI, body mass index; Max, maximum; Min, minimum; N, number of subjects in the population; n, number of subjects in the analysis; SD, standard deviation. Notes: The presented frequencies and the denominators used to calculate percentages are based on the number of subjects in the population (N). Age is in years and is the age of the subject at the time of randomization; height and weight were measured at baseline with 1 patient having a missing value as this assessment was not performed. [1] Overall demographics are same as Safety Population.			

Baseline characteristics and medical history in the Safety Population were similar between treatment groups (Table 9). There were some differences in the percentage of subjects with hepatocellular carcinoma (ETHIZIA: 21/87, 24.1%; TachoSil: 5/43, 11.6%), cholangiocarcinoma (ETHIZIA: 7/87, 8.0%; TachoSil: 10/43, 23.3%), American Society of Anesthesiologists (ASA) classification 1 (ETHIZIA: 9/87, 10.3%; TachoSil: 1/43, 2.3%), ASA classification 2 (ETHIZIA: 19/87, 21.8%; TachoSil: 16/43, 37.2%), and systemic hypertension (ETHIZIA: 40/87, 46.0%; TachoSil: 25/43, 58.1%) but otherwise, the treatment groups were similar with respect to other indications for surgery, baseline characteristics, and medical history. Malignancies and prior therapies was the most frequently occurring medical condition overall (102/130, 78.5%) and within each treatment group (ETHIZIA: 67/87, 77.0%;TachoSil: 35/43, 81.4%), as expected based on the indication for surgery being cancer in the majority of subjects.

Table 9. Baseline Characteristics and Medical History (Safety Population)				
Variable	**Statistic/Response**	**TachoSil (N=43)[1] n (%)**	**ETHIZIA (N=87) n (%)**	**Overall (N=130) n (%)**
Indication for surgery[1], n (%)	Hepatocellular carcinoma	5 (11.6)	21 (24.1)	26 (20.0)
	Colorectal metastases	15 (34.9)	28 (32.2)	43 (33.1)
	Non colorectal metastases	2 (4.7)	10 (11.5)	12 (9.2)
	Cholangiocarcinoma	10 (23.3)	7 (8.0)	17 (13.1)
	Benign tumor	3 (7.0)	5 (5.7)	8 (6.2)
	Liver donor	2 (4.7)	5 (5.7)	7 (5.4)
	Other	6 (14.0)	11 (12.6)	17 (13.1)
Child-Pugh classification, n (%)	A	12 (27.9)	25 (28.7)	37 (28.5)
	B	0	2 (2.3)	2 (1.5)
	C	1 (2.3)	0	1 (0.8)
	NA	29 (67.4)	58 (66.7)	87 (66.9)
	Missing	1 (2.3)	2 (2.3)	3 (2.3)

Table 9. Baseline Characteristics and Medical History (Safety Population)				
Variable	**Statistic/Response**	**TachoSil (N=43)[1] n (%)**	**ETHIZIA (N=87) n (%)**	**Overall (N=130) n (%)**
ASA classification, n (%)	1	1 (2.3)	9 (10.3)	10 (7.7)
	2	16 (37.2)	19 (21.8)	35 (26.9)
	3	24 (55.8)	55 (63.2)	79 (60.8)
	4	1 (2.3)	4 (4.6)	5 (3.8)
	5	0	0	0
	Missing	1 (2.3)	0	1 (0.8)
Medical history	Any medical history	43 (100.0)	86 (98.9)	129 (99.2)
	Allergies	7 (16.3)	17 (19.5)	24 (18.5)
	Smoking history/current	14 (32.6)	32 (36.8)	46 (35.4)
	Cardiac disorder(s)	7 (16.3)	18 (20.7)	25 (19.2)
	Systemic hypertension	25 (58.1)	40 (46.0)	65 (50.0)
	Renal dysfunction	3 (7.0)	4 (4.6)	7 (5.4)
	Diabetes mellitus	11 (25.6)	22 (25.3)	33 (25.4)
	Hereditary blood disorder(s)	0	2 (2.3)	2 (1.5)
	Blood transfusions in the last 3 months	0	0	0
	Previous abdominal surgery	17 (39.5)	36 (41.4)	53 (40.8)
	Liver disease	10 (23.3)	25 (28.7)	35 (26.9)
	Portal hypertension	0	2 (2.3)	2 (1.5)
	Malignancies and prior therapies	35 (81.4)	67 (77.0)	102 (78.5)
	Other critical medical conditions of previous surgery	19 (44.2)	33 (37.9)	52 (40.0)

Abbreviations: ASA, American Society of Anesthesiologists, United States; N, number of subjects in the population; n, number of subjects with the specified outcome; NA, not applicable.
Note: The presented frequencies and the denominators used to calculate percentages are based on the subjects in each group in the Safety Population (N).
[1] These were the preoperative indications; the actual diagnoses may have been different as determined by postoperative pathology.

The baseline surgical procedure details were similar in both treatment groups and summarized in Table 10. The majority of subjects had normal hepatic parenchyma, while the type of hepatic parenchyma was more frequently steatotic in TachoSil group (10/43, 23.3%) compared to the ETHIZIA group (11/87, 12.6%) . The type of surgery

was more frequently a major resection (i.e., any [extended] hemihepatectomy or trisegmentectomy) in the ETHIZIA group (14/87, 16.1%) versus the TachoSil group (5/43, 11.6%), which was also observed in the estimated total size of all resection areas (mean: 116.3 cm^2 in the ETHIZIA group and 102.6 cm^2 in the TachoSil group). Furthermore, the resections were more frequently non-anatomical resections in the ETHIZIA group (40/87, 46.0%) versus the TachoSil group (17/43, 39.5%).

The estimated blood loss during the procedures was higher in the ETHIZIA group (median: 500 mL [Q1, Q3: 300.0 mL, 1000 mL] in the ETHIZIA group and 450 mL [Q1, Q3: 200.0 mL, 950 mL] in the TachoSil group), but the rate of subjects requiring intraoperative blood transfusions was similar (13/87, 14.9% in the ETHIZIA group versus 7/43, 16.3% in the TachoSil group). Estimated blood loss during surgery and number and type of blood transfusions during hospitalization were exploratory endpoints for this study.

Table 10. Surgery Procedural Data (Safety Population)

Category	Response/Description	TachoSil (N=43)	ETHIZIA (N=87)	Overall (N=130)
Subjects taking acetylsalicylic acid up to the time of surgery, n (%)	Yes	2 (4.7)	2 (2.3)	4 (3.1)
Subjects taking any other antiplatelet therapy up to the time of surgery, n (%)	Yes	0	0	0
Subjects taking anticoagulation up to the time of surgery, n (%)	Yes	0	0	0
IV heparin within 12 hours before surgery, n (%)	Yes	1 (2.3)	0	1 (0.8)
Oral Coumadin within 2 days before surgery, n (%)	Yes	0	0	0
Antiplatelet medications within 5 days prior to surgery, n (%)	Yes	2 (4.7)	3 (3.4)	5 (3.8)
Blood inflow reduction method, n (%)	None	21 (48.8)	55 (63.2)	76 (58.5)
	Pringle maneuver	22 (51.2)	30 (34.5)	52 (40.0)
	Total vascular exclusion	0	1 (1.1)	1 (0.8)
	Other	0	1 (1.1)	1 (0.8)
Duration of blood inflow reduction (min)	n	22	31	53
	Mean (SD)	28.0 (21.48)	32.0 (18.00)	30.3 (19.42)
	Median	23.5	29.0	26.0
	Q1, Q3	11.0, 35.0	20.0, 45.0	16.0, 40.0
	Min, Max	4, 80	5, 85	4, 85
Resection method, n (%)	CUSA	21 (48.8)	32 (36.8)	53 (40.8)
	Harmonic scalpel	1 (2.3)	2 (2.3)	3 (2.3)

Table 10. Surgery Procedural Data (Safety Population)				
Category	**Response/Description**	**TachoSil (N=43)**	**ETHIZIA (N=87)**	**Overall (N=130)**
	Scalpel	0	2 (2.3)	2 (1.5)
	Bipolar electrosurgical vessel sealing device (LigaSure™)	8 (18.6)	15 (17.2)	23 (17.7)
	Other	13 (30.2)	36 (41.4)	49 (37.7)
Type of hepatic parenchyma, n (%)	Normal	30 (69.8)	66 (75.9)	96 (73.8)
	Cirrhotic	3 (7.0)	3 (3.4)	6 (4.6)
	Steatotic	10 (23.3)	11 (12.6)	21 (16.2)
	Other	0	7 (8.0)	7 (5.4)
Anatomic or non-anatomic resection, n (%)	Anatomic	26 (60.5)	47 (54.0)	73 (56.2)
	Non-anatomic	17 (39.5)	40 (46.0)	57 (43.8)
Extent of resection, n (%)	Left hemihepatectomy	3 (7.0)	11 (12.6)	14 (10.8)
	Right hemihepatectomy	14 (32.6)	29 (33.3)	43 (33.1)
	Extended left hemihepatectomy	1 (2.3)	3 (3.4)	4 (3.1)
	Extended right hemihepatectomy	2 (4.7)	7 (8.0)	9 (6.9)
	Segmentectomy	7 (16.3)	7 (8.0)	14 (10.8)
	Bisegmentectomy	3 (7.0)	7 (8.0)	10 (7.7)
	Trisegmentectomy	2 (4.7)	4 (4.6)	6 (4.6)
	Non-anatomical wedge resection – single	5 (11.6)	15 (17.2)	20 (15.4)
	Non-anatomical wedge resection – multiple	6 (14.0)	4 (4.6)	10 (7.7)
Estimated total size of all resection areas (cm^2)	n	43	86	129
	Mean (SD)	102.6 (84.67)	116.3 (107.02)	111.8 (100.00)
	Median	84.0	90.5	88.0
	Q1, Q3	40.0, 144.0	35.0, 150.0	40.0, 144.0
	Min, Max	2, 322	3, 644	2, 644
Vascular reconstruction performed, n (%)	Yes	3 (7.0)	4 (4.6)	7 (5.4)
Biliary tree reconstruction performed, n (%)	Yes	4 (9.3)	7 (8.0)	11 (8.5)

Table 10. Surgery Procedural Data (Safety Population)				
Category	**Response/Description**	**TachoSil (N=43)**	**ETHIZIA (N=87)**	**Overall (N=130)**
Visible bile leakage that was surgically treated, n (%)	Yes	3 (7.0)	8 (9.2)	11 (8.5)
Use of surgical drains, n (%)	Yes	28 (65.1)	55 (63.2)	83 (63.8)
Occurrence of any surgical complications impacting postoperative outcomes, or AEs, during surgery, n (%)	Yes	3 (7.0)	1 (1.1)	4 (3.1)
Estimated blood loss during the procedure (mL)	n	43	86	129
	Mean (SD)	728.8 (781.18)	829.7 (1053.15)	796.1 (969.04)
	Median	450.0	500.0	500.0
	Q1, Q3	200.0, 950.0	300.0, 1000.0	300.0, 950.0
	Min, Max	50, 4000	0, 6000	0, 6000
Intraoperative blood transfusion, n (%)	Yes	7 (16.3)	13 (14.9)	20 (15.4)
Type of transfusion, n (%)	Red blood cell	6 (14.0)	10 (11.5)	16 (12.3)
	Platelets	0	0	0
	Plasma	0	3 (3.4)	3 (2.3)
	Not applicable	1 (2.3)	0	1 (0.8)
Units of this type of transfusion	n	7	13	20
	Mean (SD)	1.9 (0.90)	3.2 (2.74)	2.7 (2.34)
	Median	2.0	2.0	2.0
	Q1, Q3	1.0, 3.0	1.0, 4.0	1.0, 3.0
	Min, Max	1, 3	1, 9	1, 9
Any additional transfusion, n (%)	Yes	2 (4.7)	6 (6.9)	8 (6.2)
Type of transfusion, n (%)	Red blood cell	0	0	0
	Platelets	0	3 (3.4)	3 (2.3)
	Plasma	2 (4.7)	3 (3.4)	5 (3.8)
	Not applicable	0	0	0
Units of this type of transfusion	n	2	6	8
	Mean (SD)	5.0 (4.24)	4.0 (3.29)	4.3 (3.24)
	Median	5.0	3.0	3.0
	Q1, Q3	2.0, 8.0	1.0, 8.0	1.5, 8.0
	Min, Max	2, 8	1, 8	1, 8
Abbreviations: AE, adverse event; CUSA, Cavitron Ultrasonic Surgical Aspirator; EDC, electronic data capture; IV, intravenous; Max, maximum; Min, minimum; N, number of				

Table 10. Surgery Procedural Data (Safety Population)				
Category	**Response/Description**	**TachoSil (N=43)**	**ETHIZIA (N=87)**	**Overall (N=130)**
subjects in the population; n, number of subjects with the specified outcome; Q1, Q3, first quartile, third quartile; SD, standard deviation. Note: The presented frequencies and the denominators used to calculate percentages are based on the subjects in each group in the Safety Population (N).				

The first target bleeding site in the ETHIZIA group was present on a larger estimated size of total transected parenchyma area and represented a larger target bleeding site compared to TachoSil group (Table 11). The surface of the first bleeding site being flat, irregular, or a dimple/pit in more of a cavity was comparable between the groups. The type of bleeding was less frequently venous in the ETHIZIA group (59/87, 67.8%) compared to the TachoSil group (34/43, 79.1%) and more frequently mixed in the ETHIZIA group (26/87, 29.9%) than in the TachoSil group (8/43, 18.6%). The SBSS scores were comparable between the groups and distributed across the indication of SBSS score 1 through 3. Adjunct (i.e., primary) hemostatic techniques were used slightly more frequently in the TachoSil group (20/43, 46.5%) than in the ETHIZIA group (36/87, 41.4%).

For all treated target bleeding sites, similar differences were observed as for the first bleeding site, with the use of adjunct (i.e., primary) hemostatic techniques remaining generally stable in the TachoSil group but decreasing in the ETHIZIA group.

Table 11. Bleeding Site Information (Safety Population)				
Category	**Statistic**	**TachoSil (N = 43)**	**ETHIZIA (N = 87)**	**Overall (N = 130)**
First Target Bleeding Site	n	43	87	130
Estimated total transected parenchyma area of first bleeding surface, maximum width (cm)	n	43	85	128
	Mean (SD)	9.5 (4.87)	10.3 (5.41)	10.1(5.23)
	Median	10.0	10.0	10.0
	Min, Max	1.0, 20.0	1.5, 28.0	1.0, 28.0
Estimated total transected parenchyma area of first bleeding surface, maximum length (cm)	n	43	85	128
	Mean (SD)	9.1 (5.26)	9.4 (5.77)	9.3 (5.58)
	Median	8.0	8.0	8.0
	Min, Max	2.0, 22.0	0.7, 25.0	0.7, 25.0
Estimated size of total transected parenchyma area of first target bleeding	n	43	85	128
	Mean (SD)	95.2 (74.76)	107.1 (100.14)	103.1 (92.26)
	Median	77.0	84.0	82.0

Table 11. Bleeding Site Information (Safety Population)				
Category	**Statistic**	**TachoSil (N = 43)**	**ETHIZIA (N = 87)**	**Overall (N = 130)**
site, width x length (cm^2)	Min, Max	2.0, 300.0	2.5, 644.0	2.0, 644.0
First target bleeding site, n (%)	Flat surface	22 (51.16)	44 (50.57)	66 (50.77)
	Irregular surface	16 (37.21)	29 (33.33)	45 (34.62)
	Dimple or pit	5 (11.63)	14 (16.09)	19 (14.62)
Estimated size of first target bleeding site, maximum width (cm)	n	43	87	130
	Mean (SD)	2.7 (2.52)	3.2 (2.24)	3.0 (2.34)
	Median	2.0	3.0	2.0
	Min, Max	0.1, 12.0	0.2, 12.0	0.1, 12.0
Estimated size of first target bleeding site, maximum length (cm)	n	43	87	130
	Mean (SD)	2.4 (1.61)	3.0 (2.72)	2.8 (2.43)
	Median	2.0	3.0	2.0
	Min, Max	0.1, 7.0	0.1, 20.0	0.1, 20.0
Estimated size of first target bleeding site, width × length (cm^2)	n	43	87	130
	Mean (SD)	9.7 (16.34)	13.4 (21.16)	12.2 (19.71)
	Median	4.0	7.5	6.0
	Min, Max	0.0, 77.0	0.0, 144.0	0.0, 144.0
Bleeding type, n (%)	Arterial	1 (2.33)	2 (2.30)	3 (2.31)
	Venous	34 (79.07)	59 (67.82)	93 (71.54)
	Mixed	8 (18.60)	26 (29.89)	34 (26.15)
SBSS score, n (%)	1	13 (30.23)	29 (33.33)	42 (32.31)
	2	18 (41.86)	36 (41.38)	54 (41.54)
	3	12 (27.91)	22 (25.29)	34 (26.15)
Use of adjunct hemostatic techniques, n (%)	Yes	20 (46.51)	36 (41.38)	56 (43.08)
	No	23 (53.49)	51 (58.62)	74 (56.92)

Abbreviations Max, maximum; Min, minimum; N, number of subjects in the population; n, number of bleeding sites in the analysis; SBSS Surface bleeding severity scale; SD, standard deviation.

Note: The presented frequencies and the denominators used to calculate percentages are based on the number of bleeding sites in the analysis from subjects in each group in the Safety Population (N).

D. Safety and Effectiveness Results

1. Effectiveness Results

The analysis of effectiveness was based on the 131 randomized patients at the 12-Week time point. Effectiveness outcomes are presented in Tables 12 to 16.

Primary effectiveness endpoint:

Primary effectiveness endpoint results are summarized in Table 12. ETHIZIA was demonstrated to be non-inferior to TachoSil in achieving the primary effectiveness endpoint of percentage of subjects achieving hemostasis at 3 minutes without rebleeding up to 10-minutes, at the first target bleeding site, in both the primary, Per-Protocol (PP), and the supporting, Intent To Treat (ITT), population analysis sets. Subsequent testing established ETHIZIA to be superior to TachoSil in achieving the primary effectiveness endpoint in both the PP and ITT analysis sets. The response rate for the first target bleeding site in the PP Population was statistically significantly higher in the ETHIZIA group (81/87, 93.1%) compared to the TachoSil group (33/43, 76.7%) based on the Farrington Manning test for non-inferiority ($p < 0.0001$) and the subsequent 2 sample z test for superiority ($p = 0.0038$). Similar results of non-inferiority and superiority of ETHIZIA over TachoSil were obtained in the ITT Population where the ETHIZIA group was statistically significantly higher (81/87, 93.1%) when compared to the TachoSil group (33/43, 75.0%) based on the Farrington Manning test for non-inferiority ($p < 0.0001$) and the subsequent 2 sample z test for superiority ($p = 0.0018$).

Subsequent analyses were completed for all treated target bleeding sites where similar results were obtained in the ITT Population (133/139, 95.7% in the ETHIZIA group and 49/60, 81.7% in the TachoSil group) and in the PP Population (133/139, 95.7% in the ETHIZIA treatment group and 49/59, 83.1% in the TachoSil treatment group). Results of hemostasis across all treated target bleeding sites are summarized in Table 15.

Table 12. Summary of Primary Effectiveness Endpoint Results				
Test	**TachoSil % [n/N]**	**ETHIZIA % [n/N]**	***p*-value for Non-Inferiority**	***p*-value for Superiority**
Primary endpoint success (3 min hemostasis without rebleeding within 10 min, first bleeding site) – Primary analysis set (PP)	76.7% [33/43]	93.1% [81/87]	<0.0001	0.0038
Primary endpoint success (3 min hemostasis without rebleeding within 10 min, first bleeding site) - Secondary analysis set (ITT)	75.0% [33/44]	93.1% [81/87]	<0.0001	0.0018
Abbreviations ITT, intent to treat population, PP, per protocol population; N, number of subjects in the population; n, number of events in the analysis. Note: Presented frequencies for n and the denominators used to calculate percentages were based on the subjects in each group in the ITT Population and the randomized treatment with hemostasis data available.				

Key secondary effectiveness endpoint:

Key secondary effectiveness endpoint results are summarized in Table 13 and Figure 2. The key secondary effectiveness endpoint of time to hemostasis censored at 10 minutes for the first target bleeding site in the PP Population was statistically significantly faster in the ETHIZIA group (median = 30 seconds) compared to TachoSil (median = 180 seconds) based on the Wilcoxon-Mann-Whitney test ($p < 0.0001$). The first target bleeding site treated with ETHIZIA achieved hemostasis 6 times faster than TachoSil. Results for the key secondary effectiveness endpoint in the ITT Population were similar to the PP Population.

Secondary effectiveness endpoints

Secondary effectiveness results are summarized in Tables 13 and 14. In the ETHIZIA group, hemostasis at the first target bleeding site was achieved in 66 (75.9%) subjects at 30 seconds, 76 (87.4%) subjects at 60 seconds, 81 (93.1%) subjects at 180 seconds, and 86 (98.9%) subjects at 600 seconds. In the TachoSil group, 33 (75.0%) subjects achieved hemostasis at 180 seconds and 41 (93.2%) subjects achieved hemostasis at 600 seconds. Percentage of hemostasis over 10 minutes in first target bleeding site are summarized in Table 14.

The frequency of treatment failure, defined as no hemostasis at 10 minutes, was low: 1 (1.1%) subject in the ETHIZIA group and 3 (6.8%) subjects in the TachoSil group. The number of subjects requiring rescue therapy was correspondingly low: 3 (3.4%) subjects in the ETHIZIA group and 5 (11.4%) subjects in the TachoSil group. These results are summarized in Table 13.

Additional analyses performed across all treated target bleeding sites, demonstrated that hemostasis was achieved in the ETHIZIA group in 81.3% (113/139 sites) at 30 seconds and 92.1% (128/139 sites) at 60 seconds. At 180 seconds (3 minutes), 95.7% (133/139 sites) of all target bleeding sites treated with ETHIZIA were hemostatic compared to 81.7% (49/60 sites) in the TachoSil group. The rate of hemostasis at all treated target bleeding sites increased to 99.3% (138/139 sites) in the ETHIZIA treatment group and 95.0% (57/60 sites) in the TachoSil treatment group at 600 seconds. Results for all treated target bleeding sites are summarized in Tables 15 and 16.

Table 13. Summary of Secondary Effectiveness Endpoint Results

Test	Statistic	TachoSil % [n/N]	ETHIZIA % [n/N]	*p*-value for Non-Inferiority	*p*-value for Superiority
Time-to-hemostasis (first bleeding site, PP) Uncensored	n Median (seconds)	40 180[1]	86 30	N/A	N/A
Time-to-hemostasis (first bleeding site, PP) Censored – Key secondary effectiveness endpoint	n Median (seconds) (Q1,Q3)	43 180[1] (180, 180)	87 30 (30, 30)	-	<0.0001
Time-to-hemostasis (first bleeding site, ITT) Uncensored	n Median (seconds)	41 180[1]	86 30	N/A	N/A
Time-to-hemostasis (first bleeding site, ITT) Censored - Key secondary effectiveness endpoint	n Median (seconds) (Q1,Q3)	44 180[1] (180, 210)	87 30 (30, 30)	-	<0.0001
Treatment failure = no hemostasis at 10 min - ITT	% [n/N]	6.8% [3/44]	1.1% [1/87]	N/A	N/A
Rescue therapy used - ITT	% [n/N]	11.4% [5/44]	3.4% [3/87]	N/A	N/A
Rebleeding after 10 minutes but before closure – ITT	%	0%	0%	N/A	N/A

Abbreviations: ITT, intent to treat population, PP, per protocol population; N, number of subjects in the population; n, number of events in the analysis.
Note: Presented frequencies for n and the denominators used to calculate percentages were based on the subjects in each group in the ITT Population and the randomized treatment with hemostasis data available.

Table 13. Summary of Secondary Effectiveness Endpoint Results					
Test	**Statistic**	**TachoSil % [n/N]**	**ETHIZIA % [n/N]**	***p*-value for Non-Inferiority**	***p*-value for Superiority**
[1] TachoSil requires a 3-minute compression during application. Data collection for time to hemostasis for TachoSil began after the 3-minute compression time.					

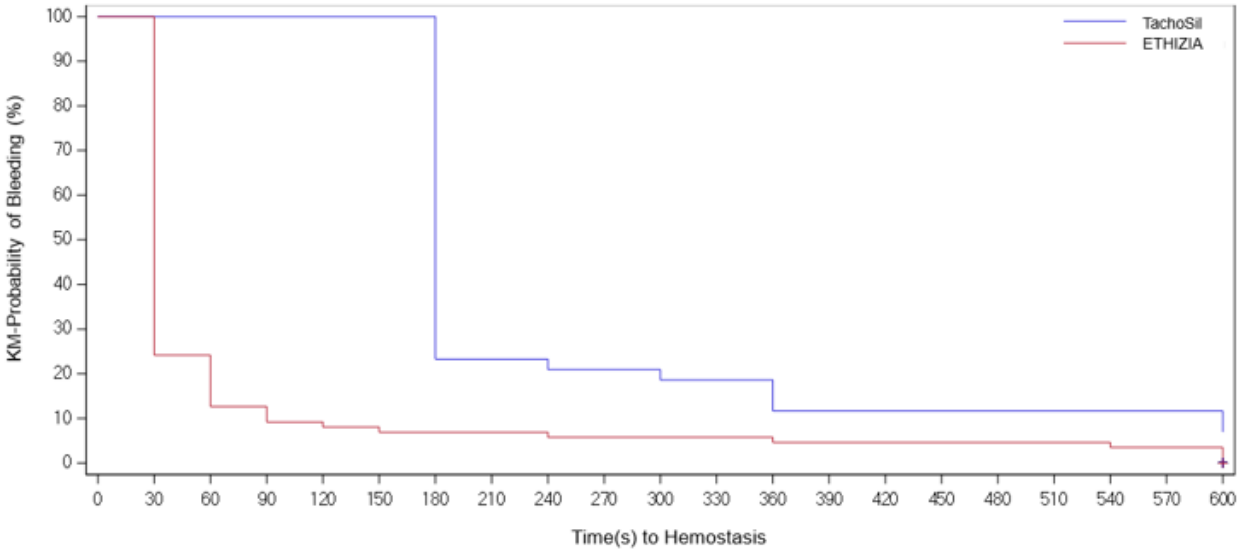

Figure 2. Time to Hemostasis-First Target Bleeding Site (PP Population)

Abbreviations: KM, Kaplan-Meier; PP, Per-Protocol; s, second(s).
Notes: Subjects were censored at 600 seconds (10 minutes) if they did not achieve hemostasis by 600 seconds (10 minutes). Only the first target bleeding site was considered for time to hemostasis.

Table 14. Percentage of Hemostasis Over 10 minutes – First Target Bleeding Site; Secondary Effectiveness Endpoint (ITT Population)		
Timepoint	**TachoSil (N = 44) [1] n (%)**	**ETHIZIA (N = 87) n (%)**
30 seconds	NA [2]	66 (75.9)
60 seconds	NA [2]	76 (87.4)
90 seconds	NA [2]	79 (90.8)
120 seconds	NA [2]	80 (92.0)
150 seconds	NA [2]	81 (93.1)
180 seconds	33 (75.0)	81 (93.1)
210 seconds	33 (75.0)	81 (93.1)
240 seconds	34 (77.3)	82 (94.3)
270 seconds	34 (77.3)	82 (94.3)
300 seconds	35 (79.5)	82 (94.3)
360 seconds	38 (86.4)	83 (95.4)
420 seconds	38 (86.4)	83 (95.4)

480 seconds	38 (86.4)	83 (95.4)
540 seconds	39 (88.6)	84 (96.6)
600 seconds	41 (93.2)	86 (98.9)

Abbreviations: ITT, Intent-to-Treat; N, number of subjects in the population; n, number of subjects in the specified category; NA, not applicable, SOC, system organ class.
Note: Presented frequencies for n and the denominators used to calculate percentages were based on the subjects in each group in the ITT Population and the randomized treatment with hemostasis data available.
[1] One subject was randomized to TachoSil but was not treated with TachoSil and instead received SOC.
[2]The initial application of ETHIZIA was 30 seconds and the initial application of TachoSil was 180 seconds (i.e., 3 minutes). Therefore, data are not available for TachoSil until 180 seconds..

Table 15. Summary of Effectiveness Results for All Treated Target Bleeding Sites

Test	Statistic	TachoSil	ETHIZIA
Cases achieving hemostasis at 3 minutes without rebleeding at the 10-minute time point - PP	% [n/N]	83.1% [49/59]	95.7% [133/139]
Cases achieving hemostasis at 3 minutes without rebleeding at the 10-minute time point - ITT	% [n/N]	81.7% [49/60]	95.7% [133/139]
Time-to-hemostasis, PP) Uncensored	n Median (seconds)	56 180[1]	138 30
Time-to-hemostasis (All treated bleeding site, PP) Censored	n Median (seconds) (Q1, Q3)	59 180[1] (180, 180)	139 30 (30, 30)
Time-to-hemostasis (ITT) Uncensored	n Median (seconds)	57 180[1]	138 30
Time-to-hemostasis (ITT) Censored	n Median (seconds) (Q1, Q3)	60 180[1] (180, 180)	139 30 (30, 30)

Abbreviations: ITT, intent to treat population, PP, per protocol population; N, number of subjects in the population; n, number of events in the analysis.
Note: Presented frequencies for n and the denominators used to calculate percentages were based on the subjects in each group in the ITT Population and the randomized treatment with hemostasis data available.
[1] TachoSil requires a 3-minute compression during application. Data collection for time to hemostasis for TachoSil began after the 3-minute compression time.

Table 16. Percentage of Hemostasis Over 10 minutes – All Treated Target Bleeding Sites (ITT Population)		
Timepoint	**TachoSil (N = 44) [1] n (%)**	**ETHIZIA (N = 87) n (%)**
30 seconds	NA [2]	113 (81.3)
60 seconds	NA [2]	128 (92.1)
90 seconds	NA [2]	131 (94.2)
120 seconds	NA [2]	132 (95.0)
150 seconds	NA [2]	133 (95.7)
180 seconds	49 (81.7)	133 (95.7)
210 seconds	49 (81.7)	133 (95.7)
240 seconds	50 (83.3)	134 (96.4)
270 seconds	50 (83.3)	134 (96.4)
300 seconds	51 (85.0)	134 (96.4)
360 seconds	54 (90.0)	135 (97.1)
420 seconds	54 (90.0)	135 (97.1)
480 seconds	54 (90.0)	135 (97.1)
540 seconds	55 (91.7)	136 (97.8)
600 seconds	57 (95.0)	138 (99.3)
Total number of bleeding sites	60	139

Abbreviations: ITT, Intent-to-Treat; N, number of subjects in the population; n, number of subjects in the specified category; NA, not applicable.
Note: Presented frequencies for n and the denominators used to calculate percentages were based on all target bleeding sites in each group in the ITT Population and the randomized treatment with hemostasis data available.
[1] One subject was randomized to TachoSil but was not treated with TachoSil and instead received standard of care.
[2] The initial application of ETHIZIA was 30 seconds and the initial application of TachoSil was 180 seconds (i.e., 3 minutes). Thus, data are not available for TachoSil until 180 seconds.

2. Effectiveness – subgroup analyses

The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes: site, geography, age, sex, SBSS, type of bleeding, type of hepatic parenchyma, portal hypertension, Child-Pugh classification, MELD-Na score, renal function, antithrombotic medication use, concomitant chemotherapy, and concomitant steroid use. No apparent patterns were noted suggesting inconsistent treatment effect across subgroups, although there was some variation seen in specific subgroups which may relate to the small number of subjects. Subgroup analyses are summarized descriptively in Table 17 below.

The study was not specifically powered for drawing statistical conclusion for any subgroup.

Table 17. Results of subgroup analysis (PP Population)		
Subgroup	**TachoSil n/N [%]**	**ETHIZIA n/N [%]**
Site		
101	7/8 (87.5)	18/18 (100)
102	0	2/2 (100)
103	2/2 (100)	3/3 (100)
104	8/9 (88.9)	15/17 (88.2)
106	2/2 (100)	4/5 (80.0)
201	0/5 (0)	9/9 (100)
301	3/4 (75.0)	7/9 (77.8)
302	8/9 (88.9)	16/17 (94.1)
303	3/4 (75.0)	7/7 (100)
Geography		
US	19/21 (90.5)	42/45 (93.3)
non-US	14/22 (63.6)	39/42 (92.9)
Age		
22-47	5/5 (100)	14/15 (93.3)
48-63	15/17 (88.2)	22/23 (95.7)
≥ 64	13/21 (61.9)	45/49 (91.8)
Sex		
Male	24/31 (77.4)	47/50 (94.0)
Female	9/12 (75.0)	34/37 (91.9)
SBSS		
1	9/13 (69.2)	26/28 (92.9)
2	16/18 (88.9)	34/37 (91.9)
3	8/12 (66.7)	21/22 (95.5)
Type of bleeding		
Venous	26/34 (76.5)	56/59 (94.9)
Arterial	1/1 (100)	2/2 (100)
Mixed	6/8 (75.0)	23/26 (88.5)
Type of hepatic parenchyma		
Normal	24/30 (80.0)	61/66 (92.4)
Cirrhotic	2/3 (66.7)	3/3 (100)
Steatotic	7/10 (70.0)	10/11 (90.9)
Other	0	7/7 (100)
Portal hypertension		
Yes	0	2/2 (100)
No	33/43 (76.7)	79/85 (92.9)
Child-Pugh classification		
A	9/12 (75.0)	23/25 (92.0)

Table 17. Results of subgroup analysis (PP Population)		
Subgroup	**TachoSil n/N [%]**	**ETHIZIA n/N [%]**
B	0	2/2 (100)
C	1/1 (100)	0
N/A	22/29 (75.9)	54/58 (93.1)
Missing	1/1 (100)	2/2 (100)
MELD-Na score		
< 17	13/16 (81.3)	31/34 (91.2)
17-20	0	0
21-22	0	0
23-26	0	0
27-31	0	0
≥ 32	19/26 (73.1)	50/53 (94.3)
Missing	1/1 (100)	0
Renal function		
Chronic dialysis	13/16 (81.3)	32/35 (91.4)
eGFR 30 - 60	3/3 (100)	5/6 (83.3)
eGFR 60 - 90	5/9 (55.6)	23/23 (100)
eGFR > 90	11/14 (78.6)	21/23 (91.3)
Missing	1/1 (100)	0
Antithrombotic medication use		
Yes	2/2 (100)	2/3 (66.7)
No	31/41 (75.6)	79/84 (94.0)
Concomitant chemotherapy		
Yes	4/4 (100)	6/7 (85.7)
No	29/39 (74.4)	75/80 (93.8)
Concomitant steroid use		
Yes	15/19 (78.9)	39/42 (92.9)
No	18/24 (75.0)	42/45 (93.3)
Abbreviations: eGFR, estimated glomerular filtration rate; N, number of subjects in the population; n, number of subjects in the specified category; MELD-Na, Model for End-Stage Liver Disease; SBSS, Surface Bleeding Severity Scale; US, United States.		

3. Safety

Overall, 326 adverse events (AE) were recorded. At least 1 AE was recorded for 97 of 130 (74.6%) subjects (Table 18). The percentage of subjects reporting AEs was similar across both treatment groups (66/87, 75.9% of subjects in the ETHIZIA group and 31/43, 72.1% of subjects in TachoSil group). A total of 86 serious AEs (SAEs) were recorded for 47 of 130 (36.2%) subjects. SAEs are presented further in Table 20.

Table 18. Overall Summary of Adverse Events (Safety Population)			
Adverse Event Type	**TachoSil (N=43) n (%) e**	**ETHIZIA (N=87) n (%) e**	**Overall (N=130) n (%) e**
Any AE	31 (72.1) 99	66 (75.9) 227	97 (74.6) 326
Any SAE	10 (23.3) 14	37 (42.5) 72	47 (36.2) 86
Any Device-related AE, per investigator	9 (20.9) 10	8 (9.2) 10	17 (13.1) 20
AESI	14 (32.6) 18	28 (32.2) 37	42 (32.3) 55
Abbreviations AE, adverse event, SAE, serious adverse event; AESI, adverse event of special interest; N, number of subjects in the population; n, number of subjects with the specified outcome; e, number of events in the analysis. Notes: The presented frequencies and the denominators used to calculate percentages were based on the subjects in each group in the Safety Population and the actual treatment received (N). The values for n and e may not match as there may be multiple events for one subject.			

Overall, 17 of 130 (13.1%) of subjects experienced device-related AEs per Investigator assessment (Table 19). None of the device-related AEs were considered unanticipated adverse device effects (i.e., UADEs). The percentage of subjects reporting device-related AEs per the Investigator assessment was higher in the TachoSil group (9/43, 20.9%) when compared to the ETHIZIA treatment group (8/87, 9.2%).

The most commonly reported device-related AE Preferred Term (PT) in the ETHIZIA group was intra-abdominal fluid collection (4/87, 4.6%) followed by post procedural bile leak (2/87, 2.3%) and abdominal pain, intraoperative hepatic hemorrhage, hematoma, and pyrexia (1/87, 1.1% of subjects each). In TachoSil group, the most commonly reported device-related AEs were intraoperative hepatic hemorrhage (6/43, 14.0%) followed by abdominal pain, post procedural bile leak, hematoma, and bacteremia (1/43, 2.3% of subjects each).

Table 19. Device-related Adverse Events Per the Investigator Assessment by System Organ Class and Preferred Term (Safety Population)			
System Organ Class Preferred Term	**TachoSil (N=43) n (%) e**	**ETHIZIA (N=87) n (%) e**	**Overall (N=130) n (%) e**
Any Device-related AE	9 (20.9) 9	8 (9.2) 10	17 (13.1) 20
Hepatobiliary disorders	6 (14.0) 6	1 (1.1) 1	7 (5.4) 7
Hepatic hemorrhage	6 (14.0) 6	1 (1.1) 1	7 (5.4) 7
Gastrointestinal disorders	1 (2.3) 1	4 (4.6) 5	5 (3.8) 6
Intra-abdominal fluid collection	0	4 (4.6) 4	4 (3.1) 4
Abdominal pain	1 (2.3) 1	1 (1.1) 1	2 (1.5) 2

Table 19. Device-related Adverse Events Per the Investigator Assessment by System Organ Class and Preferred Term (Safety Population)			
System Organ Class Preferred Term	**TachoSil (N=43) n (%) e**	**ETHIZIA (N=87) n (%) e**	**Overall (N=130) n (%) e**
Injury, poisoning and procedural complications	1 (2.3) 1	2 (2.3) 2	3 (2.3) 3
Post procedural bile leak	1 (2.3) 1	2 (2.3) 2	3 (2.3) 3
Vascular disorders	1 (2.3) 1	1 (1.1) 1	2 (1.5) 2
Hematoma	1 (2.3) 1	1 (1.1) 1	2 (1.5) 2
General disorders and administration site conditions	0	1 (1.1) 1	1 (0.8) 1
Pyrexia	0	1 (1.1) 1	1 (0.8) 1
Infections and infestations	1 (2.3) 1	0	1 (0.8) 1
Bacteremia	1 (2.3) 1	0	1 (0.8) 1
Abbreviations: AE, adverse event; N, number of subjects in the population; n, number of subjects in the analysis; e, number of events, AE, adverse event; e, number of events; PT, preferred term; SOC, system organ class. Notes: The presented frequencies and the denominators used to calculate percentages were based on the subjects in each group in the Safety Population and the actual treatment received (N). Subjects with multiple AEs within the same SOC and/or PT were only counted once within the respective frequencies. The values for n and e may not match as there may be multiple events for one subject.			

A total of 86 SAEs were reported for 47 of 130 subjects (36.2%) (Table 20). The percentage of subjects reporting SAEs was higher in the ETHIZIA group (37/87, 42.5%) when compared to the TachoSil group (10/43, 23.3%). Most serious adverse events experienced by subjects in both groups were in gastrointestinal disorders (20/130, 15.4%), events related to injury and procedural complications (17/130, 13.1%), infections and infestations (9/130, 6.9%), and cardiac disorders (6/130, 4.6%).

Table 20. Serious Adverse Events by System Organ Class and Preferred Term (Reported by ≥ 3% of Subjects in Either Treatment Group) (Safety Population)			
System Organ Class Preferred Term	**TachoSil (N=43) n (%) e**	**ETHIZIA (N=87) n (%) e**	**Overall (N=130) n (%) e**
Any SAE	10 (23.3) 14	37 (42.5) 72	47 (36.2) 86
Gastrointestinal disorders	4 (9.3) 4	16 (18.4) 19	20 (15.4) 23
Intra-abdominal fluid collection	1 (2.3) 1	8 (9.2) 8	9 (6.9) 9
Ascites	0	3 (3.4) 3	3 (2.3) 3
Injury, poisoning and procedural complications	2 (4.7) 2	15 (17.2) 17	17 (13.1) 19
Post procedural bile leak	2 (4.7) 2	15 (17.2) 15	17 (13.1) 17
Infections and infestations	1 (2.3) 1	8 (9.2) 10	9 (6.9) 11
Cardiac disorders	3 (7.0) 3	3 (3.4) 4	6 (4.6) 7
Atrial fibrillation	2 (4.7) 2	2 (2.3) 2	4 (3.1) 4
General disorders and administration site conditions	0	5 (5.7) 5	5 (3.8) 5
Multiple organ dysfunction syndrome	0	3 (3.4) 3	3 (2.3) 3
Renal and urinary disorders	1 (2.3) 1	4 (4.6) 4	5 (3.8) 5
Respiratory, thoracic and mediastinal disorders	1 (2.3) 2	4 (4.6) 5	5 (3.8) 7
Hepatobiliary disorders	0	4 (4.6) 4	4 (3.1) 4
Abbreviations: AE, adverse event; N, number of subjects in the population; n, number of subjects in the analysis; e, number of events; PT, preferred term; SOC, system organ class. Notes: The presented frequencies and the denominators used to calculate percentages were based on the subjects in each group in the Safety Population and the actual treatment received (N). Subjects with multiple AEs within the same SOC and/or PT were only counted once within the respective frequencies. The values for n and e may not match as there may be multiple events for one subject.			

A total of 55 Adverse Events of Special Interests (AESI) were reported for 42 of 130 patients (32.3%) (Table 21). The percentage of subjects reporting AESIs was comparable between the ETHIZIA group (28/87, 32.2%) and TachoSil group (14/43, 32.6%). Most AESIs experienced by subjects in both groups were post-procedural bile leak, ETHIZIA (20/87, 23.0%); TachoSil (4/43, 9.3%) and hepatic hemorrhage, ETHIZIA (5/87, 5.7%); TachoSil (10/43, 23.3%). Hepatic hemorrhage was reflected in (re)bleedings that occurred during surgery after randomization but were resolved prior to fascia closure, such as bleedings that did not reach the primary endpoint of being hemostatic at 3 minutes. No hepatic haemorrhages were observed post-procedure.

Table 21. Adverse Events of Special Interest by Category and Preferred Term (Safety Population)			
AESI Category Preferred Term	**TachoSil (N=43) n (%) e**	**ETHIZIA (N=87) n (%) e**	**Overall (N=130) n (%) e**
Any AESI	14 (32.6) 18	28 (32.2) 37	42 (32.3) 55
Bleeding-related Events	12 (27.9) 14	13 (14.9) 15	25 (19.2) 29
Hepatic hemorrhage	10 (23.3) 10	5 (5.7) 5	15 (11.5) 15
Post procedural hemorrhage	0	1 (1.1) 1	1 (0.8) 1
Abdominal wall hematoma	0	2 (2.3) 2	2 (1.5) 2
Gastrointestinal hemorrhage	0	2 (2.3) 2	2 (1.5) 2
Hematoma	1 (2.3) 1	1 (1.1) 1	2 (1.5) 2
Hematuria	2 (4.7) 2	0	2 (1.5) 2
Epistaxis	0	1 (1.1) 1	1 (0.8) 1
Haemobilia	0	1 (1.1) 1	1 (0.8) 1
Hemorrhage	0	1 (1.1) 1	1 (0.8) 1
Intra-abdominal hematoma	1 (2.3) 1	0	1 (0.8) 1
Rectal hemorrhage	0	1 (1.1) 1	1 (0.8) 1
Thromboembolic Events	0	1 (1.1) 1	1 (0.8) 1
Pulmonary embolism	0	1 (1.1) 1	1 (0.8) 1
Biloma	4 (9.3) 4	20 (23.0) 20	24 (18.5) 24
Post-procedural bile leak	4 (9.3) 4	20 (23.0) 20	24 (18.5) 24
Allergic Reaction	0	1 (1.1) 1	1 (0.8) 1
Rash	0	1 (1.1) 1	1 (0.8) 1
Abbreviations: AESI, adverse event of special interest; N, number of subjects in the population; n, number of subjects in the analysis; e, number of events; PT, preferred term. Notes: The presented frequencies and the denominators used to calculate percentages were based on the subjects in each group in the Safety Population and the actual treatment received (N). Subjects with multiple AESIs within the same PT were only counted once within the respective frequencies. The values for n and e may not match as there may be multiple events for one subject.			

Overall, 6 of 130 (4.6%) subjects experienced an AE that led to death, meaning 6 total SAEs were fatal (Table 22). The percentage of subjects with an AE leading to death in the was 5.7% (5/87) in ETHIZIA group and 2.3% (1/43) in TachoSil group. The most reported AE leading to death was general disorders and administration site conditions (3/130, 3.4%; where all 3 AEs were multiple organ dysfunction syndrome), followed by hepatobiliary disorders and infections and infestations (1/130, 1.1% of subjects each, 1 AE of hepatic failure and 1 AE of pneumonia). One AE leading to death was reported in TachoSil treatment group due to cardiogenic shock in the system organ class (SOC) of cardiac disorders. None of the subject deaths were considered device-related per the investigator, the sponsor, or the IAC assessments. None of the events were considered AESIs.

Table 22. Adverse Events Leading to Death by System Organ Class and Preferred Term (Safety Population)			
System Organ Class Preferred Term	**TachoSil (N=43) n (%) e**	**ETHIZIA (N=87) n (%) e**	**Overall (N=130) n (%) e**
Any AE Leading to Death	1 (2.3) 1	5 (5.7) 5	6 (4.6) 6
General disorders and administration site conditions	0	3 (3.4) 3	3 (2.3) 3
Multiple organ dysfunction syndrome	0	3 (3.4) 3	3 (2.3) 3
Cardiac disorders	1 (2.3) 1	0	1 (0.8) 1
Cardiogenic shock	1 (2.3) 1	0	1 (0.8) 1
Hepatobiliary disorders	0	1 (1.1) 1	1 (0.8) 1
Hepatic failure	0	1 (1.1) 1	1 (0.8) 1
Infections and infestations	0	1 (1.1) 1	1 (0.8) 1
Pneumonia	0	1 (1.1) 1	1 (0.8) 1
Abbreviations: AE, adverse event; N, number of subjects in the population; n, number of subjects in the analysis; e, number of events; PT, preferred term; SOC, system organ class. The presented frequencies and the denominators used to calculate percentages were based on the subjects in each group in the Safety Population and the actual treatment received (N). Subjects with multiple AEs within the same SOC and/or PT were only counted once within the respective frequencies. The values for n and e may not match as there may be multiple events for one subject.			

4. Exploratory Endpoints:

   Exploratory endpoints were not statistically powered, and caution must be exercised when interpreting the results.

   Procedure Duration:

   The duration of the procedure for the ITT Population is summarized in Table 23 below. The median duration of the procedure was similar in both treatment groups (median: 210.0 minutes in the ETHIZIA treatment group and 211.5 minutes in the TachoSil treatment group).

Table 23. Duration of the Procedure (ITT Population)		
Procedure Duration (minutes)	**TachoSil (N = 44)[1]**	**ETHIZIA (N = 87)**
n	44	87
Mean (SD)	236.3 (123.79)	230.6 (127.86)
Median	211.5	210.0
Min, Max	83, 581	21, 744
Abbreviations: ITT, Intent-to-Treat; Max, maximum; Min, minimum; N, number of subjects in the population; n, number of subjects in the analysis; SD, standard deviation. Note: Procedure duration (in minutes) = time of end of procedure – time of start of procedure. [1] One subject was randomized to TachoSil but was not treated with TachoSil and instead received standard of care.		

Duration of ICU Stay:

Duration of ICU stay for the ITT Population is summarized in Table 24.
The percentage of subjects requiring ICU admission after surgery was comparable between the groups at 39.1% (34/87) of subjects in the ETHIZIA treatment group and 38.6% (17/44) of subjects in the TachoSil treatment group. The median (Q1, Q3) duration of ICU stay was similar for subjects in the ETHIZIA treatment group (24.00 [24.00, 72.00] hours) and those in the TachoSil treatment group (24.00 [24.00, 24.00] hours).

Table 24. Duration of Intensive Care Unit Stay (ITT Population)		
Duration of ICU Stay (hours)	**TachoSil (N = 44)[1]**	**ETHIZIA (N = 87)**
n (%)	17 (38.6)	34 (39.1)
Mean (SD)	26.87 (10.42)	85.58 (120.76)
Median	24.00	24.00
Q1, Q3	24.00, 24.00	24.00, 72.00
Min, Max	15.53, 48.00	3.00, 504.00
Abbreviations: ICU, intensive care unit; ITT, Intent-to-Treat; Max, maximum; Min, minimum; N, number of subjects in the population; n, number of subjects in the analysis; Q1, Q3: first quartile, third quartile; SD, standard deviation. Note: Duration of ICU stay = date/time of discharge from ICU – date/time of admission to ICU. [1] One subject was randomized to TachoSil but was not treated with TachoSil and instead received standard of care.		

Total (Post-operative) Hospitalization Stay:

Postoperative stay for the ITT Population is summarized in Table 25.
The median (Q1, Q3) postoperative hospital duration was 7.0 (6.0, 11.0) days in the ETHIZIA treatment group and 6.5 (5.0, 9.0) days in the TachoSil treatment group. The observed mean (post-operative) hospitalization stay in the ETHIZIA group was slightly longer (ETHIZIA=10.1 days; TachoSil=8.5 days) likely due to uncontrolled

variables across study treatment arms, such as differences in procedures and indications for surgery.

Table 25. Postoperative Stay (ITT Population)		
Postoperative Stay (days)	**TachoSil (N = 44)[1]**	**ETHIZIA (N = 87)**
n	44	87
Mean (SD)	8.5 (6.66)	10.1 (7.63)
Median	6.5	7.0
Q1, Q3	5.0, 9.0	6.0, 11.0
Min, Max	3, 43	2, 40
Abbreviations: ITT, Intent-to-Treat; Max, maximum; Min, minimum; N, number of subjects in the population; n, number of subjects in the analysis; Q1, Q3, first quartile, third quartile; SD, standard deviation. Note: Postoperative stay = date of discharge from hospital – date of start of surgery + 1. [1] One subject was randomized to TachoSil but was not treated with TachoSil and instead received standard of care.		

Postoperative Drainage Volume, Characteristics, and Duration:

Postoperative drainage volume, characteristics and durations for the ITT population are summarized in Table 26. The duration, volume, and characteristics of postoperative drainage and the drained fluid were similar between the treatment groups, except for median (minimum, maximum) bilirubin, which was higher in the ETHIZIA treatment group (5.690 [0.19, 176.00] mg/dL) compared to TachoSil group (1.35 [0.24, 37.70] mg/dL).

Table 26. Postoperative Drainage (ITT Population)			
Category	**Statistic**	**TachoSil (N = 44)[1]**	**ETHIZIA (N = 87)**
Postoperative drainage duration (hours)	n	24	43
	Mean (SD)	163.6 (189.05)	147.9 (109.49)
	Median	112.0	117.0
	Min, Max	7, 977	6, 519
Volume of drainage (mL)	n	25	47
	Mean (SD)	2906.8 (8062.44)	2536.4 (3949.38)
	Median	940.0	1015.0
	Min, Max	115, 41110	20, 19790
Characteristic of the drained fluid, n (%)	Serous	6 (13.6)	9 (10.3)
	Sanguineous	2 (4.5)	3 (3.4)
	Serosanguinous	10 (22.7)	25 (28.7)
	Purulent	0	1 (1.1)
	Other	10 (22.7)	12 (13.8)
	Not applicable	1 (2.3)	1 (1.1)
Bilirubin measured in drainage fluid (mg/dL)	n	8	23
	Mean (SD)	7.034 (12.99)	20.137 (39.77)
	Median	1.35	5.69
	Min, Max	0.24, 37.70	0.19, 176.00

Abbreviations: ITT, Intent-to-Treat; Max, maximum; Min, minimum; N, number of subjects in the population; n, number of subjects with data available; SD, standard deviation.
Notes: Postoperative drainage duration = (time of end of drainage − time of end of drainage)/60. Presented frequencies for n and the denominators used to calculate percentages were based on the subjects in each group in the ITT Population and the randomized treatment.
[1] One subject was randomized to TachoSil but was not treated with TachoSil but instead received a different approved hemostatic patch.

Need for and cause of reoperation:

Need and cause of reoperations are summarized in Table 27. A total of 5 (5.7%) subjects in the ETHIZIA treatment group and 2 (4.5%) subjects in the TachoSil treatment group required reoperation as a result of an SAE. None of the SAEs were related to the device. In the ETHIZIA treatment group, the causes were acute postoperative bleeding, bile leakage, a burst abdomen, pleural empyema, and a small bowel obstruction in 1 (1.1%) subject each. The acute postoperative bleeding occurred in 1 subject in the ETHIZIA treatment group and was determined to not be from the target bleeding site treated with the ETHIZIA patch, but from a vascular reconstruction of the arterial stump and 2 large porta defects that was performed during the initial surgery. In the TachoSil group the causes for reoperation were an intestinal perforation in 1 (2.3%) subject and a small bowel obstruction in 1 (2.3%) subject.

Table 27. Reoperation (ITT Population)			
Category	**Response**	**TachoSil (N = 44)[1]**	**ETHIZIA (N = 87)**
Need for reoperation, n (%)	Yes	2 (4.5)	5 (5.7)
Cause of reoperation n (%)	Acute postoperative bleeding	0	1 (1.1)
	Bile leakage	0	1 (1.1)
	Burst abdomen (not otherwise specified)	0	1 (1.1)
	Intestinal perforation	1 (2.3)	0
	Pleural empyema	0	1 (1.1)
	Small bowel obstruction	1 (1.1)	1 (1.1)

Abbreviations: AE, adverse event, ITT, Intent-to-Treat; N, number of subjects in the population; n, number of subjects with the specified outcome.
Notes: Presented frequencies for n and the denominators used to calculate percentages were based on the number of subjects in each group in the ITT Population and the randomized treatment. For cause of reoperation, verbatim AE terms are presented.
[1]One subject was randomized to TachoSil but was not treated with TachoSil but instead received a different approved hemostatic patch.

Imaging of the liver resection at 6 weeks post-surgery:

Imaging of the liver resection was performed during the week 6 visit on 87.4% (76/87) in the ETHIZIA group and 95.5% (42/44) of subjects in TachoSil group (Table 28). Majority of subjects underwent ultrasound imaging (62/87, 81.6% in EHIZIA group, and 35/44, 83.3%in TachoSil group). There were no instances of rolling up or formation of pseudoaneurysms on the resection surface. There was 1 reported case of device encapsulation on the resection in the ETHIZIA group, reported as “the patch is encapsulated in the area of former segment 7/8” where a non-anatomical wedge resection was performed and 3 ETHIZIA patches were placed in a dimple/pit surface in the depth of the liver. The only difference between the treatment groups was the median (Q1, Q3) volume of fluid collections (ETHIZIA: 80.0 [10.7, 472.7] mL; TachoSil: 8.3 [4.7, 9.0] mL). The most frequent fluid collection impression was ‘nonspecific’ (9, 11.8% in ETHIZIA; 9, 21.4% inTachoSil).

Table 28. Imaging of Liver Resection at Week 6 (ITT Population)			
Category/Variable	**Response/Statistic**	**TachoSil (N=44)[1]**	**ETHIZIA (N=87)**
Was imaging of resection done, n (%)	Yes	42 (95.5)	76 (87.4)
	No	2 (4.5)	11 (12.6)
Modality of imaging, n (%)	Ultrasound	35 (83.3)	62 (81.6)
	CT	5 (11.9)	14 (18.4)
	MRI	2 (4.8)	0
	Other	0	0
Evidence of device encapsulation on the resection plane where the patch was applied, n (%)	Yes	0	1 (1.3)
	No	42 (100)	75 (98.7)
Evidence of rolled-up device on the resection plane where the patch was applied, n (%)	Yes	0	0
	No	42 (100)	76 (100)
Evidence of pseudoaneurysm at the resection plane where the patch was applied, n (%)	Yes	0	0
	No	42 (100)	76 (100)
Evidence of perihepatic fluid collection at the resection plane where the patch was applied, n (%)	Yes	14 (33.3)	20 (26.3)
	No	28 (66.7)	56 (73.7)
Fluid collection size (mL)	n	5	10
	Mean (SD)	10.6 (11.31)	352.1 (584.95)
	Median	8.3	80.0
	Q1, Q3	4.7, 9.0	10.7, 472.7
	Min, Max	1, 30	1, 1900
Fluid collection impression, n (%)	Non-specific	9 (21.4)	9 (11.8)
	Hematoma	2 (4.8)	1 (1.3)
	Biloma	0	2 (2.6)
	Abscess	0	2 (2.6)
	Other	3 (7.1)	6 (7.9)

Abbreviations: CT, computed tomography; ITT, Intent-to-Treat; Max, maximum; Min, minimum; MRI, magnetic resonance imaging; N, number of subjects in the population; n, number of subjects with the specified outcome; Q1, Q3, first quartile, third quartile; SD standard deviation.

Note: Presented frequencies for n and the denominators used to calculate percentages were based on the subjects with an imaging assessment in each group in the ITT Population and the randomized treatment (N).

[1] One subject was randomized to TachoSil but was not treated with TachoSil but instead received a different hemostatic patch.

Amount of hemostatic material needed vs bleeding surface:

Adjunct (i.e., primary) hemostatic techniques before randomized treatment were used for 36 (41.4%) first target bleeding sites in the ETHIZIA treatment group and 21 (47.7%) first target bleeding sites in the TachoSil group, and for 50 (36.0%) all treated target bleeding sites in the TachoSil group; therefore, in the ETHIZIA treatment group, adjunctive (i.e., primary) hemostatic techniques were only used in 28.0% (14/50) treated target bleeding sites that were not the first target bleeding site.

The number of hemostatic patches used per bleeding site on the first target bleeding site was comparable between the groups with the majority requiring use of ≤1 patch (74/87, 85.1% in the ETHIZIA treatment group and 35/44, 79.5% in the TachoSil group). These rates were slightly higher in both treatment groups in the assessment of all treated target bleeding sites.

The specific amount of hemostatic material needed vs. bleeding surface was smaller for the ETHIZIA group than the TachoSil treatment group, with the median cm^2 patch per cm^2 target bleeding site being 5.60 in the ETHIZIA treatment group and 11.40 in the TachoSil treatment group for the first target bleeding site and 7.50 and 11.40, respectively, for all treated target bleeding sites. The median values are unreliable because in both the ETHIZIA treatment group and TachoSil treatment group there was 1 subject in each treatment group with very small bleeding site dimensions, inflating the maximum values of the calculation of hemostatic material needed vs bleeding surface to 1250.0 in the ETHIZIA treatment group and 6840.0 in the TachoSil treatment group. Results are summarized in Table 29.

Table 29. Amount of Hemostatic Material Needed vs. Bleeding Surface (ITT Population)			
Category	**Response/Statistic**	**TachoSil (N=44) [1] n (%)**	**ETHIZIA (N=87) n (%)**
First Target Bleeding Sites	n	44	87
Use of adjunct hemostatic techniques, n (%)	Yes	21(47.7)	36 (41.4)
	No	23 (52.3)	51 (58.6)
Use of adjunctive hemostatic techniques used before randomized treatment	Cautery	7 (15.9)	16 (18.4)
	Clips	0	0
	Staples	0	0
	Sutures/ligature	3 (6.8)	1 (1.1)
	Other	11 (25.0)	19 (21.8)
Size of patch (cm^2) applied per cm^2 bleeding surface	n	43	87
	Mean (SD)	183.31 (1040.202)	32.16 (140.248)
	Median	11.40	5.60
	Q1, Q3	3.80, 22.80	3.10, 12.50
	Min, Max	0.6, 6840.0	0.7, 1250.0
Number of patches per bleeding site	≤ 1	35 (79.5)	74 (85.1)
	> 1 to ≤ 2	7 (15.9)	10 (11.5)
	> 2	1 (2.3)	3 (3.4)
All Target Bleeding Sites	n	60	139
Use of adjunct hemostatic techniques, n (%)	Yes	27 (45.8)	50 (36.0)
	No	33 (55.9)	89 (64.0)
Use of adjunctive hemostatic techniques used before randomized treatment	Cautery	8 (13.6)	25 (18.0)
	Clips	0	1 (0.7)
	Staples	0	0
	Sutures/ligature	3 (5.1)	1 (0.7)
	Other	16 (27.1)	23 (16.5)
Size of patch (cm^2) applied per cm^2 bleeding surface	n	59	139
	Mean (SD)	136.99 (888.510)	26.53 (112.362)
	Median	11.40	7.50
	Q1, Q3	3.80, 22.80	3.30, 16.70
	Min, Max	0.6, 6840.0	0.7, 1250.0
Number of patches per bleeding site	≤ 1	51 (86.4)	125 (89.9)
	> 1 to ≤ 2	7 (11.9)	10 (7.2)
	> 2	1 (1.7)	4 (2.9)

Abbreviations: ITT, Intent-to-Treat; Max, maximum; Min, minimum; N, Number of subjects in the population; n, number of bleeding sites in the analysis; Q1, Q3, first quartile, third quartile; SD, standard deviation.
Note: The presented frequencies and the denominators used to calculate percentages are based on the number of bleeding sites in the analysis from subjects in each group in the ITT Population and the randomized treatment.
[1] One subject was randomized to TachoSil but instead received standard of care.

User satisfaction (questionnaire) for ETHIZIA Hemostatic Patch:

A user satisfaction questionnaire was provided to the operating surgeon to complete for surgical cases where patients were randomized to ETHIZIA. Surgeons who treated multiple subjects may have completed more than 1 questionnaire and hence, the percentages represent the number of subjects treated and not the number of surgeons. The user satisfaction questionnaire was according to the ETHIZIA usability scale which utilized a 5-point Likert scale for responses (strongly agree, agree, neutral, disagree, strongly disagree) and is summarized using the ITT Population. A total of 83 questionnaires were completed. In most questionnaires, the surgeons indicated that they would use ETHIZIA frequently (71/83, 85.5%), that it was easy to use (79/83, 95.2%), that the various functions in ETHIZIA were well integrated (66/83, 79.5%), and that most other surgeons would learn to use it very quickly (78/83, 94.0%). According to most questionnaires, surgeons disagreed that it was unnecessarily complex (71/83, 85.5%), that they would need technical support to able to use it (79/83, 95.2%), that the product was inconsistent (76/83, 91.6%), or that it was cumbersome (77/83, 92.8%).

Physician treatment preference assessment (questionnaire):

At the end of the trial, surgeons were asked about 20 aspects of product packaging, handling, ease-of-use, performance, and safety, and whether they would favor ETHIZIA or TachoSil as a hemostatic agent. A total of 28 surgeons completed this Physician Treatment Preference questionnaire. Only a very limited number of surgeons answered they would favor TachoSil for certain aspects, with ≥ 89% for each of the 20 aspects. For the overall assessment, 71% (20/28) of surgeons preferred ETHIZA over TachoSil while 4% (1/28) preferred TachoSil, with the remaining 25% (7/28) answering “Neutral”.

5-Year Exploratory Endpoints:

Pivotal Clinical Study IDE G210325 Section X, A.2 outlines an exploratory observational follow-up for cancer for up to 5 years for patients who underwent liver resection for an indication of cancer. This ongoing observational follow-up is not in direct contact with patients, but through electronic health records and/or contact with the patient’s treating physician.

The clinical data from this observational follow up will collect the following exploratory endpoints: cancer recurrence, cancer-free survival, and overall cancer survival. This data will be provided to the FDA in annual reports until the conclusion of the 5-year follow up period. The clinical data from this observational follow up does not impact any of the trial’s primary or secondary effectiveness or safety endpoints. This trial was designed to show the hemostatic effectiveness of ETHIZIA compared to TachoSil and was not powered to detect meaningful differences between treatment groups of multifactorial cancer recurrence outcomes in small groups.

Device labeling will be updated to reflect 5 year observational follow-up findings on local cancer recurrence, disease-free survival, and overall survival of subjects treated with ETHIZIA compared to TachoSil, when data are available.

5. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

XI. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included ninety-four (94) investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The first-in-human OUS pilot study included as supplemental clinical information is summarized in Table 30:

Table 30: OUS Pilot Study Synopsis	
Study Title	A Prospective, Multicenter, Single-arm, Clinical Investigation Evaluating the Safety and Performance of ETHIZIA for Hemostasis during Open Liver Surgery.
Study Design	This was a pre-market, prospective, single arm, multicenter first-in-human clinical investigation. The clinical investigation was split into 2 stages – Stage I for monitoring initial safety and Stage II to evaluate safety and performance of ETHIZIA. The sample size was powered on the secondary endpoint to allow for assessment of non-inferiority and superiority of ETHIZIA compared to the literature-based on standard of care regarding the percentage of cases achieving hemostasis at 3 minutes. All patients were scheduled to return for follow-up visit at week 6 (± 2 weeks) to perform ultrasound examination of the resection area to identify any encapsulation or rolled-up device, evidence of a biloma or pseudo-aneurysm. In addition, relevant concomitant medications and adverse events were assessed.
Objectives	The primary performance endpoint was defined by the percentage of cases achieving hemostasis at 3 minutes. Hemostasis was defined by a grade of 0 (None/Dry) on the Surface Bleeding Severity Score (SBSS).

	The secondary performance endpoints were mean time to hemostasis (TTH) (seconds) and percentage of hemostasis at 30, 60, 90, 120 and 150 seconds. The safety endpoint was assessed by the nature, severity and incidence of device related adverse events (AEs). The AEs found for ETHIZIA were compared to the current knowledge and state of the art for hemostatic methods in open liver surgery to assess whether the device is associated with acceptable safety outcomes. The exploratory endpoints were surgery time, blood loss during surgery, blood transfusion during hospitalization, Surface Bleeding Severity Score (SBSS) at the target bleeding site, use of adjunct hemostatic agents/techniques, amount of material needed versus bleeding surfaces, and user satisfaction.
Subjects	This study enrolled 47 subjects across two stages: • Stage I: 8 subjects evaluated for initial safety of ETHIZIA. • Stage II: 39 subjects analyzed for safety and performance. All subjects in the Stage I population, full analysis set (FAS) population, and safety population were treated with ETHIZIA . All subjects in the Stage I population, 38 of the 39 subjects in the FAS population, and 46 of the 47 subjects in the safety population completed the 6-week follow-up post procedure.
Results	**Effectiveness**: • The primary performance endpoint in the stage II cohort was met with hemostasis achieved within 3 min in 38 patients (97.4%; [95% CI: 84.6%-99.9%]). • As compared with a literature-derived performance goal of 65.4%, ETHIZIA demonstrated to be non-inferior to a range of approved hemostatic agents in achieving hemostasis within 3 minutes ($P < 0.001$). • Hemostasis was achieved at 30 seconds in 32 patients (82.1%; [95% CI: 65.9%-91.9%]), at 1 minute in 37 patients (94.9%; 95% CI [81.4%-99.1%]), and at 3 minutes in 38 patients (97.4%; 95% CI [84.6%-99.9%]). • The secondary performance endpoint - mean TTH was 54.6 ± 107.48 seconds (median 30 seconds [interquartile ranges 30 seconds - 30 seconds]). • Among 47 patients and 63 target bleeding sites, hemostasis was achieved in 30 seconds in 83%, in 60 seconds in 94%, and in 3 minutes in 97% of bleeding sites. **Safety:** • There were 44 adverse events in total in 28 of the 47 subjects. • Most patients experienced gastrointestinal disorders (n=5; 10.6%), hepatobiliary disorders (n=15; 31.9%), infections and infestations (n=8, 17.0%), and/or events related to injury and procedural complications (n=4; 8.5%).

	• There were 3 severe adverse events, which were ascites, hepatic failure, and an abdominal abscess. Seven patients (14.9%) experienced a serious adverse event: perihepatic abscess, abdominal abscess, biloma, gastric perforation, hepatic failure, pneumonia, and postprocedural bile leak. • The majority of events, 36 of the 44 in total, were related to the procedure. • Three events were also possibly related to the device and were a biloma, a perihepatic abscess, and a post-procedural hematoma. • All of these events were considered to be possibly related to the device; there were no events that were probably related to the device or with a causal relationship with the device. • There were no reoperations for rebleeding or device issues. There were no deaths reported during the conduct of the study.
Protocol Deviations and Bias	There were 19 protocol deviations, of which 5 were major deviations. None of these deviations had an impact on the overall outcomes. There were no biases affecting the overall conclusions of the trial.

XIII. PANEL MEETING

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The ETHIZIA hemostatic patch has met all pre-specified primary and secondary effectiveness endpoints in the open liver IDE study, showing not only statistical non-inferiority, but also superiority in achieving hemostasis at 3 and 10 minutes relative to TachoSil group in the overall population. In addition, the median time to hemostasis for ETHIZIA was significantly shorter than TachoSil.

Across trials, results of hemostasis at all target bleeding sites treated with ETHIZIA was high at 30 seconds (Pilot: 82.7%, IDE Open: 81.3%), 60 seconds (Pilot: 93.7%, IDE Open: 92.1%), and 3 minutes (Pilot: 96.8%, IDE Open: 95.7%), demonstrating consistency in the ability of ETHIZIA to achieve quick hemostasis.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies, as well as data collected in clinical studies conducted to support PMA approval as described above. Within the open liver pivotal IDE, subjects treated with ETHIZIA experienced similar rates of overall adverse events (AE) and device-related adverse events compared to those treated with TachoSil. In addition, there were no unanticipated adverse device effects. However, more subjects in the ETHIZIA arm (37/87, 42.5%)

experienced serious adverse events (SAEs) compared to the TachoSil arm (10/43, 23.3%) and there were more deaths (5/87, 5.7%) in the ETHIZIA arm compared to TachoSil arm(1/43, 2.3%).

The higher incidence of SAEs was predominantly driven by adverse events of post procedural bile leak (ETHIZIA: 15/87, 17.2%; TachoSil: 2/43, 4.7%). This may be attributed to more complex surgical cases in the ETHIZIA arm with larger resection surfaces (total mean resection surface area 116.3 cm^2 in ETHIZIA compared to 102.6 cm^2 in TachoSil). Additionally, within subjects randomized to the ETHIZIA arm, surgeons preferred to treat multiple bleeding sites with ETHIZIA due to the shorter required compression time to reach hemostasis. This led to use of ETHIZIA on additional larger bleeding sites, other than the first target bleeding site, without application of a primary hemostat first, allowing blood to potentially occlude open bile ducts preventing intraoperative detection and treatment. Although, the site of bile leaks were not associated with ETHIZIA, they could have arisen from bile ducts occluded by blood. It should be noted that ETHIZIA is not indicated as a surgical sealant to prevent bile leakage and should not replace meticulous use of standard surgical techniques to prevent bile leakage. The use of surgical drains to mitigate potential complications as a result of bile leakage should be assessed in each specific procedure based on the surgeon's knowledge and specific anatomical and physiologic considerations encountered in surgery.

The percentage of subjects with an AE leading to death in the ETHIZIA group was higher (n=5, 5.7%) compared to TachoSil (n=1, 2.3%). However, none of these deaths appear to be related to either ETHIZIA or TachoSil or their respective application procedures.

In conclusion, the safety profile of the ETHIZIA hemostatic patch was found to be acceptable compared to standard of care with regard to the rate and types of device-related adverse events.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in clinical studies conducted to support PMA approval as described above. When ETHIZIA was used as an adjunct to hemostasis during open liver surgery to control minimal, mild, and moderate bleeding in the pivotal study, the benefits of ETHZIA included providing fast and sustained hemostasis resulting in less clinical risk of bleeding-related complications to subjects undergoing these surgeries. In the IDE G210325, ETHIZIA was shown to be statistically non-inferior and statistically superior to TachoSil for the primary effectiveness endpoint of hemostasis at 3 minutes without rebleeding within the 10-minute time point for the first target bleeding site. In addition, ETHIZIA was also shown to be statistically superior to TachoSil for the key secondary endpoint of median time to hemostasis for the first target bleeding site. As for safety, ETHIZIA had a comparable safety profile to TachoSil product in the pivotal study and revealed no increased risk of complications directly attributable to ETHIZIA. This was evident

by similar rates of overall and device related adverse events (as reported by the investigator, sponsor, and IAC assessments), which were low and comparable between groups in the Open Liver IDE G210325; all device-related SAEs were only possibly related to the device because the causality could not be fully excluded. Moreover, rates of AEs leading to death, reoperation, or device removal were low in both treatment groups. None of the deaths or SAEs leading to reoperations were considered device-related.

In addition, in the OUS pilot study, the percentage of cases achieving hemostasis at 3 minutes with ETHIZIA was 97.4% which was statistically non-inferior to a literature-based performance goal of 65.4% hemostasis at 3 minutes.

The probable risks of the device are based on data collected in clinical studies conducted to support PMA approval as described above. Across these studies, the types of adverse events and serious adverse events occurring in the ETHIZIA treated patients compared to TachoSil groups revealed no increased risk of complications directly attributable to ETHIZIA. The benefits of the reduction of intraoperative bleeding outweigh the potential risks.

1. Patient Perspective

This submission did not include specific information on patient perspectives as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for ETHIZIA, the probable benefits outweigh the probable risk for use in open liver surgery as an adjunct to hemostasis when control of minimal, mild, or moderate bleeding by conventional procedures is ineffective or impractical.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of ETHIZIA when used in accordance with the indications for use.

The results from nonclinical testing including bench testing, biocompatibility assessments, sterility, shelf life, and packaging assessments, and animal testing, and clinical testing including primary and supplementary clinical data demonstrate that ETHIZIA meets user needs and its intended use. The hemostatic performance of ETHIZIA within the clinical studies demonstrates the benefits of fast and sustained hemostasis resulting in less clinical risk of bleeding related complications. The safety assessments demonstrated no increased risk of complications directly attributable to the device when compared to standard of care. Therefore, benefits of treatment with ETHIZIA outweighs the risks associated with its use.

XV. CDRH DECISION

CDRH issued an approval order on December 15, 2025. The final clinical conditions of approval cited in the approval order are described below.

1. The Continuation of the Open Liver Clinical Study (Post-Approval observational follow-up of PMA Cohort):

   The ongoing observational follow-up in the premarket clinical study will be continued to completion and data will be provided in post-approval study (PAS) reports.

   Per agreement reached on June 12, 2025, the Post-Approval observational follow-up protocol will consist of the continued follow-up of subjects within the premarket cohorts who underwent liver resection for liver malignancy or metastases, collecting data on local cancer recurrence, disease-free survival, and overall survival. The study participants will be followed without direct contact with the subject, but through electronic health records and/or contact with the patients' treating physician. The study participants will be followed at 3 month intervals for the first year then every 6 months for the remaining 5 years in order to assess the long-term safety of their device. There were 9 investigational sites enrolling patients: 5 study sites located in the United States and 4 study sites OUS, 1 located in Germany and 3 located in the Netherlands. During each follow-up, data on results of tumor marker analyses (if applicable), performed imaging, diagnostic biopsy or surgical procedures, or other diagnostics will be collected.

   You must also update your patient and physician labeling to reflect 5 year observational follow-up findings on local cancer recurrence, disease-free survival, and overall survival of subjects treated with ETHIZIA compared to control TachoSil, as soon as these data are available, as well as any other time point deemed necessary by the FDA if significantly new information from this study becomes available.

   In addition, you must submit separate periodic reports on the progress of the Post-approval observational follow-up as follows:

   • PAS Progress Reports annually from the date of the PMA approval letter, unless otherwise specified by FDA.

   • Submit the Final PAS Report three (3) months from study completion (i.e., last subject's last follow-up date).

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XVI. APPROVAL SPECIFICATIONS

Directions for use: see the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, warnings, Precautions, and Adverse Reactions in the labeling.

Post-approval Requirements and Restrictions: See Approval Order.