FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

DATE: September 11, 2012

FROM: Kimberly Lindsey, MD, Medical Officer, Clinical Review Branch, Division of Hematology, OBRR

APPROVED
By Kimberly Lindsey at 2:12 pm, Sep 28, 2012

SUBJECT: Response to CR letter for EVARREST, Fibrin Sealant Patch (STN 125392/0) for use as an adjunct to hemostasis in soft tissue surgery final clinical review memo

APPLICANT: Ethicon

TO: File for STN 125392

THROUGH: Nisha Jain, MD, Chief, Clinical Review Branch

APPROVED
By Nisha at 3:18 pm, Sep 28

Recommendation:
Issuance of a complete response letter is recommended as the Prescribing Information of the product is not acceptable.

As of September 24, 2012 the sponsor had not addressed outstanding issues on the package insert. Due to the deficiencies in the sponsor's revised package insert dated September 21, 2012, it was decided that no additional information be considered for review. Labeling negotiations were stopped on September 24, 2012 and a regulatory decision to issue a complete response (CR, due to package insert deficiencies) was made. Please refer to the complete response letter and teleconference meeting minutes dated September 25, 2012 for labeling deficiencies.

The EVARREST package insert (PI) deficiencies included the following:

- The PI is inconsistent with the regulations (201.57) and guidance regarding the location of specific information (content) and format. This includes, but is not limited to the following
    - Content in the HIGHLIGHTS section
    - Limitations for Use
    - Dosage and Administration section in the HIGHLIGHTS
    - Contraindications
    - Warnings and Precautions
    - Adverse Reactions
    - Use In Specific Populations – Pediatrics subsection

    - Patient Counseling Information
- The Drug Listing Data Elements in the SPL file are incomplete and incorrect. These require updating.
- The formatting of the PI, as prepared in the Word document, is inconsistent throughout the PI. The Word document is replete with macros and hidden formatting that likely will confound the final outcome of the SPL.
- Certain key terms are used incorrectly. For example,
    - "Do not use in…" – signals a contraindication
    - Limitations are usually signaled by the phrase "Not for use"
    - "[use] has not been evaluated…" should be deleted from most areas of the PI (there are a few subsections located in Use in Specific Populations, in which the absence of data is part of the regulatory language). Generally, if there is no data on the use of the product in the manner, or in the population, described, the inclusion of this information in the PI could result in off label use. In the case of a warning or precaution, the risk itself should be described rather than the use.
- The newly proposed order of the Warnings and Precautions is not correct.
- The newly proposed list of Warnings and Precautions is not correct.
- The adverse reactions section has incorrect information.
- There still seems to be disagreement on the proper name.
- The PI should not have a logo.

In addition significant deficiencies were identified in the package label.

Contents of current submission:
This submission contains the Applicant's response to the Complete Response letter issued for STN 125392 on September 19, 2011.

Background:
STN 125392 was submitted to the Agency on November 19, 2010. Following the review of the data, a complete response (CR) letter was issued on September 19, 2011. The main reasons cited for the issuance of the CR included insufficient clinical information related to safety and outstanding 483 items for the Pre License Inspection performed on May 10-May 19, 2011 at ----------(b)(4)---------- the Fibrin Pad Production Facility (FPPF). Please see Appendix 1 for clinical issues identified in the CR letter and the Applicant's response as contained in the current submission is herein reproduced in its entirety.

*** Fibrin Pad and EVARREST are used interchangeably throughout the memo.**

Executive Summary

STN 125392 is a Biologics License Application (BLA) from Ethicon. EVARREST is a sterile, bioabsorable combination product consisting of a composite backing layer coated with human fibrinogen and thrombin. The active side is powdery and the non-active side has an embossed wave pattern. The backing layer component consists of a knitted

oxidized regenerated cellulose (ORC) backing layer under a layer of polyglactin 910 (PG910) non-woven fibers. Each 4 x 4 in. (10.2 x 10.2 cm) unit of EVARREST contains (nominally) 50.3 mg/in^2 (7.8 mg/cm^2) human fibrinogen and 203.2 IU/in^2 (31.5 IU/cm^2) thrombin. EVARREST is applied topically to tissue surfaces. The recommended dosage of the fibrin sealant patch depends on the size of the surface to be covered.

During surgery, surgeons may encounter bleeding that is difficult to control for reasons such as anatomic location, proximity of adjacent structures, or tissue type. There are many primary methods available for the prevention and treatment of such bleeding when it is encountered. The methods include cautery, ligature, suture, staples, packing, energy based coagulation (e.g. electrocautery, argon beam laser, and ultrasound). Fibrin patches are used as an adjunct to these primary methods.

EVARREST fibrin sealant patch is intended for use with manual compression as an adjunct to hemostasis in patients under going soft tissue surgery such as retroperitoneal, intra-abdominal, pelvic, and (non-cardiac) thoracic surgery when standard methods of hemostasis are ineffective or impractical.

Ethicon's clinical program to support the safety and efficacy of EVARREST, when used as an adjunct to hemostasis consists of four clinical trials. Studies 400-07-002, 400-08-002 evaluated the use of EVARREST as an adjunct to hemostasis in soft tissue (intra abdominal, retroperitoneal, pelvic, and (non-cardiac) thoracic surgical procedures). Study 400-10-001 evaluated the use of EVARREST as an adjunct to hemostasis during hepatic resection procedures. A small 10 subject, phase 1 study (FL-PN-001-IS), was conducted in subjects undergoing surgery for partial nephrectomy.

The original submission contained three studies: 400-07-002 which served as the primary basis for licensure, and studies 400-08-002 and FL-PN-001-IS, which were submitted as additional safety data.

Efficacy review:
Study 400-07-002 was the primary study reviewed for efficacy to support licensure. This study was previously reviewed in a clinical memorandum dated September 2011. The primary efficacy endpoint for the study was met with a large (45%) treatment effect regarding time to hemostasis within 4 minutes of application. The additional studies 400-08-002 and 400-10-001 support the efficacy of EVARREST as an adjunct to hemostasis in different, but related surgical populations. The efficacy results were not pooled due to different trial designs and inclusion/ exclusion criteria.

Safety review:
Review of the safety data from study 400-07-002 revealed an unfavorable trend against EVARREST with regard to thrombotic events (TEs). In the non-randomized part of the study 400-07-002, a total of nine TEs were reported in seven subjects of 51 subjects enrolled in the study. As the clusters of TEs were seen in the non-randomized, uncontrolled part of the study, it was not possible to draw a conclusion regarding the

association of the investigational product with these AEs. Study 400-08-002 (non-IND), a second soft tissue surgery study which was submitted in the original application, had a similar design to study 400-07-002. The safety data captured under this study did not adequately address FDA's concerns with regard to the AEs seen in the 400-07-002 because it was unclear if the patients were adequately monitored to capture the TEs**,** infections, abscesses, and adhesions. This study did not, however, have the same imbalance of thromboembolic events against the EVARREST group that was seen in study 400-07-002. The numbers of bleeding and thrombotic events were comparable between the standard of care and EVARREST groups. Additional safety data were requested in the complete response letter. Study 400-10-001, use of EVARREST as an adjunct to hemostasis in hepatic resection surgery was submitted to address the request for additional safety data. This hepatic resection study will be reviewed in detail in this memorandum. (See below)

The safety database considered to support the use of EVARREST as an adjunct to hemostasis consists of a total of 239 subjects who were treated with EVARREST in 4 clinical studies as outlined below:

1) Study 400-07-002:
This was a randomized, controlled study which evaluated the hemostasis efficacy and safety of EVARREST when used as an adjunct to hemostasis during abdominal, pelvic, retroperitoneal, and (non-cardiac) thoracic surgery. It served as the primary study to support safety and efficacy for licensure of EVARREST. The study evaluated the superiority of FP compared to Surgicel as an adjunct to hemostasis when conventional methods of control are ineffective or impractical.

Of one hundred and eleven (111) subjects, 60 were treated with EVARREST during the randomized, controlled period of the study. The comparator product was SURGICEL. The population enrolled in this study was subjects undergoing abdominal, pelvic, retroperitoneal, and (non-cardiac) thoracic surgery with mild to moderate soft tissue bleeding. 51 subjects were treated during the subsequent non-randomized phase during which all subjects received treatment with Fibrin Pad. The study was conducted in 11 sites in the USA.

The primary endpoint of the study was the proportion of subjects achieving hemostatic success at 4 minutes after randomization with no re-bleeding requiring treatment during a subsequent 6 minute observation period. Hemostasis was defined as no detectable bleeding at the Target Bleeding Site (TBS). The study met its primary efficacy endpoint. The overall treatment difference demonstrated that 59/60 (98.3%) of EVARREST treated subjects verses 16/30 (53.3%) of Surgicel treated subjects achieved hemostasis within 4 minutes (i.e. 45% treatment difference).
A total of nine TEs were reported in seven subjects of 51 subjects enrolled in the study. The cluster of TEs was seen in the non-randomized, uncontrolled part of the study. Therefore, it was not possible to conclude that the events were unrelated to EVARREST.

2) Study 400-08-002:

Fifty nine (59) subjects treated with EVARREST in this randomized, controlled, superiority non IND study conducted outside the US , evaluated the effectiveness of the Fibrin Pad (FP) compared with Standard of Care (SoC) methods utilized to control soft tissue bleeding during abdominal, pelvic, retroperitoneal, and (non-cardiac) thoracic surgery for which standard methods of achieving hemostasis were ineffective or impractical. Subjects who met the eligibility criteria were randomized 2:1 Fibrin Pad vs. SoC Control. The primary endpoint was the proportion of subjects achieving hemostasis at the TBS at 4-minutes following randomization and with no re-bleeding at the TBS any time prior to initiation of wound closure time. The post operative follow up period was 60 days.
Although the safety review did not reveal any imbalances between the treatment arms, the study did not adequately address whether subjects were adequately monitored to capture the TEs**,** infections, abscesses, and adhesions, and thrombotic adverse events, which can be associated with EVARREST due to its mechanism of action.

3) Study 400-10-001:
Fifty nine (59) subjects were treated with EVARREST in a randomized, controlled, superiority non IND study conducted outside the US evaluated the effectiveness of the fibrin pad to the standard of care methods commonly used to control bleeding in the hepatic parenchyma after standard methods to control bleeding were deemed ineffective, impractical or inappropriate.

The TBS was defined as the "first actively bleeding site identified in the hepatic parenchyma after completion of parenchymal transaction not responsive to 30 seconds of manual compression alone. The bleeding site also had to exhibit persistent bleeding requiring the surgeon's immediate attention because conventional methods to achieve hemostasis failed or were impractical or inappropriate, thus necessitating an alternative hemostatic method. The primary endpoint was the proportion of subjects achieving hemostasis at the TBS at 4-minutes following randomization and with no re-bleeding at the TBS any time prior to initiation of wound closure (last point in time where EVARREST was visible to confirm hemostasis). The post operative follow up period was 60 days. The results of this study will be reviewed in detail below.

4) Study FL-PN-001-IS:
This was a non-IND, uncontrolled small study to evaluate the safety of EVARREST. Ten (10) subjects undergoing surgery for partial nephrectomy were treated with EVARREST used as an adjunct to hemostasis. The study was conducted in Israel. Hemostasis was achieved in 9 subjects in less than 3 minutes. One subject achieved hemostasis after 4 minutes. There were no reports of rebleeding. The most common adverse events were pyrexia and nausea. The study did not suggest any safety concerns regarding the use of EVARREST as an adjunctive hemostat.

Therefore, for the purposes of this review, the safety database considered to support the use of EVARREST as an adjunct to hemostasis consists of a total of 239** subjects who were treated with EVARREST in 4 clinical studies. The supportive safety studies also confirm the efficacy of EVARREST.

This final clinical review memo will summarize the results of the supportive study of EVARREST in hepatic resection surgery (study 400-10-001). Detailed reviews of the other studies are contained in the final clinical memorandum, dated September 2011, for the original BLA submission.

Clinical review of Study 400-10-001 (conducted outside the US and not under IND): This study was evaluated by the FDA for additional supportive safety data.

Study Title: A Phase III Randomized, Controlled, Superiority Study Evaluating the Fibrin Pad Versus Standard of Care Treatment in Controlling Parenchymal Bleeding During Elective Hepatic Surgery
The original protocol was dated February 23, 2010. There were no protocol amendments during the conduct of the study.

Sites and Centers:
United Kingdom: James Garden MD, Royal Infirmary of Edinburgh, Edinburgh (Coordinating investigator, Europe) Emmanuel Huguet MD, Addenbrooke's Hospital, Cambridge Darius Mirza MD, Queen Elizabeth Hospital, Edgbaston, Birmingham

Germany Markus Büchler MD, University Hospital Heidelberg, Heidelberg Martin Schilling MD, University of Saarland Homburg, Saar

Netherlands Robert Porte MD, University Medical Center, Groningen

New Zealand: Jonathan Koea MD, Auckland City Hospital, Grafton (Coordinating investigator, Australia/NZ)

Australia: Guy Maddern MD, Queen Elizabeth Hospital, Woodville, SA Robert Padbury MD, Flinders Medical Centre, Bedford Park, SA Peter Evans MD, The Alfred Hospital, Melbourne, VIC

**One non-IND study in which EVARREST was used as a primary hemostat was also submitted to the original BLA. This study is not considered part of the review since EVARREST was not used as an adjunct to hemostasis. The study, which enrolled only 4 subjects treated with EVARREST, was conducted in Israel. One of the four EVARREST treated subjects failed to achieve hemostasis within 10 minutes. The study was terminated early due to administrative reasons. If these 4 subjects are included in the total clinical experience with EVARREST, the total safety database would be 243.

Study period: June 14, 2010 to October 17, 2011

Objectives:

- To evaluate the safety and "hemostatic effectiveness" of the Fibrin Pad (FP) versus standard of care treatment (SoC) in controlling parenchymal bleeding during hepatic surgery

Study Design:

This study was a randomized, controlled, superiority study evaluating the effectiveness of the fibrin pad to the standard of care methods commonly used to control bleeding in the hepatic parenchyma after standard methods to control bleeding were deemed ineffective, impractical or inappropriate.

The target bleeding site (TBS) was defined as the "first actively bleeding site identified in the hepatic parenchyma after completion of parenchymal transaction not responsive to 30 seconds of manual compression alone. The bleeding site also had to exhibit persistent bleeding requiring the surgeon's immediate attention because conventional methods to achieve hemostasis failed or were impractical or inappropriate, thus necessitating an alternative hemostatic method.

Blinding and Randomization:
Given the differences between the treatment and control procedures, blinding was not possible. However, in an attempt to minimize the bias in the conduct of the surgical procedure, randomization took place after the investigator identified an appropriate TBS. The randomization envelope was opened simultaneously with starting of the stopwatch Subjects were randomized with a 1:1 allocation ratio. If the subject was randomized to SoC, the un-assigned, unused treatment product was removed from the OR immediately, accounted for and documented, and then placed for destruction.

In the event that a potential subject failed intra-operative criteria (i.e. no TBS identified, and no intra-operative exclusion), and was not randomized to the study, the unopened randomization envelope was returned to the series, and used for the next subject.

Population:
Inclusion criteria (subjects met all of the inclusion criteria):

- ≥ 18 years if age requiring elective or urgent open hepatic surgery
- Presence of an appropriate parenchyma TBS as identified intra-operatively by the surgeon
- Willing to participate in the study and provide written informed consent

Exclusion criteria (subjects met all of the exclusion criteria):

Intra-operative findings were identified by the surgeon that could preclude conduct of the study procedure.

- The bleeding site was from large defects in arteries or veins where the injured vascular wall required repair with maintenance of vessel patency and which would result in persistent exposure of the FP to blood flow and pressure during healing and absorption of the product.

- TBS had major arterial bleeding requiring suture or mechanical ligation.

- Subject was admitted for trauma surgery
- Subject was undergoing a liver transplant for fulminant hepatic failure.
- TBS was within an actively infected field
- Bleeding site was in, around, or in proximity to foramina in bone, or areas of bony confine
- Subject had known intolerance to blood products or to one of the components of the study product
- Subject was unwilling to receive blood products
- Subject was known, current alcohol and/or drug abuser
- Subject had participated in another investigational drug or device research study within 30 days of enrollment
- Subject was pregnant or nursing.

Study Treatments Regimen:

Fibrin Pad:
No more than four units (10.2 x 10.2 cm / 4 x 4 inches) of FP were left implanted in subjects treated with FP. This limit was determined on the basis of non-clinical data, being equivalent to the maximum implanted dosage for which safety data were available from studies in animals.
If additional parenchymal bleeding sites were identified during the surgical procedure in subjects treated with FP, the surgeon was permitted to treat them with FP if clinically appropriate. However, the TBS was the only site to be evaluated for hemostatic efficacy during the study.

Control (Standard of Care):
The control group was e treated with the surgeon's Standard of Care (SoC) methods, i.e. continuous firm manual compression with or without gauze or sponge and with or without a topical absorbable hemostat (TAH).

Endpoints and Criteria for Study Success

Primary Efficacy Endpoint:

- Proportion of subjects achieving hemostasis at the TBS at 4-minutes following randomization and with no re-bleeding at the TBS any time prior to initiation of wound closure (last point in time where FP was visible to confirm hemostasis).

Secondary Efficacy Endpoints:

- Proportion of subjects achieving hemostatic success at 10 minutes following randomization (defined as achievement of hemostasis at 10 minutes and no further bleeding requiring re-treatment prior to wound closure);

- Absolute time to hemostasis (defined as the absolute time to achieve hemostasis at or after 4 minutes from randomization);

- The proportion of subjects who after initial hemostatic success at 4 minutes have breakthrough bleeding requiring treatment;

- The proportion of subjects who after the initial establishment of hemostasis (after 4 minutes) have breakthrough bleeding requiring treatment.

Safety Endpoints:

- Incidence of adverse events "that were potentially related" to re-bleeding at the TBS;

- Incidence of adverse events :that were potentially related" to thrombotic events;

- Incidence of adverse events.

The Applicant collected additional information during the study, to include:

- Classification of the hepatic parenchyma as Normal or Abnormal (i.e. steatotic, cirrhotic, or other);

- Surgeon's description of bleeding at the TBS (area, density, arterial/venous/mixed, characterization of intensity of flow);

- Alternative methods used to achieve hemostasis (if applicable);

- Estimated transected plane area that was treated (0-25%, 26-50%, 51-75% or 76-100%);

- Incidence of post-operative bile leaks requiring intervention

    - Bile leakage was defined as presence of bile fluid (i.e. fluid with bilirubin content at least 3 times higher than the upper normal serum level in patients with postoperatively normal serum bilirubin levels, or a 50% higher bilirubin level than the serum bilirubin level in patients with postoperatively elevated serum bilirubin levels) in abdominal drainage for more than 24 hours after the end of surgery, or

    - The need for radiologic intervention (i.e. interventional drainage) or

- Repeat laparotomy due to abdominal fluid collections with biliary content or biliary peritonitis.

- Ease of Use Questionnaire (EUQ-19)

- Other intra-operative or surgical and process-of-care details:
  - Time from liver resection to initiation of final fascial closure
  - Hepatic segment information:
    - Anatomic resection
    - Non-anatomic Resection
  - Drain usage
  - Estimated (calculated) blood loss
  - Transfusion requirements (intraoperative, post-operative during hospitalization; postoperative following hospital discharge)
  - Time from incision to initiation of final fascial closure
  - Operating Room (OR) time: Entrance to exit time

Schedule of Study Events:
(Source: Text Table 1 Study 400-10-001 CSR page 24/146)

Procedures	Screening[1] (within 21 days prior	Baseline (within 24 hours	Surgical Procedure	Post-Surgery to	Day 1 and	30-day Follow	60-day[6] Follow

	to Procedure)	prior to Procedure)		Hospital Discharge	3,4 or 5	up (± 14 days)	up (± 14 days)
Inclusion/Exclusion	X	X	X				
Informed consent	X						
Demographics	X						
Medical History	X						
Concomitant Medications		X	X	X		X	X
Physical Exam	X			X		X	
Complete Blood Count with Differential[1]	X		X	X[4]		X	
Liver function tests (bilirubin, AST, ALP, GGT, total protein, albumin	X		X	X[4]		X	
Coagulation (PT, PTT, INR, Platelet Count, Fibrinogen)	X			X[4]		X	
Hemoglobin/Hematocrit only[5]			X	X	X[5]		
Pregnancy tests (if applicable)	X						
Viral safety[3]	X						
Randomization			X				
Treatment Application			X				
Intraoperative Details			X				
Determination of Hemostasis at ATBS			X				
Bleeding and Thrombotic Complications			X	X		X	X
Adverse Events			X	X		X	X
Operative/Surgical[2] information			X	X			

1. At least one CBC with differential, Coagulation parameter, liver functions tests, and pregnancy test was needed pre-procedure. If pre-operative blood tests were repeated, the blood test closest to the date prior to surgery was used. If subject was doing autologous blood donation, Hb/HCT was to be collected before pre-operative blood donation
2. Including Length of stay (ICU and overall LOS), transfusion information, Ease of Use Questionnaire
3. A pre-procedure blood specimen had to be collected and stored for potential viral safety testing.
4. Within 24-hrs prior to discharge.
5. Hb & HCT were to be collected for blood loss calculations immediately before the surgical procedure; during Post-Operative Day 1 and once again on either day 3, 4, or 5; and just before discharge if not already collected for CBC. If subject was doing autologous blood donation, Hb/HCT was to be collected before pre-operative blood donation.

6. Follow-up could be conducted over the telephone.

Monitoring: See schedule of study events table (above).
Adverse events were collected from time of randomization, throughout the follow-up period until approximately 60 days after the procedure, specifically:

- Hematology panel (CBC with differential),
- Coagulation studies (INR, PT, aPTT, platelet count and fibrinogen
- Liver function tests (bilirubin, Alk phos, AST, GGT, albumin and total protein), thrombosis rebleeding adverse events.

Stopping Rules:
DSMB (Data Safety Monitoring Board) consisting of a third party not affiliated with ETHICON or involved in any other aspect of the study) was used for safety monitoring. . The DSMB was composed of two surgeons and one statistician.
The study would be suspended until the DSMB together with the Applicant reviewed the data and collectively arrived at a decision whether or not to continue the study based on the following:

One or more subjects developed a suspected unexpected serious adverse reaction (SUSAR) following product application

• One or more subjects developed an SAE related to TBS post-operative re-bleeding. The relatedness of a post-operative TBS bleeding SAE was to be determined via the following modalities: findings at re-operation, imaging studies demonstrating TBS rebleeding, or findings of TBS rebleeding at autopsy (if applicable).
These stopping rules applied only to the treatment group. The SoC control group subjects were to be followed according to the physician's normal practice, as clinically appropriate.

The majority vote (i.e. 2 out of 3) was required to make recommendations. A unanimous vote, however, was required for the DSMB to take a major study action such as suspension of enrollment or study termination.

The Clinical Events Committee (CEC) was charged with the development of specific criteria used for the categorization of major clinical events, establishing rules outlining the minimum amount of data required and the algorithm to be followed in order to classify a clinical event and reviewing and ruling on any deaths that occurred throughout the trial. All members of the CEC were blinded to the primary results of the trial and independently reviewed and adjudicated clinical events.

Statistical Considerations and Statistical Analysis Plan:
Three analysis sets were defined:

• Intent-to- treat set (ITT or full analysis set) consisting of all randomized subjects. Subjects who did not complete the procedure after randomization were considered as failures and included in the ITT analysis.
• Evaluable set (or per protocol; PP) consisting of all ITT subjects who had no major protocol deviations.
• Safety set consisting of all subjects who received treatment.

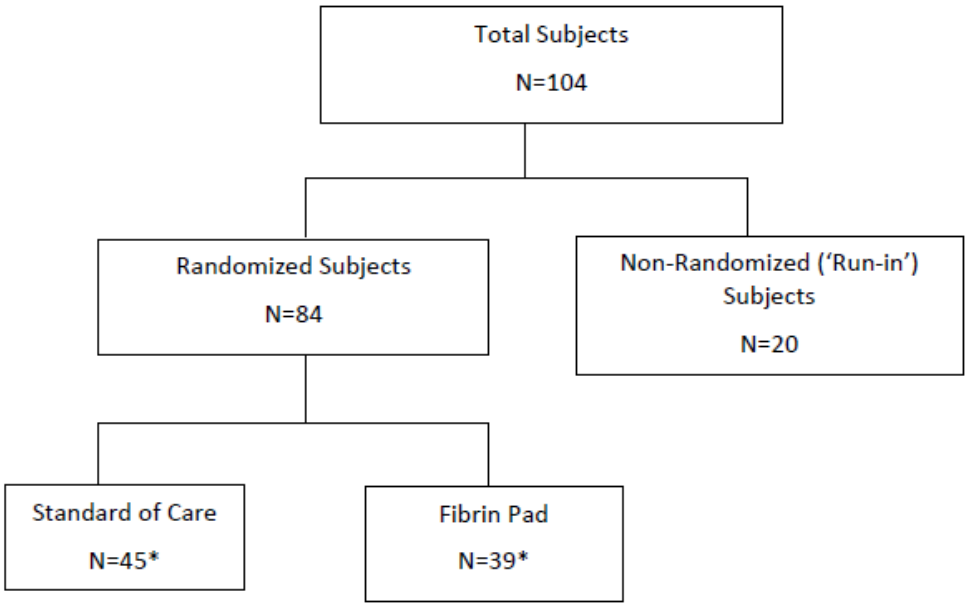
The primary endpoint analysis was based on the ITT analysis set. The evaluable analysis was considered to be supportive.
The statistical hypothesis for testing the treatment difference is presented as follows:
• H0: PC = PF;
• H1: PC ≠ PF

Where PC is the proportion of success in control subjects and PF is the proportion of success in FP subjects.
The triangular test (Whitehead, The Design and Analysis of Sequential Clinical Trials, Wiley, 1997) for a binary response variable was utilized (PEST 4.4 software) with a two-sided alpha 0.05 and power 0.90. The assumed success rate in the control arm was 50% and in the FP arm was 75%. The trial was designed and monitored using the sequential triangular test. The sample size required was therefore not fixed. Interim analysis was planned for the first 80 randomized subjects and, if needed, was to be followed by analyses at completion of every 40 subjects. The interim analyses would determine whether recruitment should be halted or continued based upon efficacy data analyzed by the sequential triangular test. If randomization was continued, subsequent interim analyses were performed after each additional 40 subjects were enrolled into the study. Randomization was stopped after the study hypothesis for efficacy had been answered or once the FP was established to be inferior to SoC Control (if applicable). The expected number of randomized subjects was between 80 and 160.

Study Results:
One hundred four subjects were enrolled into the study. Eighty four subjects were included during the randomized phase of the study and an additional 20 non randomized subjects were treated with the FP in the run-in phase.

Subject Disposition:

Figure 2 Disposition of Study Subjects by Treatment (Safety Set)



** Subject 13-204 should have been randomized to FP but was treated with SoC. This subject is analyzed in the FP group in the ITT Set and in the SoC group in the Safety Set*

Demographics

The two treatment groups were comparable for age, height, weight, BMI, race, gender and smoking history.

All subjects received the randomized study treatment during surgery except one subject (13-204 see footnote below). One hundred out of one hundred four subjects completed the study as planned.

The reasons for failure to complete the study are summarized as follows:

	FP All N=59	SoC N=45	Total N=104
Withdrew consent before study completion	0 (0.0%)	1 (2.3%)	1 (1.0%)
Lost to follow –up post operatively	1 (1.7%)	1 (2.2%)	2 (1.9%)
Series of in –patient hospitalizations during the study period and too sick to complete the study procedures within the required time frame.	1 (1.7%)	0 (0.0%)	1 (1.0%)

Source: Section 14, Table 14.1.1.1 and Table 14.1.1.1a

Protocol deviations

The most common category of protocol deviations was in the category of 'study procedures" (39/59 (66.1%) subjects treated with the FP and 31/45 (68.9%) subjects treated with the SoC). The most common deviation related to study procedure was the failure to perform specified laboratory tests.
Deviations resulting from a "visit out of window" affected 27/59 (45.8%) fibrin pad subjects and 10/45 (22.2%) SoC subjects in the safety analysis set.

Categorization of Protocol Deviations (Safety Set)

	Fibrin Pad N=59	**Standard of Care N=45**	**Total N=104**
Number of subjects with at least one Protocol Deviation Categorized as:			
Any Protocol Deviation	49 (83.1%)	36 (80.0%)	85 (81.7%)
Study Procedure	39 (66.1%)	31 (68.9%)	70 (67.3%)
Visit out of Window	27 (45.8%)	10 (22.2%)	37 (35.6%)
Informed Consent Process	5 (8.5%)	1 (2.2%)	6 (5.8%)
Randomization	1 (1.7%)	2 (4.4%)	3 (2.9%)
Inclusion/exclusion criteria	1 (1.7%)	0 (0.0%)	1 (1.0%)
Other	2 (3.4%)	1 (2.2%)	3 (2.9%)

Major deviations were defined as events that had an impact on the primary endpoint or randomization assignment. The following summary contains the major protocol deviations for the study:

Source: CSR study 400-10-001 Appendix 16.2, Listing 16.2.2

Subject #	**Treatment**	**Deviation Category**	**Details**
(b)(6)	Fibrin Pad	Study Procedure	4 min. TTH[1] evaluation performed at 4 min 30 sec.
(b)(6)	Fibrin Pad	Study Procedure	4 min. TTH evaluation performed at 4 min 30 sec
(b)(6)	Fibrin Pad	Study Procedure	Stopwatch started when FP opened, not when randomization envelop opened
(b)(6)	Fibrin Pad	Inclusion/exclusion criteria Other	Subject randomized, but major (protocol defined) arterial bleeding was present at TBS Absolute TTH not recorded.
(b)(6)	Fibrin Pad (run in)	Randomization	Subject was 2nd non randomized or run in subject treated by the investigator. Protocol only allowed 1 run in subject per investigator.
(b)(6)	Fibrin Pad	Study Procedure	Stopwatch started when FP opened, not

	(run in)		when randomization envelop opened
(b)(6)	Standard of care*	Randomization	Randomization envelop taken out of sequence. Subject should have received FP but was treated with SoC.
(b)(6)	Standard of care	Study Procedure	FP was not prepared and opened in OR prior to randomization
(b)(6)	Standard of care	Randomization	Randomization envelope (b)(6) was opened in error.

*Analyzed as FP in the ITT set

[1]TTH = Time to hemostasis

Reviewer comment:

These deviations did not impact the primary efficacy endpoint analysis. The effect size was quite large in favor of EVARREST as an effective adjunctive hemostat.

Efficacy:

The following table summarizes the number of subjects per treatment group in different population analysis sets.

Analysis datasets

	Fibrin Pad (N)	Standard of Care (N)	Total
Intent to Treat (ITT)	40	44	84
Per Protocol (PP)	35	42	77
Safety Set	59	45	104

Efficacy results:

The control group was treated with a composite of techniques/methods used by the surgeon to control severe bleeding after conventional methods (e.g. suture, ligature, and cautery) were found to be ineffective or impractical. Methods used in the control group are summarized as follows:

Hemostatic Methods in the Control Group (ITT Set) ***Source: Applicant***

Hemostatic Method	**N (%)**
Manual compression only	27/44 (61.4%)
Manual compression with topical absorbable hemostat (TAH)	15/44 (34.1%)
Oxidized regenerated cellulose (ORC)	*14/15 (93.3%)*
Gelatin	*2/15 (13.3%)*
TachoComb® (Nycomed)	*1/15 (6.7%)*
Other	2/44 (4.5%)

Manual compression, with or without a TAH was used in every case with the exception of subjects --------(b)(6)-------- .Argon beam was used for subject (b)(6); subject (b)(6) was initially treated with manual compression but the investigator reverted to conventional methods, inserting a suture and reinforcing with ORC

One or more types of TAH were used in 15 cases: ORC was used in 14/15 cases, gelatin in 2/15 cases and TachoComb (Nycomed) in one case 1/15. (Source: Clinical Study report study 400-10-001, Section 14 Table 14.1.3.4).

Surgical procedure:

Metastatic liver disease was the most common reason for hepatic resection (75%) of study subjects. Hepatocellular carcinoma (14.4%), cholangiocarcinoma (3.8%), hemangioma (2.9%) and 'other' (3.8) made of the remainder of the reasons for hepatic resection.
In the safety set, the majority (2/3) of subjects underwent an anatomic hepatic resection [FP 38/59 (64.4%) and SoC 31/45 (68.9%)]. Source: Section 14, Table 14.1.3.2a Hepatic Parenchyma classification/type, primary operative procedure, Safety analysis set page 32/160

Resection Type	Fibrin Pad N=59	Standard of Care N=45	Total N=104
Anatomic	38 (64.4%)	31 (68.9%)	69 (66.3%)
Non-anatomic	17 (28.8%)	9 (20.0%)	26 (25.0%)
Other	4 (6.8%)	5 (11.1%)	9 (8.7%)

The hepatic parenchyma was examined by the investigator and classified as Normal or Abnormal. Abnormal hepatic parenchyma was then identified as Cirrhotic, Steatotic or Other.

The classification of hepatic parenchyma in the ITT Set is summarized as follows:

Source: Section 14 CSR for study 400-10-001 Tables 4.2.1.1.4

Classification of Hepatic Parenchyma	**Fibrin Pad n=40**	**Standard of Care n = 44**	**Total n = 84**
Normal	28 (70.0%)	33 (75.0%)	61 (72.6%)
Abnormal	12 (30.0%)	11 (25.0%)	23 (27.4%)
Cirrhotic	*3 (25.0 %)*	*4 (36.4%)*	*7 (30.4%)*
Steatotic	*7 (58.3 %)*	*3 (27.3 %)*	*10 (43.5%)*
Other	*2 (16.7 %)*	*4 (36.4 %)*	*6 (26.1%)*

Source table 14.1.3.2 Hepatic Parenchyma Classification /type, primary operative procedure ITT analysis set

Primary Endpoint Analysis
The ITT analysis for the primary efficacy endpoint with missing data considered as failures revealed a higher success rate in the FP group (82.5%, 33/40 subjects) than the SoC group (29.5%, 13/44 subjects) with an overall absolute treatment difference of 53.0%. The difference in success rate was statistically significant (p<0.0001). These results were supported by the ITT sensitivity analysis.

When the data were analyzed according to the type of hepatic parenchyma at the TBS (Normal or Abnormal), the treatment difference between FP and SoC was greater in subjects with abnormal parenchyma compared to subjects with normal parenchyma (65.2% versus 48.8% respectively). In subjects with normal parenchyma, the success rate with FP was 82.1% (23/28) as compared to 33.3% (11/33) in the SoC group (p 0.0001) whereas in subjects with abnormal parenchyma the success rate was 83.3% (10/12) in the FP group as compared to 18.2% (2/11) in the SoC group (p 0.0009).

Text Table 16 Primary Endpoint Results (PP Set)

Classification of Hepatic	Fibrin Pad	Standard of Care	p-value	Treatment Difference
All	33/40 (82.5%)	13/44 (29.2%)	<0.0001	53.0%
Normal	23/28 (82.1%)	11/33 (33.3%)	<0.0001	48.8%
Abnormal	10/12 (83.3%)	2/11 (18.2%)	0.0009	65.2%

Source: Clinical study report for study 400-10-001 Section 14, Table 4.2.1.2.4

In the ITT population, the median time to hemostasis in the fibrin pad group was 4.0 minutes (range 4.0 to 13.2 minutes) compared to 9.7 minutes (range 4.0 to 31.3 minutes) in the SoC group.

Failures for the primary efficacy endpoint (ITT population)

In the ITT Set, 7 subjects treated with FP were considered treatment failures for the primary efficacy endpoint.

Narratives as provided by Applicant:

Subject (b)(6)
Subject (b)(6) did not achieve hemostasis at 4 minutes. The TBS was diffuse and a combination or arteriovenous bleeding, which was not pulsatile. There was adequate coverage of the TBS with the Fibrin Pad however visibility to the area was constrained by the amount of gauze padding utilized during compression of the TBS following Fibrin Pad application. The gauze remained in place due to evidence of seepage at the margins of the padding at 4 minutes post randomization, indicating that compression should continue. The bleeding was absent with hemostasis achieved by 10 minutes.

Reviewer comment: It would appear that this bleeding site exhibited very diffuse bleeding and the TBS was not too amenable to achievement of rapid hemostasis with the fibrin pad (either due to the site selection or some characteristic of the hepatic parenchyma) One might question if the bleeding had optimally been addressed initially with primary hemostatic methods, as required by the protocol.

Subject (b)(6)
During the randomization of subject (b)(6) an out of sequence randomization envelope was used (envelope (b)(6)). The subject was randomized to the treatment assignment of randomization envelope (b)(6) (Standard of Care) and treated accordingly. The subject was a treatment failure and did not meet the criteria of the primary efficacy endpoint. When the error was noted, the subject was re-assigned to the correct randomization number, which was the next sequential randomization number to be used ((b)(6)) in the clinical database. Randomization number (b)(6) was a Fibrin Pad treatment assignment. Since the subject was a treatment failure and subjects analyzed for the primary analysis are ITT, the subject was counted as not meeting the criteria of the primary efficacy endpoint.

Subject (b)(6)
Failure occurred due to difficulty of the TBS location being an area within a metastasectomy. The resection of the mass was 3x 4 cm and conical/cylindrical in shape, making the geometric shape difficult to cover with the Fibrin Pad. This resulted in bleeding in the area of the lowest Fibrin Pad edge, which was substantially decreased from the amount of bleeding observed prior to Fibrin Pad application. The initial Fibrin Pad was removed and replaced with a second Fibrin Pad and hemostasis was achieved at 10 minutes.
Reviewer comment: The fibrin pad, once in place, should not be removed because it could lead to additional bleeding. The TBS was probably inappropriate because of the shape. It would seem that the fibrin pad is best placed on flat and regular bleeding surfaces.

Subject (b)(6)
Treated with a Fibrin Pad and was hemostatic at 4 minutes. The whole Fibrin Pad was wrapped around the liver, partially underneath the liver where full apposition was difficult due to the anatomical structure and position. Hemostasis was maintained until 9 minutes when the FP inadvertently became dislodged. The initial Fibrin Pad was therefore removed and a second Fibrin Pad applied with 4 minutes of manual compression. Hemostasis was achieved at 13 minutes 10 seconds.

Reviewer comment: Wrapping the fibrin pad around the liver is probably not the intended manner of use for the fibrin pad. The bleeding surface needs to be conducive to a relatively flat surface for optimal placement of the pad.

Subject (b)(6)
Subject had an atypical resection of segment 7. Hemostasis was not achieved at 4 minutes and the FP was saturated with blood. The Fibrin Pad was removed which revealed an arterial bleed not previously seen. The arterial bleed was sutured and the resected plane was treated with an argon bean and additional sutures to achieve hemostasis. The TBS treated was an exclusion criteria listed in the protocol, since it was a bleeding site with a major arterial bleed requiring suture or mechanical ligation and reported as a major protocol violation.

Reviewer comment: Agree with Applicant that this was an inappropriate TBS as defined in the protocol.

Subject (b)(6)**:**
Hemostasis was assessed by the surgeon at 4 min 30 seconds post randomization.

Reviewer comment: As defined in the protocol, hemostasis was to be assessed at 4 minutes post randomization.

Subject (b)(6)**:**
Hemostatic efficacy was assessed at 4 min 31 seconds post randomization.
By protocol definition, the hemostatic efficacy was to be determined at 4 minutes post randomization, therefore, both were considered treatment failures for the primary efficacy endpoint. The Applicant states that the incorrect assessment times were due to site error.

Reviewer comment: All cases above are appropriately categorized as failures for the primary efficacy endpoint and in most cases appeared to be due to inappropriate use of the FP.

Bleeding requiring additional treatment (ITT population):
In the ITT Set, among subjects who had achieved hemostasis at 4 minutes, additional treatment for bleeding was required in 1/38 subjects (2.6%) treated with FP compared to 1/44 (2.3%) subjects in the SoC group. Of subjects who achieved hemostasis at a time-point later than 4 minutes, additional treatment was required by 4/40 (10%) in the FP group as compared to 27/44 (61.4%) in the SoC group.

Bleeding Requiring Retreatment (ITT set)

Classification of Hepatic Parenchyma	Time of initial Hemostasis	Fibrin Pad N=40	Standard of Care N=44
All	At 4 minutes	1/38 (2.6%)	1/44 (2.3%)
	After 4 minutes	4/40 (10%)	27/44 (61.4%)
Normal	At 4 minutes	0/26 (0.0%)	1/33 (3.0%)
	After 4 minutes	3/28 (10.7%)	20/33 (60.6%)
Abnormal	At 4 minutes	1/12 (8.3%)	0/11 (0.0%)
	After 4 minutes	1/12 (8.3%)	7/11 (63.6%)

Source: CSR for study 400-10-001 Section 14, Tables 14.2.1.1.1, 14.2.1.1.2 and 14.2.1.1.3.

Retreatment in the 5 cases in the FP group consisted of reapplication of FP in 3 cases, manual compression in one case and suture and argon beam in one case.
Retreatment methods used for the 28 subjects in the SoC group included the use of suture, cautery, argon beam, gelatin, ORC, manual compression with or without TAH and 'other' methods. Other methods included the use of diathermy, ligaclips plus diathermy, FloSeal (Baxter Biosurgery) and TachoSil (Nycomed).

Breakthrough bleeding requiring retreatment
The proportion of subjects for whom there was initial hemostatic success at 4 minutes or later and experienced breakthrough bleeding requiring treatment was defined as a secondary efficacy endpoint. Two subjects met this criterion. The narratives are excerpted verbatim from the Applicant:

(b)(6) **(FP group)**
This subject was treated with a Fibrin Pad and was hemostatic at 4 minutes. The whole Fibrin Pad was wrapped around the liver, partially underneath the liver where full apposition was difficult due to the anatomical structure and position. Hemostasis was maintained until 9 minutes when the FP inadvertently became dislodged. The initial Fibrin Pad was therefore removed and a second Fibrin Pad applied with 4 minutes of manual compression. Hemostasis was achieved at 13 minutes 10 seconds.
Reviewer comment: Wrapping the fibrin pad around the liver is probably not the intended manner of use for the fibrin pad. The bleeding surface needs to be conducive to a relatively flat surface for optimal placement of the pad.

(b)(6) **(SoC group)**
This subject was randomized to treatment with SoC and was hemostatic at 4 minutes. The SoC treatment was manual compression with ORC. At 4 minutes 47 seconds the TBS re-bled, and was subsequently treated with suture and additional ORC. The absolute time to hemostasis was 10 minutes post randomization.

Sensitivity Analyses for primary efficacy endpoint
Additional ITT analyses imputing missing data as successes in both groups (analysis #2), or as failures in the FP group and successes in the SoC group (analysis #3) are as follows:

Sensitivity Analysis (ITT Set)

Analysis #	Imputation of Missing Data	Fibrin Pad	Standard of Care	p-value	Treatment Difference
1†	Failure	33/40 (82.5%)	13/44 (29.5%)	<0.0001	53.0%
2	Success	35/40 (87.5%)	13/44 (29.5%)	<0.0001	58.0%
3	FP Failure, SoC Success	33/40 (82.5%)	13/44 (29.5%)	<0.0001	53.0%

Source: Clinical study report for study 400-10-001 Section 14, Tables 4.2.1.1.4
†Primary efficacy endpoint

Safety results:

The safety population consisted of 59 subjects treated with the fibrin pad and 45 subjects treated with SoC. One subject was randomized to receive treatment with FP but was erroneously treated with SoC (Subject (b)(6)). This subject is analyzed with the FP group in the ITT Set and with the SoC group in the Safety Set.

The use of FP to treat additional parenchymal bleeding sites, separate from the TBS, was permitted in the FP treatment group. Additional treatment was applied in 27/59 subjects in the Safety Set (45.8%)

Deaths
No deaths occurred in either treatment group during the study.

Adverse Events
Adverse events that occurred during or post-treatment are summarized by MedDRA preferred term and System Organ Class (SOC).

The most frequently occurring type of AE by SOC was Gastrointestinal Disorders; 81/104 subjects (77.9%) experienced one or more events of this type. Within this class nausea, constipation and vomiting were the most frequently reported events, occurring in 59/104 (56.7%), 42/104 (40.4%) and 34/104 (32.7%) of all subjects, respectively.

Reviewer Comment: These adverse events are common during abdominal surgical procedures. In my overall safety review, these types of adverse events were evaluated based on reasonable association among bowel obstruction or adhesions, proximity of placement of the fibrin pad or SoC treatment article (TAH or ORC) was placed, and temporal relationships.

Events that occurred in ≥10 % of subjects following either treatment are summarized in Table 14.3.1.3

Overall, anemia, nausea, constipation, vomiting, pain, pyrexia, hypokalemia and hypotension were the most common events, occurring in more than 20% of all subjects. *Reviewer comments: While it is true that these events are commonly seen in patients following major surgical procedures of long duration in the abdomen, the safety review was conducted to take into consideration plausible adverse events that might be attributable to use of the fibrin pad (infection due to a retained foreign body, and hemostatic failure of the pad leading to rebleeding events, thrombosis).*

Source: Section 14, Table 14.3.1.3

AEs occurring in ≥ 10% of subjects in either treatment group (safety set)

		Number (%) of Subjects Experiencing Event	
System Organ class	Preferred term	FP (N=59)	SoC (N=45)
Blood and Lymphatic System Disorders	Anemia	14 (23.7%)	11 (24.4%)
Cardiac Disorders	Tachycardia	6 (10.2%)	5 (11.1%)
Gastrointestinal Disorders	Constipation	22 (37.3%)	20 (44.4%)
	Localized intra-abdominal fluid collection	2 (3.4%)	6 (13.3%)
	Nausea	31 (52.5%)	28 (62.2%)
	Vomiting	20 (33.9%)	14 (31.1%)
General Disorders and Administration Site Conditions	Edema, peripheral	4 (6.8%)	9 (20.0%)
	Pain	15 (25.4%)	18 (40.0%)
	Pyrexia	15 (25.4%)	12 (26.7%)
Injury, Poisoning and Procedural Complications	Procedural pain	12 (20.3%)	7 (15.6%)
Metabolism and Nutrition Disorders	Hyperglyecemia	1 (1.7%)	5 (11.1%)
	Hypokalemia	14 (23.7%)	11 (24.4%)
	Hypomagnesemia	9 (15.3%)	3 (6.7%)
Musculoskeletal and Connective Tissue Disorders	Arthralgia	8 (13.6%)	7 (15.6%)
	Dizziness	9 (15.3%)	7 (15.6%)
Psychiatric Disorders	Anxiety	8 (13.6%)	3 (6.7%)
	Confusional state	3 (5.1%)	5 (11.1%)
	Hallucination	3 (5.1%)	5 (11.1%)
	Insomnia	9 (15.3%)	7 (15.6%)
Renal and Urinary Disorders	Incontinence	0 (0.0%)	5 (11.1%)
Respiratory, Thoracic and Mediastinal Disorders	Pleural Effusion	7 (11.9%)	8 (17.8%)
Vascular disorders	Hypertension	6 (10.2%)	10 (22.2%)
	Hypotension	21 (35.6%)	17 (37.8%)

The Applicant lists 3 AEs with potential causal relationship to study treatment
Source: Appendix 16.2, Listing 16.2.7.1
AEs with Potential Causal Relationship to Study Treatment (Safety Set)

Subject #	Treatment Group	Adverse Event	SAE?	Causal Relationship
(b)(6)	Fibrin Pad	Post operative bleeding	Yes	Possibly related
(b)(6)	Fibrin Pad	Intra-abdominal bleed with serosanguinous blood in drains	Yes	Possibly related
(b)(6)	Fibrin Pad (run- in)	Abdominal collection	Yes	Possibly related

Reviewer comment:
Reviewer concurs with Applicant's assessment that based on review of the available data it is possible that the events were related to the use of the fibrin pad. No reoperation and no imaging studies were conducted to discern whether the re bleeding was at the TBS. The events did not lead to deaths.

Adverse events were assessed for potential relationship to rebleeding at the TBS or thrombotic events. These are considered adverse reactions because they occur with EVARREST and with drugs in the same pharmacologically active and chemically related class (§201.57(c)(7)(i)).

Four AEs in the FP group (4/59; 6.8%) and one in the SoC group (1/45; 2.2%) were considered by the investigators to be potentially related to bleeding at the TBS.

The following table provided by the Applicant lists AEs deemed potentially related to the bleeding at the TBS:

AEs potentially related to bleeding at the TBS (safety set)

Subject #	Treatment group	Preferred Term	Timing of event	Potentially related to study treatment
(b)(6)	Fibrin pad	Post-procedural hemorrhage	Post operative	Yes
(b)(6)	Fibrin pad	Intra-abdominal hemorrhage	Intraoperative	No
(b)(6)	Fibrin pad	Intra-abdominal hemorrhage	Intraoperative	Yes
(b)(6)	Fibrin Pad (run-in)	Operative hemorrhage	Intraoperative	No
(b)(6)	Standard of Care	Operative hemorrhage	Intraoperative	No

Source: Section 14, Table 14.3.1.1, Appendix 16.2, Listing 16.2.7.3 and Appendix 14.3.5.

Reviewer comment:
Case (b)(6) *CRFs state that site of intra abdominal bleed was unknown. From available data, one cannot conclude that it was not related to product failure, but seems unlikely due to the large amount of the bleed (1.2 liters on post op day 1).*

Case (b)(6) *was a run in subject. According to the operative note the estimated blood loss during surgery was 2500 ml. Hemostasis was obtained within 4 minutes after application of EVARREST to the target bleeding site. It appears from the case report form that the bleeding was due to the operative procedure. This is plausible.*

Case (b)(6) *had incomplete hemostasis and required tamponade.*

Reviewer concurs with Applicant's assessment that based on review of the available data it is possible that the events for subjects ------(b)(6)------ *were related to the use of the fibrin pad.*

The Applicant reports that one event in the FP group (1/59; 1.7%) and two events in the SoC group (2/45; 4.4%) were assessed as being potentially related to thrombotic events.

Source: Text table 32 AEs potentially related to thrombotic events (safety set)

Subject #	Treatment group	Preferred Term	Potentially related to study treatment
(b)(6)	Standard of Care	Vena Cava thrombosis	No
(b)(6)	Standard of Care	Portal vein thrombosis	No
(b)(6)	Fibrin Pad	Pulmonary embolism	No

Reviewer comments:

Subject (b)(6) - *Subject underwent a resection of segments IV and V of the liver, exploratory laparotomy and adhesiolysis, cholecsystectomy, lymph node dissection within the hepatoduodenal ligament and incisional hernia repair. The right pulmonary embolism adverse reaction occurred on post op day 2. The subject was treated and recovered. Pulmonary embolism is a known potential complication of hepatic resections. One cannot rule out that the use of EVARREST was not related to the complication.*

Reviewer safety summary for study 400-10-001:
The review summary for adverse events targeted medical events of significant interest due to their potential associations with the mechanism of action of the fibrin sealant portion of the combination product or the device component The following events were evaluated for safety: bleeding, thromboembolic events, cardiac events, hypersensitivity reactions, nausea and vomiting (due to obstruction), post operative wound infection, other infections, and laboratory parameters such as hemoglobin, hematocrit, PT, aPTT,

fibrinogen, and DIC markers, which might be associated with bleeding or thrombotic complications.

Specifically,

- Bleeding events were evaluated based on coagulopathy, possible relationship to antibody to thrombin, efficacy and safety failure

- Thrombotic events were evaluated based on the mechanism of action of the thrombin and fibrinogen in clot formation as well as thromboembolic events linked to the development of antibodies to thrombin

- Cardiac events were evaluated based on the possibility that microemboli resulting from the fibrin sealant directly and disintegration of the device component could lead to a variety of cardiac symptoms such as arrhythmias, congestive heart failure, and infarction.

- Hypersensitivity events were evaluated because the fibrin pad components can trigger skin, or anaphylactic reactions in sensitized subjects.

- Nausea and vomiting were evaluated since these symptoms can be associated with bowel obstruction secondary to adhesions and inflammatory reactions associated with the implantation of the fibrin pad

- Wound infections, including infections associated with postoperative abscesses or fluid collections at or in proximity to the surgical site, were evaluated because of the known increase in wound infections when foreign materials remain following surgery.

The groupings of adverse events under a particular heading were categorized based on verbatim terms. Under each major heading, verbatim terms that could be associated with the major heading were listed (lumped). Case report forms were used to verify that the adverse event was captured. Narratives were consulted to provide additional details.

*Control is standard of care- manual compression with or without gauze OR with or without out topical adjunctive hemostat

Control N=45 Fibrin Pad N=59

Study No.:400-10-001

Treatment Emergent AEs	Fibrin Pad (No. of subjects)	Fibrin Pad (No. of events)	Control (No. of subjects)	Control (No. of events)
Death	0	0	0	0
Chest pain/pressure/tightness	2	2	1	1
CHF, etc	0	0	2	2
Fluid overload	0	0	2	2
Card. arrest, etc	0	0	0	0
MI, etc	3	3	0	0
Myocardial infarction	2	2	0	0
Myocardial ischemia	0	0	0	0
Angina pectoris	0	0	0	0
Unstable angina	0	0	0	0
Acute coronary syndrome	1	1	0	0
Cardiac arrhythmias	15	16	12	13
arrhythmia	2	2	1	1
Atrial fibrillation	2	2	3	3
Atrial flutter	0	0	0	0
bradycardia	2	2	0	0
tachycardia	3	4	5	5
V-extrasystoles	0	0	0	0
Supraventricular tachycardia	0	0	1	1
V-tach	2	2	0	0
Atrial tachycardia	0	0	0	0
Bundle branch block	1	1	0	0
Sinus tachycardia	3	3	2	3

Study No.: 400-10-001

Treatment Emergent AEs	Fibrin Pad (No. of subjects)	Fibrin Pad (No. of events)	Control (No. of subjects)	Control (No. of events)
Pneumonia, aspiration pneumonia, respiratory failure/insufficiency	3	3	3	3
Pneumonia	3	3	3	3
Respiratory distress.etc	7	7	8	8
Pleural effusions	7	7	8	8
Gastrointenstinal pain, nausea, vomiting	56	73	48	60
Abdominal pain	1	1	3	3
Vomiting	18	21	14	20
Nausea	32	44	28	34
Ileus/ bowel dysfunction	2	2	1	1
Bowel obstruction	0	0	1	1
RUQ pain	3	5	1	1
Coagulation	5	5	5	6
Coagulation disorder	1	1	0	0
Abnormal coagulation test	0	0	1	2
INR increased	0	0	2	2
Fibrinolysis	0	0	1	1
Prothrombin time prolonged	3	3	1	1
Activated partial thromboplastin time prolonged	1	1	0	0
Thrombosis	1	1	2	2
Vena cava	0	0	1	1
Portal vein	0	0	1	1
Pulmonary embolism	1	1	0	0

Study No.: 400-10-001

Treatment Emergent AEs	Fibrin Pad (No. of subjects)	Fibrin Pad (No. of events)	Control (No. of subjects)	Control (No. of events)
Hemorrhage/bleeding	6	6	7	7
anemia	1	1	6	6
Hemorrhage			1	1
Ulcer hemorrhage	1	1	0	0
Intra-operative hemorrhage	0	0	0	0
Post-op hemorrhage	1	1	0	0
Hematuria	1	1	0	0
Intra abdominal hemorrhage	2	2	0	0
Hypotension events	19	24	17	23
Pyrexia/fever/increased temperature	15	18	12	19
Pruritis	1	1	0	0
Rash	0	0	1	1
Pain	40	53	32	41
Not otherwise specified (NOS)	15	23	16	23
Post op Pain	14	19	7	9
Back Pain	3	3	1	1
Neck pain	2	2	0	0
Shoulder pain	6	6	5	5
Leg pain	0	0	2	2
Hand/wrist pain	0	0	1	1
Leak (bile)	3	3	4	4
wound	1	1	3	3
GI tract	2	2	0	0
Urinary tract	2	2	1	1
Mouth (fungal)	1	1	0	0
Chest	2	2	0	0
Drain tube	1	1	1	1

Not otherwise specified	0	0	1	1
Eye	0	0	2	2
PICC line	0	0	1	1
Extended beta lactamase infection	0	0	1	1
Study No.: 400-10-001				
Treatment Emergent AEs	Fibrin Pad (No. of subjects)	Fibrin Pad (No. of events)	Control (No. of subjects)	Control (No. of events)
Hypotension	19	24	17	23
Intraabdominal fluid	5	5	2	2
Localized intraabdominal fluid collection	2	2	2	2
Peritoneal effusion	1	1	0	0
Abscess	1	1	0	0
Biloma	1	1	0	0

Reviewer conclusions from adverse event tables:
In study 400-10-001 there were no imbalances in the overall medical events of special interest, particularly, thrombotic, rebleeding and infection adverse events.

Given the prior history of thromboembolic events potentially associated with the use of the fibrin pad in study 400-07-002 (US soft tissue surgery study) subjects enrolled in the hepatic resection trial were evaluated for VTE risk.

Safety Population: Total Risk score (VTE)

The total risk for VTE score is derived from the following variables:

- Serious trauma
- History of SVT or DVT/PE
- Family history of SVT or DVT/PE
- Cancer (current/previous)
- Recent major surgery
- Recent bedrest > 72 hours
- Minor surgery last 30 days
- Swollen legs (currently)
- Heart attack
- Congestive heart failure
- Serious sepsis/infection
- Lung disease
- Central venous access

- Restricted mobility
- COPD
- Varicose veins

The following chart excerpted from Caprini et al[1] below outlines the risk factors and points given to determine the total VTE risk score.

Deep Vein Thrombosis (DVT)
Prophylaxis Orders
(For use in Elective General Surgery Patients)

Thrombosis Risk Factor Assessment
(Choose all that apply)

BIRTHDATE

NAME

CPI No.

SEX M F VISIT No. _____

Each Risk Factor Represents 1 Point

- ❑ Age 41-60 years
- ❑ Acute myocardial infarction
- ❑ Swollen legs (current)
- ❑ Congestive heart failure (<1 month)
- ❑ Varicose veins
- ❑ Medical patient currently at bed rest
- ❑ Obesity (BMI >25)
- ❑ History of inflammatory bowel disease
- ❑ Minor surgery planned
- ❑ History of prior major surgery (<1 month)
- ❑ Sepsis (<1 month)
- ❑ Abnormal pulmonary function (COPD)
- ❑ Serious Lung disease including pneumonia (<1 month)
- ❑ Oral contraceptives or hormone replacement therapy
- ❑ Pregnancy or postpartum (<1 month)
- ❑ History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant
- ❑ Other risk factors_____

Subtotal:

Each Risk Factor Represents 2 Points

- ❑ Age 61-74 years
- ❑ Central venous access
- ❑ Arthroscopic surgery
- ❑ Major surgery (>45 minutes)
- ❑ Malignancy (present or previous)
- ❑ Laparoscopic surgery (>45 minutes)
- ❑ Patient confined to bed (>72 hours)
- ❑ Immobilizing plaster cast (<1 month)

Subtotal:

Each Risk Factor Represents 3 Points

- ❑ Age 75 years or older
- ❑ **Family History of thrombosis***
- ❑ History of DVT/PE
- ❑ Positive Prothrombin 20210A
- ❑ Positive Factor V Leiden
- ❑ Positive Lupus anticoagulant
- ❑ Elevated serum homocysteine
- ❑ Heparin-induced thrombocytopenia (HIT)
  (Do not use heparin or any low molecular weight heparin)
- ❑ Elevated anticardiolipin antibodies
- ❑ Other congenital or acquired thrombophilia
  If yes: Type_____

*** most frequently missed risk factor**

Subtotal:

Each Risk Factor Represents 5 Points

- ❑ Stroke (<1 month)
- ❑ Multiple trauma (<1 month)
- ❑ Elective major lower extremity arthroplasty
- ❑ Hip, pelvis or leg fracture (<1 month)
- ❑ Acute spinal cord injury (paralysis) (<1 month)

Subtotal:

TOTAL RISK FACTOR SCORE:

[1]All moderate-risk and high-risk patients should receive UFH, LMWH, or FXa I unless contraindicated by bleeding risk
Scores of 2–3: IPC perioperatively and during hospitalization
Scores of 3–4: UFH, LMWH, FXa I, foot pump, or IPC during hospitalization Start AC 12–24 h postoperatively
Scores of 5–8: AC _ IPC during hospitalization and 7–10 d UFH, LMWH, or FXa I Start AC 12 h preoperatively
Scores of ≥8: AC _ IPC during hospitalization and 30 d UFH, LMWH, or FXa I

AC = anticoagulation; FXa I = factor Xa inhibitor; IPC = intermittent pneumatic compression; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin

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1 Caprini JA. Risk assessment as a guide for the prevention of the many faces of venous thromboembolism. The American Journal of Surgery 2010;199(1S):S3-S10.

Venous thromboembolism assessment risk

Category/Statistic	FP All (n=59)	SoC (n=45)	Total (n=104)
Mean (std)	14.1 (2.5)	14.3 (2.4)	14.2 (2.4)
Median (range)	14.0 (9.0, 23.0)	14.0 (10.0, 22.0)	14.0 (9.0, 23.0)
Number (missing)	59 (0)	45 (0)	104 (0)
95% CI of mean	13.5, 14.8	13.6, 15.0	13.7,14.7

Total risk factor score, sum of all individual score (points), total score includes 2 points for current study surgery. If bedrest & restricted mobility are both yes, only counts as 1 point in the total.

Reviewer comment: *In study 400-10-001 the FP and SoC groups were comparable in terms of baseline VTE risk*.

Integrated Overview of Efficacy:
Hemostatic efficacy is summarized for each individual study since the clinical trial designs were different.

Integrated Overview of Safety:
Although the Applicant presented the integrated safety summary, since the standards of care (i.e. TachoSil, topical adjunctive hemostat with or without manual compression, other fibrin sealants) varied across the trials, the most important studies were reviewed separately (not pooled) in this memorandum. Protocols 400-07-002 (US soft tissue surgery study) and 400-08-002 (phase 3 soft tissue surgery study conducted outside the US) and have been previously summarized.

Immunogenicity:
To address immunogenic potential of the fibrin pad, the Applicant submitted an immunogenicity report entitled, "Antibody Response to Human Thrombin and Fibrinogen in Subjects Participating in Clinical Study Evaluating the Efficacy and Safety of Fibrin Pad versus Standard of Care Treatments- Study Code 400-08-002.

Study subjects were randomized into two treatment groups: Fibrin Pad and SoC in a 2:1 ratio respectively. Blood samples were collected from subjects at baseline (24 hours prior to surgery) and at 30 and 60 days post surgery. ELISA using purified human plasma derived fibrinogen or thrombin was used to detect levels of specific antibodies to human thrombin and fibrinogen. The background level of antibodies to thrombin or fibrinogen in an untreated population was used to set a cut off value of 25% in attempt to be more conservative than previous immunogenicity assessments for -----(b)(4)----- (cut off value set a 5%).

Regarding the methodology, there two types of analyses conducted: 1) A quasi-quantitative method in which titer results for each subject were evaluated for being above the cut off and for a significant increase over time following treatment with FP or SoC (at 30 and 60 days) 2) Comparison of the proportion of positive samples (higher than the cutoff) in different groups at different time points.

Samples from a total of 65 subjects (FP, N=46 and SoC, N=19) from both treatment groups were available for analysis.

Immunogenicity study, Applicant reported results:
A total of 5 subjects in the two treatment groups had specific anti-thrombin signals that were higher than the cut off at 30 and/or 60 days while the baseline samples of these subjects had values below the cut-off. The Applicant concludes that the fluctuations along the cut-off, and low calculated titers (titer=50) across the time points for these three subjects do not support a real change in the detection signal. The ---------(b)(4)---------- across the study period of three of the subjects ((b)(6) -SoC,) were very close to the cut-off, suggesting that the differences between time points are within the assay's variability.

Two subjects from the FP group ---------(b)(6)---------- had a low, transient increase in antibody response for fibrinogen which is not thought to be indicative of a response or real change in the detection signal. In the FP group, 1/46 (2.2%, 95% CI 0.1-11.5) subjects experienced a slight increase in antibody response to human thrombin with no clinical manifestations. This subject (#(b)(6)) had undergone two previous major surgeries in 2006 and 2009; therefore, the possibility of repeat exposure cannot be ruled out. The 2% rate of increase in specific detection signal of thrombin antibodies is within the expected rate as demonstrated in the literature after treatment with human thrombin and far below the rate demonstrated after treatment with bovine thrombin. [2,3]

The rate of increase in anti-human thrombin in the SoC group was not statistically different from the FP (2/19, 95% CI 1.3-33). One subject from the SoC group had a significant increase in antibody response for human fibrinogen after treatment (----(b)(6)----, SoC group). This subject experienced a strong, unusual seroconversion response as indicated by the assays for human thrombin and fibrinogen antibodies, but without any clinical manifestations. The etiology of this finding is unclear. An additional subject (b)(6) in the SoC group met the criteria of increase in the specific antibodies to human thrombin after T0.The fluctuation of anti-thrombin signals below and above the cutoff during the study period between T0 and T60 was similar to the normal healthy population.

There were no reported observed clinical correlations or any adverse events that can be attributed to the immune response in the positive subjects.

Reviewer Comment: Reviewer concurs with Applicant's assessment. The Applicant has been advised to continue immunogenicity monitoring throughout the clinical development program as they work toward a general adjunct to hemostasis indication.

[2]Chapman, WC et al. Phase 2, randomized, double-blind, placebo-controlled, multicenter clinical evaluation of recombinant human thrombin in multiple surgical indications. 2006, J Thromb Haemost. 4:2083-2085.

[3] Chapman, WC et al. A Phase 3, randomized, double-blind comparative study of the efficacy and safety of topical recombinant human thrombin and bovine thrombin in surgical hemostasis. 2007, JAm Coll Surg. 205(2):256-265.

Pediatric Use and PREA Considerations:
PREA was triggered as a new indication was being sought. Ethicon requested a pediatric waiver for neonates (age 0- 30 days) and a deferral for children greater than one month of age to 16 years 11 months.
The pediatric plan for a deferred study was presented to the Pediatric Review Committee (PeRC) on September 5, 2012. The PeRC agreed with the Division to grant a deferral of pediatric studies and a waiver for the neonatal pediatric population 0—30 days). The neonatal population was waived because EVARREST may be ineffective or unsafe in this group of subjects due to the size limitations of the organs and inability to administer the product as described in the instructions for use (dosage and administration) section of the package insert. EVARREST's package insert will note the limitation for use in the neonatal population.

Reviewer conclusions:
The totality of the summary of clinical information submitted in the original BLA and the complete response amendment suggest that the fibrin pad is effective as an adjunct to hemostasis in the soft tissue surgical setting.

The safety of the Fibrin Pad has been evaluated in an extensive clinical program to include primarily studies conducted outside the US and not under IND. Since the trial designs and settings varied the safety information was not integrated.

In summary, the safety review included evaluation of case report forms, operative notes clinical visit notes and subject narratives. The study serving as the basis for licensure (study 400-07-002) was a randomized, controlled, clinical study evaluating the superiority of FP compared to Surgicel as an adjunct to hemostasis when conventional methods of control are ineffective or impractical met the primary endpoint. The ITT analysis (90 randomized subjects) for the primary efficacy endpoint revealed a higher success rate in the FP group (98.3%, 59/60 subjects) than in the SURGICEL group (53.3%, 16/30 subjects). The overall absolute treatment difference was 45%. Although the primary endpoint was met, the study did identify some potential safety signals of thromboembolic events, infections, adhesions, fistulas and obstructions. There were more fatal events in the FP arm compared to the Surgicel arm (6 vs. 1) and the number of thrombotic adverse events in the non randomized portion of the clinical trial was significant enough to warrant additional information. A total of nine TEs were reported in seven subjects of 51 subjects enrolled in the study. The cluster of TEs was seen in the non-randomized, uncontrolled part of the study. The information to assess plausible relationship to the investigational product was lacking and based on the safety information submitted one cannot exclude the possibility that some of the serious adverse events were related to the investigational product (i.e. the FP). While it is true that the patients enrolled in the trial were at increased risk for thromboembolic events, the baseline demographics did not appear to suggest that a possible explanation for an imbalance of AEs against the FP arm could be that the two groups were dissimilar in terms of degree of illness or predisposition for a given serious adverse event.
The case report forms often did not capture the specific sites of the fibrin pad placement or details of the operative procedures were lacking. Furthermore, it was unclear if the

patients were adequately monitored to capture thromboembolic events, infections, abscesses, adhesions/ obstructions.

Study 400-08-002 (a non-IND study), a second soft tissue surgery study which was submitted in the original application, had a similar design to study 400-07-002. The safety data captured under this study did not adequately address FDA's concerns with regard to the AEs seen in the 400-07-002 because the case report forms often did not capture the specific sites of the fibrin pad placement or details of the operative procedures were lacking. Furthermore, it was unclear if the patients were adequately monitored to capture thromboembolic events, infections, abscesses, adhesions/ obstructions. This study did not, however, have the same imbalance of thromboembolic events against the fibrin pad group that was seen in study 400-07-002. The numbers of bleeding and thrombotic events were comparable between the standard of care and fibrin pad groups.

Study 400-10-001 (a non-IND study), use of the fibrin pad as an adjunct to hemostasis in hepatic resection surgery, did not reveal any clinically significant imbalances in numbers of bleeding, thrombotic, cardiac, and infection adverse events or reactions. Patients were monitored and assessed for venous thromboembolism risk. This was particularly important since patients undergoing hepatic resection are at increased risk for thromboembolic events.

Reviewer Recommendation:
The submission is approvable from a clinical standpoint. The totality of data submitted suggests that EVARREST is safe and effective for use with manual compression as an adjunct to hemostasis for soft tissue bleeding during open retroperitoneal, intra-abdominal, pelvic, and non-cardiac thoracic surgery when control of bleeding by standard surgical methods of hemostasis (e.g., suture, ligature, cautery) is ineffective or impractical.

Discussion of Regulatory Options:
Based on the supplemental study information contained in this submission, the overall safety profile for EVARREST is acceptable for approval. A pediatric post marketing study will be required. Ethicon plans to enroll pediatric subjects in their US clinical program to support a general adjunct to hemostasis indication. Discussions of the appropriate clinical setting and trial design will be further discussed with the Agency as the clinical program continues to expand.
Due to the ongoing nature of the clinical program I do not recommend a post marketing requirement for immunogenicity. This information can be collected during the expansion of their US clinical program for which a general adjunct to hemostasis indication is being sought.
Repeat exposure to EVARREST may present a safety concern in terms of immunogenicity and surgical site implantation issues such as adhesions, inflammation, and retained product. At this time, preclinical studies are recommended to address this issue. Depending on the results of these studies, it may or may not be necessary to require repeat exposure clinical studies as part of a post marketing requirement.

APPENDIX 1

Clinical:
1. Review of the submitted data shows an unfavorable trend against the investigational product (FP)* with regards to thrombotic events (TEs). Specifically, our review identifies the following:

a. In the non randomized part of the study 400-07-002, a total of nine TEs were reported in seven subjects of 51 subjects enrolled in the study. As the cluster of TEs were (*sic.* was) seen in the non-randomized, uncontrolled part of the study, it is not possible to draw a conclusion regarding the association of the investigational product with these AEs.

b. Given the lack of sufficient detail regarding operative placement of all investigational products used per patient, it is difficult to conclude with any degree of certainty that the FP did not contribute to the thrombotic events.

c. The safety data captured under Protocol 400-08-002 (non-IND study) do not adequately address FDA's concern with regards to the AEs seen in the 400-07-002 study because it is unclear if the patients were adequately monitored to capture the TEs.

d. Furthermore, it is unclear if the patients were adequately monitored to capture thromboembolic events, infections, abscesses, adhesions/obstructions.

Therefore, in order to support licensure of Fibrin Pad for use as an adjunct to hemostasis in soft tissue surgery, please submit data from an additional adequate and well controlled study designed primarily to assess safety in the proposed population. The study should be designed to include a prospective monitoring plan for thrombotic events.
Alternatively, you may submit safety data from an adequate and well controlled study with the Fibrin Pad in an ongoing study in a different surgical population.

Applicant response:
A non-IND clinical study using Fibrin Pad in liver surgery (Study # 400-10-001 entitled "A Phase III Randomized, Controlled, Superiority Study Evaluating the Fibrin Pad Versus Standard of Care Treatment in Controlling Parenchymal Bleeding During Hepatic Surgery") has been recently completed outside the US (OUS) (UK, Netherlands, Germany, Australia and New Zealand).

The Clinical Study Report of this study is included in this response, as well as all related CTD clinical documents from the Original BLA, which have been revised to include the data collected from this study.

In addition, the immunogenicity report for the soft tissue surgery study recently completed outside the US (OUS) (clinical study report # 400-08-002) is provided.

Addendum: Recommendation to issue a CR due to outstanding labeling deficiencies