

STN 125392 Omrix Fibrin Pad

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| Application Type | Biologics License Application |
| Application Number(s) | STN 125392 |
| Received Date(s) | November 19, 2010 |
| PDUFA Goal Date | September 19, 2011 |
| Division / Office | Division of Hematology/OBRR |
| Priority Review | No |
| Reviewer Name(s) | Kimberly Lindsey, MD, Medical Officer, Clinical Review Branch, Division of Hematology, OBR |
| Review Completion Date / Stamped Date | August 8, 2011 |
| Sponsor/Applicant | Omrix Biopharmaceuticals |
| Established Name | Fibrin Pad (Human fibrinogen and human thrombin) |
| (Proposed) Trade Name | Evarrest |
| Pharmacologic Class | Biologic Device Combination product |
| Formulation(s), including Adjuvants, etc | EVARREST consists of a composite Matrix coated with human fibrinogen and thrombin. The active side is powdery and the non-active side has an embossed wave pattern. The Matrix 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/in² (7.8 mg/cm²) human fibrinogen and 203.2 IU/in² (31.5 IU/cm²) thrombin |
| Dosage Form(s) and Route(s) of Administration | Topical administration only |
| Dosing Regimen | Dosed to cover area |
| Indication(s) and Intended Population(s) | Proposed Indication: Fibrin Pad is indicated as an adjunct to hemostasis for soft tissue bleeding during retroperitoneal, intra-abdominal, pelvic, and (non-cardiac) thoracic surgery when control of bleeding by standard surgical methods of hemostasis is ineffective or impractical. Proposed Population: Adult patients (over 16 years of age) undergoing “soft tissue” surgery whereby the Fibrin Pad is |

**used as an adjunctive measure to
achieve hemostasis(i.e. after primary methods –
ligature, cautery, suture, to control bleeding
have
been used to address the bleeding)**

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1. EXECUTIVE SUMMARY

Summary of Clinical Findings for the principal clinical study:

The phase 2 study (400-07-002), evaluating the hemostatic efficacy of the Fibrin Pad (FP) when used as an adjunct to hemostasis in mild or moderate soft tissue bleeding during abdominal, pelvic, retroperitoneal, and (non-cardiac) thoracic surgery was a randomized, controlled, study evaluating the superiority of FP compared to Surgicel as an adjunct to hemostasis when conventional methods of control are ineffective or impractical. Main entry criteria included: age greater than or equal to 18 requiring non-emergent abdominal, retroperitoneal, pelvic, or thoracic (non- cardiac) surgical procedures and the presence of an appropriate soft tissue target bleeding site (TBS) as identified intraoperatively by the surgeon.

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 TBS. The primary efficacy endpoint was met.

FDA had advised the sponsor that study 400-07-002 was not designed to support licensure. In addition, review of the submitted data raised safety concerns with regard to thromboembolic events, adhesions and infections. However, the sponsor concluded that “No safety concerns were identified by the study. The incidence of clinically meaningful AEs (adverse events) was similar in the two treatment groups and the events were of the types that were expected following these major surgical procedures.” Since the baseline demographics were matched in the two arms, one cannot exclude that the imbalance in AEs was not product-related. The majority of the adverse events can be traced to common product lots and a specific time frame (last quarter of 2008 to January 2009). The sponsor claims to have thoroughly investigated the manufacturing and use of these lots. They were not able to find a manufacturing or investigator use of the products as explanations for the adverse events. FDA facilities and manufacturing inspections did not reveal any differences in production of FP lots that could reasonably account for the specific lot related thromboembolic events.

From review of the operative reports and case report forms one cannot be certain where the FP or Surgicel was applied (other than in general terms such as thoracic muscle). Since the protocol allowed the use of additional FP or Surgicel (according to assigned treatment) if additional bleeding sites were identified, it is important to know the primary site of application to understand if the product might have been placed in a location that predisposed to thrombotic or other adverse events.

Overall this phase 2 study design comports with a preliminary safety and effectiveness assessment for two categories of bleeding (mild and moderate). It is important to note

that a lack of validated bleeding severity scale limits assessment of product performance, outcome reproducibility and repeatability.

Additional issues identified from the review of the data submitted from study 400-07-002 include the following:

- Sample size per anatomic site was too small for independent assessment per anatomic site;
- Outcomes of device use (hemostasis) and. adverse events may not be poolable across anatomic sites, e.g.: pneumothorax;
- Currently marketed products, vicryl and oxidized regenerated cellulose (ORC) devices are not explicitly indicated for use at anatomic sites of cancer resection. The use of these materials in patients with active oncologic disease should be studied independently to assess influence of local recurrence and progression of oncologic disease, as well as survival.
- The follow up period of the subjects should have been 60 days as the product is expected to fully resorb in 60 days.

Study 400-07-002 was not designed as a pivotal study. The venous thromboembolism (VTE) risk factors, short length of follow up (30 days) and potential thrombotic risk factors suggest that a confirmatory study should be conducted. Based on my review of the clinical data, in order to support an indication for soft tissue surgery for initial US licensure, an additional study with or without different surgical settings, to include additional safety monitoring, should be requested.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

The Fibrin Pad is intended for use 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.

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 Pads are used as an adjunct to these primary methods.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently available adjuncts to hemostasis in the US are:

Devices- gelatin, collagen preparations, absorbable cellulose-based preparations

Biological- EVICEL (human), Recothrom (human) and Thrombin JMI (bovine).

Combination-(usually device/biologic): Tachosil

2.3 Safety and Efficacy of Pharmacologically Related Products

There are a variety of adjuncts to hemostasis regulated primarily by CDRH (devices) and CBER (biologics). Fibrin sealants have, to date, enjoyed a relatively safe history. All fibrin sealants approved by CBER contain the following warning/precaution:

Air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer fibrin sealants. This event appears to be related to the use of the spray device at higher than recommended pressures and in close proximity to the tissue surface.

When applying fibrin sealants using a spray device, be sure to use the pressure within the pressure range recommended by the spray device manufacturer. In the absence of a specific recommendation avoid using pressure above 20-25 psi. Do not spray closer than the distance recommended by the spray device manufacturer. In the absence of a specific recommendation avoid spraying closer than 10-15 cm from the surface of the tissue. When spraying the fibrin sealant, changes in blood pressure, pulse, oxygen saturation and end tidal CO₂ should be monitored because of the possibility of occurrence of air or gas embolism.

In addition, the Highlights of the Prescribing Information has been updated as follows:

Air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer fibrin sealants. These events appear to be related to the use of the spray device at higher than recommended pressures and in close proximity to the surface of the tissue.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Prior Human Experience:

Phase I Study (FL PN 001 IS)

A Phase I study, entitled “A prospective, open label, Phase I study, evaluating the safety of Fibrin Pad in partial nephrectomy” was conducted in Israel and enrolled 10 eligible patients undergoing elective partial nephrectomy.

Objective: Evaluation of the safety of fibrin fleece in open partial nephrectomy surgical procedures

Study Design: Prospective, single-center, open-label, non-randomized, non- controlled.

Number of patients (planned and analyzed): 10 patients were enrolled into the study.

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria: aged 18 to 75 years undergoing elective open partial nephrectomy; willing to participate in the study, and provide written informed consent; negative pregnancy test and using reliable contraception (if applicable).

Intraoperative inclusion criteria: a bleeding site (mild to moderate bleeding) was identified, after conventional surgical techniques had been exhausted; the collection system of the kidney was confirmed to be intact.

Exclusion criteria: any additional surgical intervention which extended beyond the procedure eligible for inclusion into the trial; patients with only 1 functional kidney; known intolerance to blood products or other components of the product; pregnancy or breastfeeding; tumor diameter >4 cm; surgical procedures requiring cooling of the kidney; participation in another investigational drug research study within 30 days of enrollment; patients medically unfit or at major risk if enrolled into the study, e.g. known coagulopathy or recent use of anticoagulants or anti-aggregates; abnormal PT and/or INR >1.3.

Fibrin Fleece was administered topically onto a wound site during surgery.

Fibrin Pad was used in this study as an adjunct to hemostasis (after attempts to control bleeding with conventional surgical techniques had been made). Patients were followed up for 8 weeks post-operatively. Main evaluation parameters in the study included: adverse events, clinically abnormal laboratory and coagulation assessments, time to hemostasis, incidence of treatment failures, occurrence of re-bleedings, number of units applied, amount of intra-operative bleeding, need for blood/blood product transfusion and volume and duration of drainage.

Reviewer Comment: The dataset was very small for safety and efficacy evaluation.

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Study 400-08-002

The final study report for protocol 400-08-002 was submitted on June 13, 2011. An analysis of the final study report is included in this memorandum. (See Section 6 clinical studies)

Liver Surgery Study

There is an ongoing non- IND study conducted outside the US. In this study the FP is being evaluated as an adjunct to hemostasis in hepatic resection. The study proposes to evaluate the ability of the FP to address “more challenging bleeding” –i.e. bleeding that the sponsor contends is more than mild to moderate, but less than severe.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

- | | |
|-----------------|---|
| August 2006- | Request for Designation |
| September 2007- | PreIND meeting for use of the Omrix fibrin pad to treat severe bleeding. FDA noted that regulatory pathway for adjuncts to hemostasis for treatment of severe bleeding has yet to be defined. |
| November 2007- | IND 13563 submitted for use of Omrix fibrin pad to treat mild-moderate bleeding. |
| October 2009- | Pre BLA meeting for the fibrin pad soft tissue surgery indication |

Regulatory Background Information (FDA-Sponsor Meetings, Advisory Committee Meetings, Commitments)

Request for designation (RFD) August 9, 2006:

The product has two modes of action. One action is that of the fibrinogen, modified by the thrombin, to polymerize into a fibrin clot to achieve and maintain hemostasis at the actively bleeding site. The other action is that of the synthetic composite matrix to provide a large and irregular surface area for integration of the biological components and physical support for clot formation on the tissue surface. Since the product’s primary mode of action is attributable to the role of the biological product components in creating hemostasis by means of a fibrin clot formed at the bleeding site, CBER was assigned as the lead center for review of the product.

2.6 Other Relevant Background Information

See Clinical and Regulatory Background Section 2.5 Summary of Pre-submission Regulatory Activity Related to Submission

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices

BIMO issued inspection assignments for three clinical investigators at the following study sites:

| Site Number | Study Site | Location | Number of Subjects | Form FDA 483 Issued |
|-------------|---|---------------------|--------------------|---------------------|
| Site 011 | R. Adams Cowley Shock Trauma Center | Baltimore, MD | 18 | Yes |
| Site 014 | Medical College of Georgia, Section of Urology | Augusta, Georgia | 28 | No |
| Site 022 | University of Alabama, Division of Cardiothoracic Surgery | Birmingham, Alabama | 32 | Yes |

Major findings of BIMO inspections:

- No inspectional issues were found for Ronald Lewis M.D., Medical College of Georgia, Augusta, GA
- An information letter to Robert J. Cerfolio, M.D., University of Alabama, Birmingham, Alabama

Sixteen of thirty two subjects were enrolled in another investigational study while participating in Protocol 400-07-002 at the above site, and there was no documented evidence of sponsor and/or IRB notification and/or approval to enroll the subjects in concurrent studies.

- Grant V. Bochicchio, M.D., M.P.H., R. Adams Cowley Shock Trauma Center, Baltimore, MD

According to section 9.6.1 of the Clinical Study Report, all investigators were required to attend training sessions conducted by James Hart, M.D., Vice-President of Medical Affairs for Ethicon, a Johnson & Johnson Co. located in Somerville, New Jersey

Two clinical investigators, Grant V. Bochicchio and (b)(6), for the study 400-07-002 (US soft tissue surgery study) were issued significant inspectional observations. The following summarize the major observations:

OBSERVATION 1

Failure to prepare or maintain case histories with respect to observations and data pertinent to the investigation.

Specifically, the protocol requires that certain Inclusion and Exclusion criteria be determined by the clinical investigator during surgery, where study specific procedures, such as randomization and the application of the study drug, are to be performed.

Operation Reports for subjects 11104, 11106,11108,11109,11113, 11114,11115, and 11203, which constitute more than a third of the study subjects, do not mention the use of the study drug during surgery, yet this data was submitted to the Sponsor, as stated in the *Soft Tissue Study Worksheets* (found in the subject's records) and in the data listings provided by the Sponsor. For seven of the eight aforementioned subjects, the Attending Surgeon was neither the Clinical Investigator nor the Sub-Investigator

Reference: 21 CFR 312.62(b)

OBSERVATION 2

A study drug was administered to subjects not under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator. Specifically, the *Operation Report* for subject 11112, dictated by ----(b)(6)---- (not listed in the Statement of Investigator, Form FDA 1572), describes the use of the study drug during his surgery but does not mention the Clinical Investigator or Sub-Investigator as being present at any point during the procedure. The *Nurse Intraoperative Report* also does not list the Clinical Investigator or Sub-Investigator as being present during the surgery.

OBSERVATION 3

An investigation was not conducted in accordance with the investigational plan.

Specifically,

A. The protocol states that: "Prior to participation, the study procedures and any known or likely risks will be explained to the subjects by the investigator or other medically qualified co-investigator." In 4 of 18 instances, the study procedures and any known or likely risks were explained to potential subjects (who were eventually enrolled into the study) by Study Coordinators who also signed the Informed Consent Form, when the Clinical Investigator or Sub-Investigator were not available to do so. Except for a letter from the Sponsor dated 03/10/2011, provided to me during the inspection by Dr. Bochicchio, a Co-Investigator is not defined anywhere in the protocol as a Study Coordinator or any other study staff member. This letter states that the term "medically qualified co-investigator" should have been edited as "or designee", yet this is not an edit reviewed and approved by the IRB. Study Coordinators listed in the "Delegation of Authority" for protocol 400-07-002, which is signed by Dr. Bochicchio, are not qualified to practice medicine.

B. There is no evidence that five members from the research study staff, listed in the "Delegation of Authority" as being Study Coordinators, authorized to obtain Informed

Consent, complete Case Report Forms, obtain Medical History and conduct subject follow-up, were qualified and trained on the specifics of the protocol to do so.
Reference: 21 CFR 312.60

B. The “Site Initiation Training” attendance log, dated April 10,2008, provided by -----(b)(4)-----, at the University of Maryland Medical Center, does not list the following individuals as being present during the site initiation training, yet they are listed in the “Delegation of Authority” (Exhibit 3) for this study: ----(b)(6)-----, Sub-Investigator (attended protocol-specific training on 06/24/2008, but was not present at the site initiation), -----(b)(6)-----, Study Coordinator, -----(b)(6)-----, Study Coordinator, -----(b)(6)-----, Study Coordinator, -----(b)(6)-----, Study Coordinator, and -----(b)(6)-----, Study Coordinator.

Clinical Reviewer comments:

The BIMO inspections reveal concerns regarding the conduct of the trial. It is possible, based on practice of medicine, that surgical residents were part of the operative team and the attending surgeon (the investigator) was not present during the entire surgical procedure. As per the protocol, when a target bleeding site was identified, and the attending surgeon was not there, the residents were supposed to apply pressure to the site and wait for the attending to come into the operating room to verify the appropriateness of the site and bleeding intensity. Absence of information such as where the fibrin pad was placed (specific location, not a general one, and where additional investigational product was placed, if any) are critical to analyzing the adverse events. This information was not routinely captured in any of the clinical trials involving the fibrin pad.

There were also questions about investigator training. If the PI was not present during the majority or even part of the surgery, it cannot be ascertained that the FP or Surgical was appropriately applied or that routine procedures were followed?

It is also best if the principal investigator (PI), who was supposed to attend the wet lab demonstration to gain hands on experience with the FP, to consent the patient; not residents or clinical research nurses who are “medically qualified”. The sponsor contends that the intent of the protocol was to allow” medically qualified personnel” (i.e. nurses, PI, sub-investigators or others) to obtain consent. This is an ambiguous definition and raises questions about trial conduct. It is questionable hat all potential medically qualified personnel were sufficiently familiar with the Investigator Brochure and its contents.

Reviewer comment: In the clinical reviewer’s opinion, it raises questions about the adequacy of the Sponsor’s training program to ensure that potential Investigator’s understand what is required in the conduct of a clinical trial and trial site monitoring (i.e. trial conduct issues).

3.3 Financial Disclosures

The sponsor provided an FDA form 3454 Financial Disclosure which states that the sponsor certifies to the following:

Principal Investigators have not entered into any financial arrangement with the clinical investigators “whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a)”

Each listed clinical investigator who was required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests, and

No listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Please refer to CMC reviewer’s, Dr. Natalya Ananyeva, memo.

4.2 Assay Validation

Please refer to CMC reviewer’s, Dr. Natalya Ananyeva, memo.

4.3 Nonclinical Pharmacology/Toxicology

Please refer to Dr. La Nissa Brown-Baker memo.

4.4 Clinical Pharmacology

Product Description:

The fibrin pad is a bio-absorbable combination product and is composed of a flexible composite matrix, coated with human plasma-derived fibrinogen and thrombin. The product is intended to be implanted *in vivo* on actively oozing sites during a single surgical procedure. The pad is an off-white absorbable pad coated with -----(b)(4)----- human biologics, primarily consisting of fibrinogen and thrombin. These biological components are -----(b)(4)----- . The matrix component consists of an oxidized regenerated cellulose (ORC) backing with polyglactin 910 non-woven fibers. The polyglactin 910 fibers are processed into a -----(b)(4)----- onto the ORC to produce the composite matrix. -----

----- (b)(4) -----

----- . The amount of Fibrin pad needed will depend upon the area and location of the bleeding site. Multiple pieces of the product can be applied and the edges overlapped if required to cover the bleeding site.

The active ingredients used to coat the matrix consist of -----(b)(4)----- human fibrinogen and human thrombin. The fibrinogen and thrombin concentrates are prepared from pooled human plasma obtained from licensed suppliers in the United States and tested for HBsAg, HCV-Ab, and HIV-1/HIV-2 Ab. Additional Nucleic Acid Amplification Technology (NAT) testing is

performed, and the biological components also undergo discrete virus inactivation/removal steps. -----

----- (b)(4) -----

----- individually packaged in a tray and foil pouch. The final product is sterilized by electronic beam radiation.

4.4.1 Mechanism of Action

Upon contact with a bleeding wound site, the biological components, fibrinogen and thrombin, on the matrix hydrate and initiate the last steps of blood coagulation as the fibrinogen is converted into fibrin monomers by the thrombin. The fibrin monomers spontaneously polymerize into a fibrin clot, forming a sealing layer that adheres to the tissue surface and integrates into the matrix, allowing for rapid sealing and hemostasis.

The composite matrix acts as a physical support to provide a large and irregular surface area for incorporation of the biologic components and to provide mechanical integrity to the product.

The product is absorbed by the body in approximately 8 weeks (56 days) with 95% of the matrix degraded at that time. The biological components are metabolized by fibrinolysis and phagocytosis, similar to endogenous fibrin.

4.4.2 Human Pharmacodynamics (PD)

Not applicable.

4.4.3 Human Pharmacokinetics (PK)

Not applicable.

4.5 Statistical

The statistical reviewer, John Scott, PhD. verified that the primary endpoint analyses cited by the Sponsor were supported by the submitted data.

4.6 Pharmacovigilance

The sponsor submitted a pharmacovigilance plan; however, based on my review of the data, this is premature, as an additional trial is recommended.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The primary study reviewed was entitled, “Protocol 400-07-002, A Prospective, Randomized, Controlled Superiority Evaluation of Fibrin Patch (Fibrin Pad) as an Adjunct to Control Soft Tissue Bleeding during Abdominal, Retroperitoneal, Pelvic, and Thoracic Surgery”. Additional supportive studies reviewed are listed in the table below under section 5.2.

5.2 BLA/IND Documents Which Serve as the Basis for the Clinical Review

Materials Reviewed by Reviewer:

STN 125392 Modules 1, 3, 4 and 5 of the BLA.

5.3 Table of Studies/Clinical Trials

Table of Clinical Studies

| Study ID | No. of Centers | Study Start Enrollment Status, Date Total Enrollment / Enrollment Goal Study Status | Design & Control Type | Control | Study Objective | # subjects By arm entered/ completed | Duration of treatment | Sex Median Age (range) | TBS Inclusion criteria | Primary Endpoints |
|------------|----------------|---|---|----------|--|--|---|----------------------------|--|--|
| 400-07-002 | 11 US centers | Study complete | A Prospective, Randomized, Controlled Superiority Evaluation of Fibrin Patch (Fibrin Pad) as an Adjunct to Control Soft | SURGICAL | To evaluate the safety and hemostatic effectiveness of the Fibrin Pad (FP) as an adjunct to control soft tissue bleeding | Group 1: 60 Group 2: 30 Non-randomized : 51 Total = 141 | Subject treated intra-operatively only. Safety follow-up through 30-day | Subjects ≥ 18 years of age | The first actively bleeding site identified in the soft tissue with challenging mild to moderate | Proportion of subjects achieving hemostatic success at 4 minutes after randomization with no re-bleeding |

Tissue Bleeding during Abdominal, Retroperitoneal, Pelvic, and Thoracic Surgery

during abdominal, pelvic, retroperitoneal, and (non-cardiac) thoracic surgery.

visit (+ 14-day window)

bleeding, where conventional methods of control (i.e., suture, ligature, cautery) are ineffective or impractical, and an adjunctive product is required to achieve hemostasis. The TBS must be a site where occlusion of the injured tissue surface blood vessels is required to achieve hemostasis. This excludes large defects in large arteries or veins where the injured vascular

requiring treatment during a subsequent 6-minute observation period. Hemostasis is defined as no detectable bleeding at the TBS.

**wall
requires
repair with
maintenanc
e of vessel
patency and
with
persistent
exposure of
the FP to
blood flow
and
pressure
during
healing and
resorption
of the
product. It
must be
possible to
cover the
TBS
adequately,
with an
appropriate
overlap,
using a
single 4 x 4
in. FP as is
necessary to
achieve
hemostasis.**

STN 125392 Omrix Fibrin Pad

| Study ID | No. of Study Centers | Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal Study Status | Design & Control Type | Control | Study Objective | # subjects By arm entered/ completed | Duration of treatment | Sex Median Age (range) | TBS Inclusion criteria | Primary Endpoints |
|-------------------------------------|----------------------|--|---|-----------------------|--|--------------------------------------|------------------------------|------------------------|--|---|
| FL-PN IS (Phase 1) | | Study complete | A Prospective, Open-Label, Phase I Study Evaluating the Safety of Fibrin Fleece in Partial Nephrectomy | Not applicable | Evaluation of the safety of fibrin fleece in open partial nephrectomy surgical procedures | 10 | Single Administration | 18 to 75 years | Subjects 18 to 75 years undergoing elective open partial nephrectomy; with a bleeding site (mild to moderate bleeding) identified, after conventional surgical techniques had been exhausted and the collection system of the kidney was confirmed to be intact | Efficacy was not evaluated during the study. |

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

Not applicable.

5.4.2 External Consults/Collaborations:

CDRH medical officer consultation Roxolana Horbowyj MD:

The following excerpt from the consultation memorandum summarizes the Medical Officer consultative review:

SUMMARY

- Overall, phase 2 study design represents pilot (exploratory / proof of concept / preliminary safety and effectiveness assessment) study for two categories of bleeding severity, which are not objectively defined.
- Lack of a validated bleeding severity scale limits assessment of product performance, outcome reproducibility and repeatability,
- Sample size per anatomic site were too small for independent assessment per anatomic site;
- Outcomes of device use (hemostasis) and AEs(sic. adverse events) are not poolable across anatomic sites, e.g.: pneumothorax;
- There are notably higher incidence of abscess (all types) and pneumothorax in the investigational arm;
- Not all deep venous thrombosis (DVT) / pulmonary embolus (PE) cases can be clearly considered likely not related to the investigational product (Fibrin Pad).

Dr. Horbowyj also noted that currently marketed products, vicryl and oxidized regenerated cellulose (ORC) devices are not explicitly indicated for use at anatomic sites of cancer resection. The use of these materials in patients with active oncologic disease should be studied independently to assess influence of local recurrence and progression of oncologic disease, as well as survival.

5.5 Literature Reviewed

References

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.

Synopsis:

The article describes results from a randomized double blind placebo controlled multicenter evaluation of recombinant human thrombin (rh thrombin) in four surgical settings: arteriovenous (AV) graft formation for hemodialysis access, major hepatic resection, peripheral arterial bypass surgery (PAB), and spinal surgery

Recombinant human Thrombin was evaluated in combination with absorbable gelatin sponges or Surgifoam. There were no major differences in adverse event rates between the two treatment groups.

This article was reviewed to get information on adverse event rates seen routinely during general surgery procedures.

Cheng, CM et al. A review of three stand-alone topical thrombins for surgical hemostasis 2009, Clin Ther. 31(1):32-41.

Synopsis:

This review evaluated the literature on the efficacy and safety of Recothrom, Evithrom and Thrombin JMI. The article confirmed that bovine thrombin does carry the risk of formation of cross reactive antibodies to bovine thrombin and factor V. The article did not find studies comparing the human products, the highly purified bovine thrombin preparation or placebo controlled studies involving bovine thrombin.

Overall the information from the article did not conclude that bovine thrombin was safer than the recombinant or human thrombin preparations.

This article was reviewed in the context of the immunogenicity study that the sponsor conducted for the FP.

Smith, Brian, R. et al. Deep Venous Thrombosis After General Surgical Operations at a University Hospital, 2011 Ach Surg., (204) E1-E4

Synopsis:

This was a retrospective data review to characterize the location, incidence and timing of deep venous thrombosis after general surgical procedures.

The authors concluded that, “In the presence of prophylaxis, the incidence of DVT after general surgical operation is low, with more than 80% of cases diagnosed in the inpatient setting. Since more than half of the DVTs are catheter induced, efforts for DVT prevention should include more attention to the need for a central catheter, limiting the amount of time of a central catheter, and possibly the use of anticoagulation in the presence of a central catheter.”

The article also included an outpatient checklist for assessing DVT risk.

The article was reviewed to gain more insight as to the incidence of DVT in the surgical setting, to understand current DVT prophylaxis regimens and DVT risk categories.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1:

Protocol 400-07-002: “A Prospective, Randomized, Controlled Superiority Evaluation of Fibrin Patch (Fibrin Pad) as an Adjunct to Control Soft Tissue Bleeding during Abdominal, Retroperitoneal, Pelvic, and Thoracic Surgery”

6.1.1 Objectives (Primary, Secondary, etc)

To evaluate the safety and hemostatic effectiveness of the Fibrin Patch (FP) as an adjunct to control soft tissue bleeding during abdominal, pelvic, retroperitoneal, and non-cardiac thoracic surgery.

6.1.2 Design Overview

This 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. The sample size required for the trial was not fixed. Subjects were to be randomized with a 2:1 allocation ratio of Fibrin Patch to Surgicel. Subjects were stratified according to bleeding severity: mild or moderate.

The trial was monitored using a sequential triangular test. This method allowed for interim analysis at any number of patients enrolled, however, the first interim analysis for the proposed study was after the first 90 patients. The interim analyses were to determine whether recruitment should be halted or continued based upon efficacy data analyzed by the sequential triangular test. An independent biostatistician conducted the analysis. If randomization was continued, after the first analysis, subsequent interim analyses were to be performed after every additional 30 subjects were enrolled into the study. Randomization was to be stopped once a stopping boundary had been crossed. The expected number of randomized subjects was between 90 and 180; not exceed 210. Additional non-randomized subjects were continued to be enrolled and treated with FP, until a minimum of 200 subjects were enrolled in the FP arm.

A Data Safety Monitoring Board (DSMB) was established and had the responsibility for the review of data and identification of any potential safety issues throughout the study. If necessary, the DSMB was to make recommendations regarding protocol revisions, and recommend whether the study should proceed based on the safety data considering established stopping rules.

Subjects were followed for safety and efficacy parameters throughout the study period. After study completion following the 30 day visit (+ 14 days), an additional blood draw at 8 weeks (=14 days) was required for potential antibody testing.

6.1.3 Population

Subjects undergoing non-emergent abdominal, retroperitoneal, pelvic or thoracic (non cardiac surgery procedures, wherein an appropriate soft tissue TBS (target bleeding site) is identified.

Eligibility Criteria:

Inclusion:

1. Age greater than or equal to 18 requiring non-emergent abdominal, retroperitoneal, pelvic, or thoracic (non-cardiac) surgical procedures
2. Presence of an appropriate soft tissue TBS as identified intraoperatively by the surgeon
3. Willing to participate in the study and written informed consent

Exclusion:

1. Intra-operative findings identified by surgeon that may preclude conduct of study procedure
2. TBS within an actively infected field

3. Bleeding site in around or in proximity to foramina in bone, or areas
4. Subjects with known intolerance to blood products or to one of the components of the study product
5. Subjects unwilling to receive blood products
6. Subjects with immunodeficiency diseases (including HIV)
7. Subjects who are known , current alcohol abusers and/or drug abusers
8. Participation in another investigational drug or device study within 30 days of enrollment
9. Pregnant or nursing

Number of Subjects:

The expected number of randomized subjects was between 90 and 180; not to exceed 210. Additional non-randomized subjects continued to be enrolled and treated with FP, until a minimum of 200 subjects are enrolled in the FP arm.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The TBS (target bleeding site) was identified during the soft tissue dissection related to the primary operative procedure. This was the site selected for evaluation of hemostatic effectiveness. However, up to 4 pads could be left *in situ* per patient. Additional FP or Surgicel units were permitted.

The TBS was to be the only soft tissue site or region to be evaluated for hemostasis in this clinical study. Parenchymal, vascular anastomotic or gastrointestinal/ genitourinary organ bleeding sites were not to be included.

Surgical procedures:

Surgical procedures with challenging soft tissue target bleeding sites deemed appropriate for evaluation included, but were not limited to the following:

- Abdominoperitoneal resection
- Adrenalectomy
- Cystectomy
- Colectomy (with or without anal anastomosis)
- Gastrectomy
- Lymphadenctomy
- Low anterior resection
- Pancreatectomy
- Pyeloplasty
- Primary tumor reduction surgery (i.e. for ovarian cancer)
- Radical prostatectomy
- Radical pancreaticoduodenectomy
- Radical hysterectomy
- Radical cystectomy
- Retroperitoneal tumor resection
- Simple or radical nephrectomy

TBS Bleeding Intensity Definitions:

Mild Bleeding:

A TBS with a small area of capillary, arteriole or venule oozing

Moderate Bleeding:

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

OR

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

Once the TBS was identified, and the bleeding severity was classified, the surgeon randomized the subject into the study. The bleeding severity described the intensity of the bleeding that was present at the TBS at the time that the surgeon determined that an adjunctive hemostatic product was required (because conventional methods were ineffective or impractical). The TBS was stratified into two groups, according to bleeding severity: mild to (*sic* or) moderate.

The FP or Surgicel was applied immediately at the actively bleeding TBS. Manual compression was applied continuously for each treatment group until 4 minutes post randomization. Hemostasis was assessed at 4 minutes from randomization, and following an additional 6 minute observational period. Success was defined as the achievement of hemostasis at 4 minutes and no further bleeding requiring treatment during the additional 6 minute observation period.

6.1.5 Sites and Centers

Multiple US sites. The following table found in section 16.1.4 of protocol 400-07-002 was provided by the Sponsor:

16.1.4.1 *Principal Investigators and Site Information*

| Center | Principal Investigator | Institution | Address |
|--------|--|--|---|
| 11 | Bochicchio, Grant | University of Maryland Medical Center | 22 South Greene St. Baltimore, MD 21201 |
| 22 | Cerfolio, Robert | University of Alabama Division of Cardiothoracic Surgery | 739 Zeigler Building 703 19th Street South Birmingham AL 35294-0007 |
| 12 | Fischer, Craig (Co-ordinating Investigator) | Weill Medical College of Cornell University Department of Surgery | The Methodist Hospital 6550 Fannin Street, SM 1661 Houston, Texas 77030 |
| 13 | Henry, Gavin | St. Agnes Healthcare, Inc Clinical Research Center | 900 Caton Avenue Box 212 Baltimore, MD 21229 |
| 14 | Lewis, Ronald | Medical College of Georgia Department of Surgery Surgical Research Service | CJ-1117 1120 15th Street Augusta, GA 30912-4005 |
| 15 | Miller, Daniel | Chief of Thoracic Surgery Emory University Hospital | 1365 Clifton Road, NE Suite 2200 Atlanta, Georgia 30322 |
| 21 | Mosca, Paul | Department of Surgery Lehigh Valley Hospital | 1200 S. Cedar Crest Blvd. GSB 2nd Floor Allentown, PA 18103 |
| 19 | Roychoudhury, Ashok | Jacksonville Center for Clinical Research | 4085 University Blvd. South, Suite 1 Jacksonville, FL 32216 |
| 23 | Viamonte, Manuel | Mercy Hospital | 9195 Sunset Drive Suite 230 Miami FL 33173 |
| 20 | Wood, Christopher | The U of Texas M.D. Anderson Cancer Center | 1515 Holcombe Boulevard Houston, TX 77031 |
| 16 | Zeltsman, David | Long Island Jewish Medical Center Division of Thoracic Surgery | 410 Lakeville Rd Suite 203 New Hyde Park NY 11040 |

6.1.6 Surveillance/Monitoring

SCHEDULED ASSESSMENTS

| Procedure | Screening ³ | Baseline | Surgical Procedure | Post-surgery to hospital discharge | 30-Day Follow-up (+ 14 days) |
|--|------------------------|----------|--------------------|------------------------------------|------------------------------|
| Inclusion/ Exclusion | X | X | X | | |
| Demographics | X | | | | |
| Medical History | X | | | | |
| Concomitant Medications | X | X | X | X | X |
| Physical exam | X | | | X | X |
| CBC w/diff | X | X | | X | X |
| Coagulation studies | X | X | | X | X |
| Pregnancy tests | X | X | | | |
| Additional lab (antibody)² | | X | | | X |
| Randomization | | | X | | |
| Product application | | | X | | |
| Intra-operative details | | | X | | |
| Determination of Hemostasis at TBS | | | X | | |
| Use of other hemostatic Measures | | | X | | |
| Bleeding, thrombotic, and Transfusion related Complications | | | X | X | X |
| Adverse events | | | X | X | X |
| Operative/ Surgical¹ information | | | X | X | |
| Informed consent | X | | | | |

¹ including length of stay (ICU and overall length of stay), transfusion information, ease of use

² An additional antibody test will be required at least 8 weeks (+ 14 days) after the date of surgical procedure

³ At least one CBC with differential, coagulation parameter, and pregnancy test are needed pre-procedure. If pre-operative blood tests are repeated, the blood test closest to the date prior to study start was used.

Reviewer comment:

After study was nearly completed it was ascertained by the pharm- tox reviewer that the actual resorption time was at least 60 days and since this absorption time is largely due to the device component, CBER suggested that in all subsequent trials, the follow up period should comport with the CDRH standard of following patients until the product is completely absorbed. In this case, the recommended follow up period should be at least 60 days. CBER communicated this to the sponsor and the sponsor incorporated this suggestion in an amended protocol for the soft tissue surgery study conducted outside of the US (i.e. study protocol 400-08-002).

6.1.7 Endpoints and Criteria for Study Success

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 TBS.

Secondary Endpoints

- Proportion of subjects achieving hemostatic success at 10 minutes following randomization (Success at 10 minutes was defined as the achievement of hemostasis within 10 minutes and no further bleeding requiring treatment during the final 6 minute observation period)
- Incidence of treatment failures (if hemostasis was not achieved within 4 minutes or if bleeding requiring additional intervention during the 6 minute observation period)
- Incidence of adverse events that were potentially related to the bleeding at the TBS
- Incidence of adverse events that were potentially related to thrombotic events
- Incidence of adverse events potentially related to transfusion exposure (TRALI (transfusion related acute lung injury), MOF (multiple organ failure) , infection, transfusion reactions
- Incidence of re-treatment at the TBS
- Incidence of adverse events

6.1.8 Statistical Considerations & Statistical Analysis Plan

Stopping Rules and Study Discontinuation Criteria:

A third party DSMB composed of two surgeons and one statistician reviewed safety and effectiveness data as prospectively described in the DSMB charter document. If one of the following occurred during the enrollment period, the study was suspended until the Data Safety Monitoring Board (DSMB), together with the sponsor, reviewed the data and a decision was made whether or not to continue the study:

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

- Three or more patients had intra-operative TBS re-bleeding events following final observation period that required re-intervention
- One or more patients developed a serious adverse event related to TBS post operative re-bleeding. The relatedness of a post-operative TBS bleeding SAE was determined via the following modalities: findings at re-operation, imaging studies demonstrating TBS rebleeding, or findings of TBS rebleeding at autopsy (if applicable).

Statistical Analysis Plan:

The statistical hypothesis for testing the treatment difference:

Ho: $P_C = P_F$

H1: $P_C \neq P_F$

Where P_C is the proportion of success in control patients and P_F is the proportion of success in fibrin Patch patients.

The triangular test for a binary response variable was utilized with a two-sided alpha 0.05 and power 0.90. The assumed success rate in the control arm was 50% and in the Fibrin Patch arm was 75%. Assumptions were based on the results of control arm success in the FS2 Retroperitoneal study BB-IND (b)(4).

6.1.9. Results

6.1.9.1 Populations Enrolled/Analyzed

6.1.9.1.1 Demographics Reproduced from Sponsor table 14.1.2.1 and confirmed by reviewer

| Variable | Category /Statistic | Surgical (n=30) | FP Randomized (n=60) | FP Non-Randomized (n=51) | Total (n=141) |
|---------------------|----------------------------|------------------------|-----------------------------|---------------------------------|----------------------|
| Age (years) | Mean (std) | 58.5(14.4) | 59.9(11.8) | 63.4(10.8) | 60.9(12.1) |
| | Median | 58.0 | 59.5 | 65.0 | 62.0 |
| | (range) | (26.0,89.0) | (35.0,85.0) | (31.0,84.0) | (26.0,89.0) |
| Age (grouped,years) | 18-<50 years | 9(30.0%) | 11(18.3%) | 5(9.8%) | 25(17.7%) |
| | 50-<65 years | 12(40.0%) | 28(46.7%) | 19(37.3%) | 59(41.8%) |
| | 65-<75 years | 5(16.7%) | 12(20.0%) | 20(39.2%) | 37(26.2%) |
| | >=75 years | 4(13.3%) | 9(15.0%) | 7(13.7%) | 20(14.2%) |

No difference was seen in the baseline demographics in the three groups

6.1.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

The types of operations were well balanced between the control and FP arms

Anatomical Location of TBS (safety set) source: section 14, tables 14.1.3.2 and 14.1.3.2a

| Anatomical Location | FP | | | Total |
|---------------------|----------------------|----------------------|---------------------|------------|
| | Randomized N = 60 | SURGICEL (N = 30) | FP All (N = 111) | |
| Retroperitoneal | 22 (36.7%) | 11 (36.7%) | 49 (44.1%) | 60 (42.6%) |
| Thoracic | 22 (36.7%) | 10 (33.3%) | 40 (36.0%) | 50 (35.5%) |
| Pelvic | 12 (20.0%) | 7 (23.3%) | 16 (14.4%) | 23 (16.3%) |
| Abdominal | 4 (6.7%) | 2 (6.7%) | 6 (5.4%) | 8 (5.7%) |

Tissue Type at Target Bleeding Site (safety set) Source: Tables 14.1.3.2 and 14.1.3.2a

| Tissue Type | FP | | | Total (N = 141) |
|----------------|------------------------|----------------------|---------------------|--------------------|
| | Randomized (N = 60) | SURGICEL (N = 30) | FP All (N = 111) | |
| Lymph node bed | 20 (33.3%) | 8 (26.7%) | 36 (32.4%) | 44 (31.2%) |
| Fat | 15 (25.0%) | 5 (16.7%) | 30 (27.0%) | 35 (24.8%) |
| Loose areolar | 10 (16.7%) | 5 (16.7%) | 17 (15.3%) | 22 (15.6%) |
| Muscle | 10 (16.7%) | 3 (10.0%) | 10 (9.0%) | 13 (9.2%) |
| Lymphatic | 1 (1.7%) | 2 (6.7%) | 2 (1.8%) | 4 (2.8%) |
| Other | 4 (6.7%) | 7 (23.3%) | 16 (14.4%) | 23 (16.3%) |

6.1.9.1.3 Subject Disposition

A total of 141 subjects were enrolled in study 400-07-002. Ninety subjects were randomized (60 to FP and 30 to Surgicel), and the remaining 51 were treated with FP in the non-randomized portion of the study. All 141 enrolled subjects received the allocated study treatment. Of the 141 subjects enrolled, 126 (89%) completed the study as planned. The disposition of the remaining 15 subjects was as follows: two subjects withdrew consent prior to study completion, four subjects were lost to follow-up post-operatively, seven subjects died prior to study completion, one subject was unwilling to travel to the center for follow-up and one subject was withdrawn because the clinic failed to notify the study site coordinator of visit rescheduling. Table 4 below from the sponsor's clinical study report summarizes this information by treatment group:

Text Table 4: Reasons for Failure to complete Study as Planned

| | FP | | | Total N=141 |
|------------------|--------------------|---------------------------|------------------|----------------|
| | Randomized N=60 | FP Non-Randomized N=51 | SURGICEL N=30 | |
| Withdrew Consent | 1 (1.7%) | 1 (2.0%) | 0 (0.0%) | 2 (1.4%) |

| | | | | |
|-----------|----------|----------|----------|----------|
| Lost to | | | | |
| Follow-up | 0 (0.0%) | 2 (3.9%) | 2 (6.7%) | 4 (2.8%) |
| Death | 2 (3.3%) | 4 (7.8%) | 1 (3.3%) | 7 (5.0%) |
| Other | 1 (1.7%) | 0 (0.0%) | 1 (3.3%) | 2 (1.4%) |

There were 180 documented protocol deviations, the most common of which were visit out of window and failure to perform specified laboratory tests. Four of the deviations were classified by study personnel as ‘major’; these are summarized in Table 6 of the clinical study report.

Major Protocol Violations

| Subject # | Treatment | Deviation Category | Details |
|-----------|-----------------------|------------------------------|--|
| 21-103 | FP Randomized | Randomization | Prior to the randomization procedure, envelope 21102 was misplaced, making 21103 the next sequential number to randomize for mild bleeding. The subject was treated as randomized. |
| 22-114 | FP Randomized | Study Procedure | PT, APTT and INR not performed prior to the procedure |
| 12-201 | FP Randomized | Inclusion/Exclusion Criteria | The TBS did not meet the criteria described in the protocol.* |
| 14-108 | FP non- randomized | Study Procedure | FP was not applied according to protocol (i.e. was applied upside-down) |

6.1.10 Efficacy Analyses

6.1.10.1 Analyses of Primary Endpoint(s)

Where is the information on the primary efficacy endpoint?
From statistical reviewer’s (John Scott, PhD) memo:

“Analyses of Secondary Endpoints The pre-specified logistic regression analyses for the secondary endpoints were not provided in the clinical study report. Results from these analyses were requested by CBER in a Deficiencies letter dated January 31, 2011, and were provided by the sponsor in Amendment 3 to the BLA submission on March 17, 2011. These results are presented in the table labeled Stats Output 16.1.9.2.1. There were nominally statistically significant advantaged for FP relative to Surgicel on the secondary endpoints of 10-minute hemostasis, treatment failure, TBS retreatment, bleeding-related AE incidence. There was no statistically significant difference in incidence of potential thrombotic-related AEs. The p-values from these analyses should be interpreted with caution, as the secondary endpoints are strongly correlated with the primary endpoint, and no adjustment has been made to the secondary endpoint analyses for the triangular test monitoring as described in Section 5.8 of Whitehead, 1992.”

Stats Output 16.1.9.2.1
Secondary effectiveness - Model including treatment and center
ITT analysis set

| Variable | Category | Treatment | | Log-Odds-Ratio ^ (Fibrin Pad/Surgicel) | | p-value |
|--------------------------------|----------|----------------------|--------------------|---|-------------------|---------|
| | | Fibrin Pad (N=60) | Surgicel (N=30) | Estimate | 95% C.I. Limit | |
| Success at 10 mins(secondary)& | Yes | 59(98.3%) | 22(73.3%) | 2.446 | (0.908, 3.983) | 0.0003 |
| | No | 1(1.7%) | 8(26.7%) | | | |
| Treatment failure + | Yes | 1(1.7%) | 14(46.7%) | -2.856 | (-4.231, -1.481) | <.0001 |
| | No | 59(98.3%) | 16(53.3%) | | | |
| Any TBS retreatment (incl SoC) | Yes | 1(1.7%) | 14(46.7%) | -2.856 | (-4.231, -1.481) | <.0001 |
| | No | 59(98.3%) | 16(53.3%) | | | |
| Potential bleeding related | Yes | 0(0.0%) | 3(10.0%) | -2.110 | (-4.207, -0.014) | 0.0305 |
| | No | 60(100.0%) | 27(90.0%) | | | |
| Potential thrombotic related | Yes | 1(1.7%) | 2(6.7%) | -1.193 | (-3.532, 1.145) | 0.0826 |
| | No | 59(98.3%) | 28(93.3%) | | | |

“In addition to the ITT and PP analyses, the Sponsor provided a summary of hemostatic efficacy for the safety set, comprised of control subjects and both randomized and non-randomized FP subjects (Table 16). The non-randomized FP subjects showed similar hemostatic success to the randomized FP subjects.”

Text Table 16 Summary of Hemostatic Efficacy (Safety Set)

| Parameter | FP All N=111 | SURGICEL N=30 | Treatment Difference |
|---|--------------------|------------------|-------------------------|
| Hemostasis at 4 min; no rebleeding during 6 min observation period | 109/111 (98.2%) | 16/30 (53.3%) | 44.90% |
| Hemostasis at 10 min; no rebleeding during final 6 min observation period | 110/111 (99.1%) | 22/30 (73.3%) | 25.80% |
| No retreatment of the TBS required (including use of SoC) | 109/111 (98.2%) | 16/30 (53.3%) | 44.90% |
| No re-bleeding at TBS between final observation and wound closure | 111/111 (100%) | 27/30 (90%) | 10% |

6.1.10.3 Subpopulation Analyses

There were no analyses by gender, race, age or other subgroup populations specified in the protocol, and the sponsor did not present the results of any such analyses.

6.1.10.4 Dropouts and/or Discontinuations

Most of the drop outs were due to death from progressive disease. Only two subjects withdrew consent. Four subjects (2 FP non randomized and 2 Surgicel) were lost to follow up. Overall 30 day follow up assessments (excluding laboratory evaluations) were completed for 59 FP randomized subjects, 45 FP non-randomized subjects and 27 Surgicel subjects. These dropouts/ discontinuations are not expected to influence the overall conclusions from the study.

6.1.10.5 Exploratory and Post Hoc Analyses

Per the request of FDA (IR dated 5/31/2011) the sponsor provided a post hoc summary of estimated VTE (venous thromboembolism) Scores by treatment allocation. The information was requested because the sponsor concluded that the trend toward the increased VTE's in the FP was related to the number of VTE risk factors per patient in the FP arm. It should be noted that the estimated VTE risk scores in the SoC and FP patient populations are not significantly different. Furthermore, this VTE risk stratification is post hoc. Information regarding VTE prophylaxis during and post surgery were not uniformly available for all patients, particularly for those patients who experienced thromboembolic adverse events during the clinical trial period.

Safety analysis dataset

| Variable | Statistical measure | FP all (N=111) | Surgicel (N=30) |
|--------------------------|---------------------|-----------------|-----------------|
| Estimated VTE risk score | Mean (std) | 6.6 (1.3) | 6.1 (1.2) |
| | Median (range) | 7.0 (2.0, 10.0) | 6.0 (3.0, 8.0) |
| | Number (missing) | 111 (0) | 30 (0) |
| | 95% CI of mean | 6.4,6.8 | 5.7, 6.6 |

Reviewer comment: The patients were at high risk for VTE's; however, it is noted that in many cases the preoperative and postoperative VTE prophylaxis regimens for individual patients was not specified. In a future trial, a formal Thrombosis Risk Factor assessment should be completed for all subjects.

6.1.11 Safety Analyses

6.1.11.1 Methods

Adverse event tables for the entire safety population were submitted by the sponsor. These tables are reproduced herein in their entirety. Reviewer tables for adverse events were generated using different groupings for medical conditions and special adverse events that might be seen with the product due to its composition and implantation *in vivo*. The review AE tables are as follows according to adverse events per patient and per episode reported in verbatim terms and preferred terminology MedDRA version 8.1.

6.1.11.2 Overview of Adverse Events

According to the sponsor, the following tables reflect the adverse events during/post treatment) for the safety analysis set. Note that the numbers and percentages refer to patients not episodes or events.

Adverse events with a frequency difference between treatments of $\geq 5\%$ (Safety Set)

(Source: Text table 25)

| System Organ Class | Preferred Term | Number (%) of Subjects Experiencing Event | |
|--|------------------------|---|-------------------|
| | | FP All (N = 111) | SURGICEL (N = 30) |
| Blood and Lymphatic System Disorders | Anemia | 19 (17.1%) | 7 (23.3%) |
| | Leukocytosis | 13 (11.7%) | 5 (16.7%) |
| Gastrointestinal disorders | Constipation | 23 (20.7%) | 4 (13.3%) |
| | Nausea | 46 (41.4%) | 14 (46.7%) |
| General Disorders and Administration Site Conditions | Edema | 1 (0.9%) | 3 (10.0%) |
| | Pyrexia | 22 (19.8%) | 12 (40.0%) |
| Infections and Infestations | Abdominal Infection | 1 (0.9%) | 3 (10.0%) |
| | Operative Hemorrhage | 1 (0.9%) | 3 (10.0%) |
| Injury, Poisoning and Procedural Complications | Postoperative Ileus | 2 (1.8%) | 3 (10.0%) |
| | Procedural Hypotension | 4 (3.6%) | 3 (10%) |
| Investigations | Urine Output Decreased | 6 (5.4%) | 0 (0.0%) |
| | Hypocalcemia | 13 (11.7%) | 8 (26.7%) |
| Metabolism and Nutrition Disorders | Hypoglycemia | 1 (0.9%) | 2 (6.7%) |
| | Hypomagnesemia | 44 (39.6%) | 15 (50.0%) |
| Musculoskeletal and Connective Tissue Disorders | Hypophosphatemia | 24 (21.6%) | 10 (33.3%) |
| | Hypovolemia | 9 (8.1%) | 0 (0.0%) |
| Psychiatric Disorders | Muscle Spasms | 1 (0.9%) | 2 (6.7%) |
| | Insomnia | 8 (7.2%) | 5 (16.7%) |
| Respiratory, Thoracic and Mediastinal Disorders | Pneumothorax | 13 (11.7%) | 2 (6.7%) |
| | Rhonchi | 6 (5.4%) | 4 (13.3%) |
| Vascular Disorders | Hypertension | 13 (11.7%) | 2 (6.7%) |

Reviewer Adverse Event Tables:

Test= Fibrin Pad (FP) , N=111

Control= Surgicel Original, N=30

NOS= not otherwise specified

| Study No.: 400-07-002 | | | | |
|---|--------------------------------|-------------------------------|---------------------------------------|-------------------------------------|
| Treatment Emergent AEs | FP (No of subjects) | FP (No. of events) | Surgical (No. of subjects) | Surgical (No. of events) |
| Death | 6 | 6 | 1 | 1 |
| Hypertension/BP increased/hypertensive crisis/malignant hypertension/systolic hypertension/SVR | | | | |
| Hypertension | 13 | 15 | 2 | 2 |
| Chest pain/pressure/tightness | 2 | 2 | 2 | 2 |
| Pulmonary edema | 6 | 6 | 1 | 1 |
| Fluid /volume overload | 7 | 8 | 2 | 2 |
| CVA, TIA, cerebral infarct, etc | | | | |
| Stroke | 1 | 1 | 0 | 0 |
| Pneumonia, aspiration pneumonia, respiratory failure/insufficiency | | | | |
| Pneumonia- Klebsiella | 0 | 0 | 1 | 1 |
| Pneumonia | 8 | 8 | 3 | 4 |
| Pleural effusion | 13 | 16 | 5 | 5 |
| Effusion (NOS) | 1 | 1 | 0 | 0 |
| Respiratory distress.etc | | | | |
| ARDS | 1 | 1 | 0 | 0 |
| Respiratory distress | 4 | 4 | 1 | 1 |
| Atelectasis | 21 | 20 | 5 | 5 |
| Resp failure | 4 | 5 | 1 | 1 |
| Shortness of breath | 5 | 5 | 2 | 2 |
| Rhonchi/wheezing | 6 | 6 | 4 | 4 |
| Pulmonary fistulae | | | | |

Study No.: 400-07-002

| Treatment Emergent AEs | FP (No of subjects) | FP (No. of events) | Surgical (No. of subjects) | Surgical (No. of events) |
|-------------------------------|----------------------------|---------------------------|-----------------------------------|---------------------------------|
| Bronchopleural fistula | 0 | 0 | 2 | 2 |
| Alveolar fistula | 5 | 5 | 1 | 1 |
| Anastomotic leak | 1 | 1 | 0 | 0 |

Other pulmonary

| | | | | |
|--------------|----|----|---|---|
| Pneumothorax | 11 | 13 | 1 | 1 |
| Hemothorax | 0 | 0 | 1 | 1 |
| Air leak | 2 | 2 | 0 | 0 |

Oliguria, etc.

| | | | | |
|------------------------|---|---|---|---|
| Oliguria | 4 | 4 | 0 | 0 |
| Renal failure- acute | 1 | 1 | 2 | 2 |
| Renal failure | 0 | 0 | 0 | 0 |
| Urinary retention | 4 | 4 | 1 | 1 |
| Elevated renal values | 0 | 0 | 1 | 1 |
| Decreased urine output | 3 | 3 | 0 | 0 |

Hypoxia, etc.

| | | | | |
|---------|---|---|---|---|
| Hypoxia | 4 | 4 | 1 | 1 |
|---------|---|---|---|---|

Hypovolemia

| | | | | |
|-------------|---|---|---|---|
| Hypovolemia | 6 | 6 | 0 | 0 |
| Dehydration | 5 | 5 | 0 | 0 |

Gastrointestinal pain, nausea, vomiting

| | | | | |
|---------------------------------|----|----|----|----|
| Abdominal pain | 1 | 1 | 0 | 0 |
| Vomiting | 11 | 11 | 1 | 1 |
| Nausea | 45 | 50 | 14 | 16 |
| Ileus | 13 | 13 | 6 | 6 |
| Abdominal distention | 2 | 2 | 0 | 0 |
| Partial small bowel obstruction | 1 | 1 | 0 | 0 |
| Small bowel obstruction | 2 | 2 | 0 | 0 |
| Perforated jejunum with sepsis | 1 | 1 | 0 | 0 |
| Pseudo obstruction | 1 | 1 | 0 | 0 |

Study No.: 400-07-002

| Treatment Emergent AEs | FP (No of subjects) | FP (No. of events) | Surgical (No. of subjects) | Surgical (No. of events) |
|---------------------------------|--------------------------------|-------------------------------|---------------------------------------|-------------------------------------|
| Fistula | | | | |
| Fistula (NOS) | 0 | 0 | 1 | 1 |
| Pancreatic fistula | 0 | 0 | 1 | 1 |
| Bile leak | 1 | 1 | 0 | 0 |
| Hepatobiliary/pancreatic | | | | |
| Pancreatitis | 1 | 1 | 0 | 0 |
| Coagulation | | | | |
| Coagulopathy | 0 | 0 | 1 | 1 |
| DIC | 1 | 1 | 0 | 0 |
| Thrombocytopenia | 1 | 1 | 1 | 1 |
| Increased INR | 1 | 1 | 1 | 1 |
| DVT | 1 | 1 | 1 | 1 |
| Pulmonary embolism | 4 | 4 | 1 | 1 |
| Thromboembolic event | 1 | 1 | 0 | 0 |
| Blood clot in trachea | 1 | 1 | 0 | 0 |
| Embolism infarct to small bowel | 1 | 1 | 0 | 0 |
| anemia | 19 | 19 | 7 | 7 |
| GI hemorrhage | 1 | 1 | 2 | 2 |
| Post-op hemorrhage | 1 | 1 | 0 | 0 |
| Hypotension | 16 | 16 | 0 | 0 |
| TBS bleed | 0 | 0 | 3 | 3 |
| Worsened low hematocrit | 1 | 1 | 1 | 1 |
| Retroperitoneal bleed | 1 | 1 | 0 | 0 |
| Rebleed | 1 | 1 | 0 | 0 |
| Sepsis/septic shock | | | | |
| Sepsis | 2 | 2 | 0 | 0 |
| Septic shock | 1 | 1 | 0 | 0 |
| Multiple organ failure | 0 | 0 | 0 | 0 |
| SIRS | 0 | 0 | 1 | 1 |
| Infection | | | | |
| Infection | 14 | 17 | 6 | 6 |
| Abscess | 2 | 2 | 3 | 3 |
| Cellulitis | 2 | 3 | 1 | 1 |
| Leukocytosis | 13 | 14 | 5 | 5 |

Study No.: 400-07-002

| Treatment Emergent AEs | | FP (No of subjects) | FP (No. of events) | Surgical (No. of subjects) | Surgical (No. of events) |
|-------------------------------|----|--------------------------------|-------------------------------|---------------------------------------|-------------------------------------|
| Peritonitis | | 1 | 1 | 0 | 0 |
| GI virus/gastroenteritis | | 1 | 2 | 0 | 0 |
| MI, etc | | | | | |
| Myocardial infarction | 2 | 2 | 0 | 0 | |
| Angina pectoris | 1 | 1 | 0 | 0 | |
| Cardiac arrhythmias | | | | | |
| Arrhythmia | 1 | 1 | 0 | 0 | |
| Atrial fibrillation | 10 | 10 | 4 | 4 | |
| Atrial flutter | 2 | 2 | 0 | 0 | |
| Bradycardia | 3 | 3 | 1 | 1 | |
| Tachycardia | 16 | 16 | 6 | 6 | |
| V-tach | 1 | 2 | 0 | 0 | |
| Sinus tachycardia | 4 | 4 | 2 | 2 | |
| General | | | | | |
| Post op pain | 0 | 0 | 5 | 5 | |
| Pain (NOS) | 26 | 31 | 1 | 1 | |
| Fever/ elevated temperature | 16 | 17 | 8 | 8 | |
| Rash | 2 | 2 | 2 | 2 | |
| Wound dehiscence/breakdown | 1 | 1 | 1 | 1 | |
| Itching | 13 | 13 | 3 | 3 | |
| Metabolic | | | | | |
| Hypocalcemia | 13 | 14 | 8 | 8 | |
| Hypomagnesemia | 14 | 15 | 6 | 7 | |
| Hypophosphatemia | 24 | 25 | 8 | 9 | |
| Hypokalemia | 29 | 32 | 8 | 9 | |
| Electrolyte disturbances | 0 | 0 | 1 | 1 | |
| Other | | | | | |

| Study No.: 400-07-002 | | | | |
|------------------------------|---------------------|--------------------|----------------------------|--------------------------|
| Treatment Emergent AEs | FP (No of subjects) | FP (No. of events) | Surgicel (No. of subjects) | Surgicel (No. of events) |
| General | | | | |
| Post op pain | 0 | 0 | 5 | 5 |
| Pain (NOS) | 26 | 31 | 1 | 1 |
| Fever/ elevated temperature | 16 | 17 | 8 | 8 |
| Rash | 2 | 2 | 2 | 2 |
| Wound dehiscence/breakdown | 1 | 1 | 1 | 1 |
| Itching | 13 | 13 | 3 | 3 |
| Metabolic | | | | |
| Hypocalcemia | 13 | 14 | 8 | 8 |
| Hypomagnesemia | 14 | 15 | 6 | 7 |
| Hypophosphatemia | 24 | 25 | 8 | 9 |
| Hypokalemia | 29 | 32 | 8 | 9 |
| Other | | | | |
| Fistula | 5 | 5 | 5 | 5 |
| Increased/high ostomy output | 2 | 2 | | |
| Sub Q emphysema/crepitus | 5 | 6 | 2 | 2 |
| Allergic reaction | 1 | 1 | 0 | 0 |

Reviewer comments:

The patients enrolled in this trial were ill. Most had underlying advanced malignancies which is a precondition for several of the adverse events of concern with use of both the Fibrin Pad and Surgicel. Specifically, infection, extent of operative procedure, comorbidities such as obesity, smoking history, altered immune status from prior chemotherapy and thrombotic tendencies due to malignancy or prolonged immobility all affect thrombotic, infectious and adhesion complications. There are AE imbalances for pain, atelectasis, fistula, obstructions, and thrombosis. These imbalances are against the FP arm and given the adverse events reported with oxycellulose implants (i.e. adhesions, infections, fluid collections,) may be related to the FP.

6.1.11.3 Deaths

There were seven deaths in the safety set during the study, 6 in the FP group (5.4%) and 1 in the control group (3.3%). Only one death was judged by the investigator to be

possibly related to study therapy. These deaths are summarized in the following table provided by the Sponsor (text 30, section 12.3.1.1 and appendix 16.2.7.4)

Serious Adverse Events with Fatal Outcome (Safety Set)

| Subject # | Treatment | SAE | Potential Causal Relationship to: Study Treatment | Surgical Procedure Possibly related |
|------------------|------------------|--|--|--|
| 14-215 | FP | Cardiopulmonary arrest | None | related |
| 14-218 | FP | Retroperitoneal bleed (not TBS) | None | Possibly related |
| 15-203 | FP | Sepsis related to perforated jejunum | None | None |
| 21-109 | FP | Cardiopulmonary arrest secondary to post-operative ileus | None | Related |
| 21-207 | FP | Massive GI bleed (not TBS) | Possibly related | Possibly related |
| 22-116 | FP | Stroke | None | related |
| | | Respiratory failure | None | None |
| 23-201 | SURGICEL | Progression of cancer | None | Possibly related |

Reviewer comment: From the available data from the submission and detailed case narratives, it does seem reasonable that disease progression or other co-morbidities likely contributed to some of the fatal outcomes. The information on the potential carcinogenicity of this implanted device biologic product is lacking. As noted by the CDRH medical officer consultant, Dr. Roxolana Horbowyj, the -----(b)(4)----- component has not been evaluated for carcinogenicity.

6.1.11.4 Nonfatal Serious Adverse Events

See Reviewer adverse event tables, above.

6.1.11.5 Adverse Events of Special Interest (AESI)

The protocol pre specified re-bleeding and thromboembolic complications as adverse events of special interest. The following table provided by the sponsor summarizes the AEs potentially related to thrombotic events (safety dataset) and the postoperative day of onset (Note: Day 0 is the same day as the operation).

Reviewer comment: It is notable that 9 thromboembolic events are listed in the non

Text Table 28 AEs Potentially Related to Thrombotic Events (Safety Set)

* Day 0 is the day of surgery

| Subject # | Treatment Group | Preferred Term | Post-Operative Day of Onset |
|------------------|------------------------|-----------------------------------|------------------------------------|
| 22-106 | SURGICEL | Pulmonary Embolism | Day 19 |
| 22-203 | SURGICEL | Deep Vein Thrombosis | Day 4 |
| 11-101 | FP Randomized | Embolism | Day 28 |
| 11-202 | Non-Randomized FP | Pulmonary Embolism | Day 2 |
| 12-209 | Non-Randomized FP | Pulmonary Embolism (Suspected) | Day 0* |
| 14-109 | Non-Randomized FP | Deep Vein Thrombosis | Day 0* |
| | | Pulmonary Embolism | Day 20 |
| 14-216 | Non-Randomized FP | Deep Vein Thrombosis | Day 20 |
| | | Pulmonary Embolism | Day 2 |
| 22-116 | Non-Randomized FP | Stroke | Day 1 |
| 22-124 | Non-Randomized FP | Pulmonary Embolism | Day 15 |
| 22-125 | Non-Randomized FP | Intestinal Infarction | Day 13 |

randomized FP arm portion of the study. Of these 9 events, 6 are within 14 days of the index operation. Extrapolating from data known about fibrin sealants (EVICEL) in particular, the fibrin sealant is expected to be completely adsorbed within 10-14 days of application. The device component of the fibrin pad does not completely resorb until about 60 days post application. The available data from the submission do not allow one to conclude with certainty that these thromboembolic events were not related to investigational product use.

6.1.11.6 Clinical Test Results

The most frequently occurring AE by SOC was metabolism and nutritional disorders, and within this class hypomagnesemia was the most frequently reported event (41.8% of all subjects). Hyperglycemia, hypokalemia and hypophosphatemia all occurred in more than 20% of patients.

Reviewer comment: Given the underlying disease (cancer) and associated co-morbidities, general inanition, malnutrition, and the surgical operations, it is not surprising that many subjects experienced electrolyte disturbances. The Fibrin Pad is not expected to impact on these laboratory parameters in any significant way. On the other hand, coagulation disturbances might be influenced by the Fibrin Pad.

6.1.11.7 Dropouts and/or Discontinuations

Most of the drop outs were due to death from progressive disease. Only two subjects withdrew consent. Four subjects (2 FP non randomized and 2 Surgicel) were lost to follow up. Overall 30 day follow up assessments (excluding laboratory evaluations) were completed for 59 FP randomized subjects, 45 FP non-randomized subjects and 27 Surgicel subjects.

Reviewer comment: These dropouts/ discontinuations are not expected to influence the overall conclusions from the study.

6.2 Supportive safety information

Trial #2

Study 400-08-002 “A Prospective, Randomized, Controlled Superiority Evaluation of Fibrin Patch (Fibrin Pad) as an adjunct to Control Soft tissue Bleeding during Abdominal, Retroperitoneal, Pelvic, and Thoracic Surgery”

In the initial BLA submission dated November 19, 2011 the sponsor had completely evaluated 35 subjects. The final study report was submitted in a BLA amendment on June 13, 2011.

For the purpose of this study, severe bleeding was defined as: *bleeding (arterial, venous, or mixed) that is rapidly flowing, pulsatile or spurting that in the surgeon’s judgment requires rapid control to prevent hemodynamic consequences (e.g. hypovolemia, tachycardia, or hypotension) and could involve major volume loss which if not treated rapidly could be life threatening. Fibrin Pad should not be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial bleeding.*

Synopsis:

This trial was a randomized, controlled, superiority, study evaluating the effectiveness of the Fibrin Pad (FP) compared with Standard of Care (SoC) methods utilized to control challenging severe soft tissue bleeding during abdominal, pelvic, retroperitoneal, and (non-cardiac) thoracic surgery for which standard methods of achieving hemostasis are ineffective or impractical. Subjects who met the eligibility criteria were randomized 2:1 Fibrin Pad vs. SoC Control.

The trial was monitored using the sequential triangular test. The first analysis is planned for the first 90 randomized subjects. The interim analyses will determine whether randomization should be halted or continued based upon efficacy data analyzed by the sequential triangular test.

If randomization was continued after the first analysis, subsequent interim analyses were performed after every additional 30 subjects were enrolled into the study. Randomization was stopped once a stopping boundary has been crossed. The expected number of randomized subjects was between 90 and 180.

Subjects underwent elective, open, abdominal, retroperitoneal, pelvic or thoracic (non-cardiac) surgery procedures. The site evaluated as the TBS was the first actively bleeding site identified in the soft tissue related to the primary operative procedure with persistent, challenging severe bleeding, where conventional methods of control (i.e. suture, ligation, and cautery) have been deemed ineffective or impractical and an alternative method was required. The TBS had to be a site where occlusion of the injured tissue surface blood vessels was required to achieve hemostasis. This excluded large defects in arteries or veins where the injured vascular wall requires repair with maintenance of vessel patency and which would result in persistent exposure of the FP to blood flow and pressure during healing and absorption of the product. In addition, the FP was not be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial bleeding. Subjects were followed for safety up to 60 days +/- 10 days.

Reviewer comment: The 60 day follow-up was added after the trial was started and approximately 30 patients had already been enrolled.

Major findings from the study:
Demographics and disposition of patients:

Text table 8 Subject demography (Safety Set)

| Category | Statistic | Fibrin Pad N = 59 | Standard of Care N = 32 | Total N = 91 |
|---------------|----------------|----------------------|----------------------------|--------------|
| Age (years) | Median (Range) | 65 (33 - 83) | 67 (41 -82) | 65 (33 -83) |
| Age (grouped) | 18-<50 years | 9 (15.3%) | 4 (12.5%) | 13 (14.3%) |
| | 50 - <65 years | 20 (33.9%) | 11 (34.4%) | 31 (34.1%) |
| | 65-<75 years | 19 (32.2%) | 9 (28.1%) | 28 (30.8%) |
| | ≥75 years | 11 (18.6%) | 8 (25.0%) | 19 (20.9%) |

Text Table 9 Summary of Primary operative procedure

| Procedure | Fibrin Pad N = 59 | Standard of Care (N = 32) | Total N = 91 |
|---|-------------------------|---------------------------------|-----------------|
| Pulmonary Resection | 12 (20.3%) | 7 (21.9%) | 19 (20.9%) |
| Gastrectomy | 8 (13.6%) | 1 (3.1%) | 9 (9.9%) |
| Pancreatic duodenectomy, radical | 4 (6.8%) | 4 (12.5%) | 8 (8.8%) |
| Colectomy with or without primary anastomoses | 3 (5.1%) | 2 (6.3%) | 5 (5.5%) |
| Cystectomy, radical | 4 (6.8%) | 1 (3.1%) | 5 (5.5%) |

| | | | |
|---------------------------------|---------|---------|---------|
| | 3 | 1 | 4 |
| Prostatectomy, radical | (5.1%) | (3.1%) | (4.4%) |
| | 2 | 2 | 4 |
| Esophageal resection | (3.4%) | (6.3%) | (4.4%) |
| | 2 | 1 | 3 |
| Cholecystectomy | (3.4%) | (3.1%) | (3.3%) |
| | 2 | 1 | 3 |
| Hysterectomy TAH/BSO | (3.4%) | (3.1%) | (3.3%) |
| | 1 | 2 | 3 |
| Pancreatectomy | (1.7%) | (6.3%) | (3.3%) |
| | 1 | 1 | 2 |
| Abdominoperineal resection | (1.7%) | (3.1%) | (2.2%) |
| | 2 | 0 | 2 |
| Prostatectomy, simple | (3.4%) | (0.0%) | (2.2%) |
| | 1 | 0 | 1 |
| Retroperitoneal tumor resection | (1.7%) | (0.0%) | (1.1%) |
| | 1 | 0 | 1 |
| Hysterectomy, total | (1.7%) | (0.0%) | (1.1%) |
| | 0 | 1 | 1 |
| Nephrectomy, partial | (0.0%) | (3.1%) | (1.1%) |
| | 1 | 0 | 1 |
| Nephrectomy, radical | (1.7%) | (0.0%) | (1.1%) |
| | 12 | 8 | 20 |
| Other | (20.3%) | (25.0%) | (22.0%) |

Text Table 10 Anatomical location of TBS (ITT set)

| Anatomical Location | Fibrin Pad N = 59 | Standard of Care (N = 32) | Total N = 91 |
|---------------------|-------------------|---------------------------|--------------|
| Abdominal | 23 (39.0%) | 15 (46.9%) | 38 (41.8%) |
| Thoracic | 17 (28.8%) | 10 (31.3%) | 27 (29.7%) |
| Pelvic | 12 (20.3%) | 4 (12.5%) | 16 (17.6%) |
| Retroperitoneal | 7 (11.9%) | 3 (9.4%) | 10 (11.0%) |

Text Table 11 Tissue Type at TBS (Safety Set)

| Tissue Type | Fibrin Pad | Standard of Care | Total N = 91 |
|-------------|------------|------------------|--------------|
|-------------|------------|------------------|--------------|

| | (N = 59 | (N = 32) | |
|-----------------------------|---------------|---------------|---------------|
| Muscle | 22 (37.3%) | 4 (12.5%) | 26 (28.6%) |
| Fat | 12 (20.3%) | 8 (25.0%) | 20 (22.0%) |
| Lymph node bed | 5 (8.5%) | 6 (18.8%) | 11 (12.1%) |
| Loose areolar connective | 7 (11.9%) | 2 (6.3%) | 9 (9.9%) |
| Lymphatic | 2 (3.4%) | 2 (6.3%) | 4 (4.4%) |
| Other | 11 (18.6%) | 10 (31.3%) | 21 (23.1%) |

The primary method of hemostasis at the TBS prior to randomization was cautery in 16.5% of cases (15/91), suture in 5.5% of cases (5/91), ligation in 1.1% of cases (1/91) and ‘other’ in 18.7% of cases (17/91). Other methods included packing, compression and Surgicel. No hemostatic methods were used at the TBS prior to study treatment in 58.2% of cases (53/91) as they were deemed to be impractical by the surgeon.

Estimated venous thromboembolism (VTE) risk scores

| Statistic | FP (n=59) | SoC (n=32) | Total (n=91) |
|------------------|------------------|----------------|------------------|
| Mean | 13.3 (2.8) | 13.7 (2.9) | 13.0 (6.0, 20.0) |
| Median | 13.0 (7.0, 19.0) | 13 (6.0, 20.0) | 13 (6.0, 20.0) |
| Number (missing) | 59 (0) | 32 (0) | 91 (0) |
| 95% CI of mean | 12.6, 14.7 | 12.6, 14.7 | 12.8,14.0 |

Reviewer comment: The patients are at high risk for thromboembolic events.

Target Bleeding Site (TBS) and application on the TBS ITT analysis set

Efficacy Analyses from Study 400-08-002:

The following summary of hemostasis was provided by the Sponsor and verified as correct by FDA (John Scott PhD statistical reviewer)

Primary efficacy :

Table 14.2.1.1 Summary of Hemostasis ITT analysis set

| Variable | Category/ Statistic | FP (n=59) | SoC (n=32) |
|-------------------------------|------------------------|--------------|---------------|
| Hemostasis at 4 minutes | Yes | 52 (88.1%) | 14 (43.8%) |
| | No | 1 (1.7%) | 16 (50.0%) |
| | Unknown | 6 (10.2%) | 2(6.3%) |
| Hemostasis achieved at 10 min | Yes | 59 (100%) | 25 (78.15) |
| | No | 0 (0.0%) | 7 (21.9%) |

| | | | |
|---------------------------------------|-------------------------|-------------------------|-------------------------|
| Bleeding requiring treatment | Yes | 3 (5.1%) | 17 (53.1%) |
| | No | 56 (94.9%) | 15 (46.9%) |
| Absolute time hemostasis (min) | Mean (std) | 6.1 (13.5) | 17.8 (32) |
| | Median (range) | 4.0 (4.0, 107.3) | 6.0 (4.0, 130.3) |
| | Number (missing) | 59 (0) | 31 (1) |
| | 95% CI of mean | 2.5, 9.6 | 6.1, 29.6 |
| Success at 10 min (secondary) | Yes | 58 (98.3%) | 22 (68.8%) |
| | No | 1 (1.7%) | 10 (31.3%) |
| Primary endpoint success at #1 | Yes | 50 (84.7%) | 10 (31.3%) |

Safety analysis data from study 400-08-002:

Seven deaths occurred during the study, four in subjects treated with FP (4/59; 6.8%) and three in subjects randomized to SoC (3/32; 9.4%). In one subject randomized to treatment with FP, the event which resulted in death was assessed by the investigator as possibly related to study treatment. This event was a massive gastric aspiration due to ileus. In all other cases, the event which led to the death of the subject was assessed by the sponsor as having no causal relationship with the study product.

Text Table 31 SAEs with fatal Outcome (Safety Set)

| Subject # | Treatment Group | SAE | Potential Causal Relationship to: | |
|-----------|-----------------|---|-----------------------------------|--------------------|
| | | | Study Treatment | Surgical Procedure |
| (b)(6) | FP | Disease Progression | None | Possibly related |
| (b)(6) | FP | Progression of bladder cancer | None | None |
| (b)(6) | FP | Massive gastric aspiration due to ileus | Possibly related | Related |
| (b)(6) | FP | Abdominal hemorrhage | None | Related |
| (b)(6) | SoC | Empyema | None | Possibly related |
| (b)(6) | SoC | Postoperative hepatorenal syndrome | None | Possibly related |
| (b)(6) | SoC | Respiratory failure | None | None |

The sponsor reports, “No analysis of SAEs was planned or undertaken. However, the profile of SAEs was consistent with the patient population and the nature of surgical procedures performed.”

The sponsor reports, “There were no apparent differences between treatment groups in the laboratory parameters assessed.” However, there was an increase in fibrinogen in the FP arm (though not statistically significant).

AEs that were considered to be related or possibly related to study product were experienced by 5/59 subjects (8.5%) in the FP group and 1/32 subjects (3.1%) in the SoC group.

Reviewer comment: From the available data one cannot conclude that the gastric aspiration was not due o the FP.

Text Table 27 AEs with Potential causal Relationship to Study Treatment (Safety Set)

| Subject # | Treatment Group | Adverse Event | SAE? | Causal Relationship |
|-----------|------------------|--|------|---------------------|
| (b)(6) | Pad | Massive gastric aspiration due to ileus caused by ischemic bowel | Yes | Possibly related |
| | | Distended abdomen | No | Possibly related |
| (b)(6) | Fibrin Pad | Increased fibrinogen(Discharge) | No | Related |
| (b)(6) | Fibrin Pad | Pleural effusion/prolonged secretion | No | Possibly related |
| (b)(6) | Fibrin Pad | Increased fibrinogen(Discharge) | No | related |
| (b)(6) | Fibrin Pad | Increased fibrinogen(Discharge) | No | Possibly related |
| | | Increased fibrinogen(Day 60) | No | related |
| (b)(6) | Standard of Care | Pleural effusion/prolonged secretion | No | Possibly related |
| | | Increased fibrinogen(Discharge) | No | related |

Reviewer comment: The sponsor should be requested to explain the elevated fibrinogen levels in the FP arm.

REVIEWER SAFETY TABLES

Fibrin Pad (FP), N=59

Standard of Care (SOC) N=32

| Product: | | Study No.: 400-08-002 | | |
|---|------------------------------|----------------------------|-----------------------|---------------------|
| Omrix Fibrin Pad | | | | |
| Treatment Emergent AEs | Fibrin Pad (No. of subjects) | Fibrin Pad (No. of events) | SOC (No. of subjects) | SOC (No. of events) |
| Death | 4 | 4 | 3 | 3 |
| Hypertension/BP increased/hypertensive crisis/malignant hypertension/systolic hypertension/SVR increased | 5 | 5 | 1 | 2 |
| Hypertension | 5 | 5 | 1 | 2 |
| Chest pain/pressure/tightness | 2 | 2 | 2 | 2 |
| CHF, etc | 1 | 1 | 1 | 1 |
| Pulmonary edema | 1 | 1 | 1 | 1 |
| MI, etc | 0 | 0 | 0 | 0 |
| Cardiac arrhythmias | 22 | 24 | 14 | 17 |
| Arrhythmia | 3 | 3 | 1 | 1 |
| Atrial fibrillation | 5 | 5 | 3 | 3 |
| Atrial flutter | 0 | 0 | 0 | 0 |
| Bradycardia | 7 | 7 | 5 | 6 |
| Tachycardia | 7 | 9 | 4 | 6 |
| Supraventricular Tachycardia | | | 1 | 1 |
| CVA, TIA, cerebral infarct, etc | 0 | 0 | 0 | 0 |

| Product: Omrix Fibrin Pad | | Study No.: 400-08-002 | | |
|---|---------------------------------|-------------------------------|--------------------------|------------------------|
| Treatment Emergent AEs | Fibrin Pad (No. of subjects) | Fibrin Pad (No. of events) | SOC (No. of subjects) | SOC (No. of events) |
| Pneumonia, aspiration pneumonia, respiratory failure/insufficiency | 2 | 3 | 7 | 8 |
| Pneumonia-Klebsiella | 0 | 0 | 0 | 0 |
| Pneumonia | 1 | 2 | 6 | 7 |
| Empyema | 1 | 1 | 1 | 1 |
| Respiratory distress.etc | 16 | 17 | 13 | 15 |
| ARDS | | | | |
| Respiratory distress | 1 | 1 | 0 | 0 |
| Resp. failure (excluding neonatal) | 2 | 2 | 3 | 3 |
| Pneumothorax | 4 | 4 | 2 | 2 |
| Pleural effusion | 9 | 10 | 8 | 10 |
| Oliguria, etc. | 10 | 10 | 8 | 9 |
| Oliguria | 7 | 7 | 6 | 7 |
| Renal failure- acute | 2 | 2 | 1 | 1 |
| Hepatorenal syndrome | 0 | 0 | 1 | 1 |
| Hypoxia, etc. | 7 | 8 | 2 | 2 |
| Decreased oxygen sat | 1 | 2 | 0 | 0 |
| Hypoxia | 3 | 3 | 1 | 1 |
| Dyspnea/short of breath | 3 | 3 | 1 | 1 |
| Hypovolemia | 3 | 3 | 2 | 2 |
| Dehydration | 3 | 3 | 2 | 2 |

| Product: Omrix Fibrin Pad | | Study No.: 400-08-002 | | |
|--|-------------------|-----------------------|-------------------|-----------------|
| Treatment | Fibrin Pad | Fibrin Pad | SOC | SOC |
| Emergent AEs | (No. of subjects) | (No. of events) | (No. of subjects) | (No. of events) |
| Oliguria, etc. | 10 | 10 | 8 | 9 |
| Oliguria | 7 | 7 | 6 | 7 |
| Renal failure-acute | 2 | 2 | 1 | 1 |
| Hepatorenal syndrome | 0 | 0 | 1 | 1 |
| Hypoxia, etc. | 7 | 8 | 2 | 2 |
| Decreased oxygen sat | 1 | 2 | 0 | 0 |
| Hypoxia | 3 | 3 | 1 | 1 |
| Dyspnea/short of breath | 3 | 3 | 1 | 1 |
| Hypovolemia | 3 | 3 | 2 | 2 |
| Dehydration | 3 | 3 | 2 | 2 |
| Gastrointestinal pain, nausea, vomiting | 63 | 69 | 27 | 32 |
| Abdominal pain | 6 | 8 | 3 | 3 |
| Increased abdominal pain | 1 | 1 | | |
| Vomiting | 16 | 17 | 9 | 12 |
| Abdominal distension | 1 | 1 | 1 | 1 |
| Dyspepsia | 2 | 2 | 0 | 0 |
| Dysphagia | 1 | 1 | 0 | 0 |
| Nausea | 35 | 39 | 14 | 16 |
| Ileus | 1 | 1 | 2 | 2 |

| Product: Omrix Fibrin Pad | | Study No.: 400-08-002 | | |
|---------------------------------|------------------------------------|----------------------------------|-----------------------------|---------------------------|
| Treatment Emergent AEs | Fibrin Pad (No. of subjects) | Fibrin Pad (No. of events) | SOC (No. of subjects) | SOC (No. of events) |
| Hepatobiliary/pancreatic | 2 | 2 | 1 | 1 |
| Blood albumin decreased | 2 | 2 | 0 | 0 |
| LFTs abnormal | 0 | 0 | 1 | 1 |
| Coagulation | 11 | 12 | 7 | 9 |
| Hypercoagulopathy | 1 | 1 | 0 | 0 |
| Coagulopathy | 0 | 0 | 2 | 4 |
| Thrombocytopenia | 1 | 1 | 1 | 1 |
| Fibrinogen increased | 5 | 6 | 3 | 3 |
| Increased platelets | 2 | 2 | 0 | 0 |
| Thrombosis | 2 | 2 | 1 | 1 |
| Hemorrhage/bleeding | 18 | 19 | 9 | 14 |
| anemia | 11 | 12 | 8 | 13 |
| Abdominal hemorrhage | 1 | 1 | 0 | 0 |
| Rectal hemorrhage | 1 | 1 | 0 | 0 |
| Post-op hemorrhage | 2 | 2 | 0 | 0 |
| Nose bleed | 1 | 1 | 0 | 0 |
| Hemoglobin decreased | 2 | 2 | 0 | 0 |
| Vaginal hemorrhage | 0 | 0 | 1 | 1 |

| Product: Omrix Fibrin Pad | | Study No.: 400-08-002 | | |
|---------------------------------|---------------------------------|-------------------------------|--------------------------|------------------------|
| Treatment Emergent AEs | Fibrin Pad (No. of subjects) | Fibrin Pad (No. of events) | SOC (No. of subjects) | SOC (No. of events) |
| Sepsis/septic shock | 3 | 3 | 6 | 7 |
| Sepsis | 3 | 3 | 6 | 7 |
| Ischemia/ischemic events | 0 | 0 | 0 | 0 |
| Infections | 17 | 20 | 10 | 10 |
| Infection (NOS) | 1 | 1 | 0 | 0 |
| Urinary tract infection | 5 | 5 | 2 | 2 |
| Wound infection | 2 | 3 | 1 | 1 |
| Subphrenic collection/abscess | 1 | 2 | 0 | 0 |
| Chest infection | 5 | 6 | 5 | 5 |
| Sacral wound infection | 1 | 1 | 0 | 0 |
| Bile drain | 1 | 1 | 0 | 0 |
| A line | 1 | 1 | 0 | 0 |
| Jejunostomy site | 0 | 0 | 1 | 1 |
| Skin | 0 | 0 | 1 | 1 |
| Abscess | 1 | 2 | 0 | 0 |
| Leaks | 4 | 4 | 4 | 4 |
| Anastomotic leak | 0 | 0 | 1 | 1 |
| Urinary leak | 0 | 0 | 1 | 1 |
| Bile leak | 1 | 1 | 0 | 0 |
| Pancreatic leak | 1 | 1 | 1 | 1 |
| Air leak | 1 | 1 | 0 | 0 |
| Leak at tracheostomy site | 1 | 1 | 0 | 0 |

Product: Omrix Fibrin Pad Study No.: 400-08-002

| Treatment Emergent AEs | Fibrin Pad (No. of subjects) | Fibrin Pad (No. of events) | SOC (No. of subjects) | SOC (No. of events) |
|---------------------------|------------------------------|----------------------------|-----------------------|---------------------|
| Presacral collection/leak | 0 | 0 | 1 | 1 |
| Fistula | 0 | 0 | 1 | 1 |
| Pancreatic | 0 | 0 | 1 | 1 |
| General | 53 | 51 | 35 | 56 |
| Peripheral edema | 2 | 2 | 5 | 6 |
| Edema (NOS) | 2 | 2 | 0 | 0 |
| Fever/pyrexia/febrile | 11 | 16 | 13 | 15 |
| Pain (NOS) | 29 | 20 | 14 | 16 |
| Pain (back) | 1 | 1 | 1 | 2 |
| Pain (leg) | 0 | 0 | 1 | 1 |
| Pain (perineal) | 0 | 0 | 1 | 1 |
| Pain (pelvic) | 1 | 1 | 0 | 0 |
| Pain (pharyngeal) | 2 | 2 | 0 | 0 |
| Pain (musculoskeletal) | 4 | 6 | 0 | 0 |
| Pain (neck) | 1 | 1 | 0 | 0 |

Laboratory Value Abnormalities:

The sponsor reports, “There were no apparent differences between treatment groups in the laboratory parameters assessed.” However, there was an increase in fibrinogen in the FP arm (though not statistically significant).

Clinically significant increases in fibrinogen levels were reported as possibly related to treatment in 3/59 subjects (5.1%) treated with FP and 1/32 subjects (3.1%) treated with SoC; all four subjects were treated in the same centre. Timepoints when elevated fibrinogen levels were observed were as follows:

- Subject (b)(6) (FP): Fibrinogen was high (clinically significant) at discharge but within the normal range at Screening, Day \pm 30 and Day \pm 60.
- Subject (b)(6) (FP): Fibrinogen was high (clinically significant) at Screening, Discharge and Day \pm 30 but within the normal range at Day \pm 60.
- Subject (b)(6) (FP): At Screening, fibrinogen was flagged as high, but not clinically significant. At Discharge and Day \pm 60 levels were high and considered clinically significant. At Day 30, fibrinogen was within the normal range.
- Subject (b)(6) (SoC): Fibrinogen was high (clinically significant) prior to Discharge and at Day-30, but within the normal range at Screening and Day-60.

Reviewer comment: The sponsor should be requested to explain the elevated fibrinogen levels in the FP arm.

7. INTEGRATED OVERVIEW OF EFFICACY

The Sponsor did not submit an integrated overview of efficacy. Furthermore, the studies submitted by the sponsor cannot be pooled for efficacy since they have different trial designs and indications.

7.1 Methods of Integration

Not applicable.

7.2 Demographics

Not applicable.

7.3 Subject Disposition

Not applicable.

7.4 Analysis of Primary Endpoint(s)

Not applicable.

7.5 Analysis of Secondary Endpoint(s)

Not applicable.

7.6 Other Endpoints

Not applicable.

7.7 Subpopulations

Not applicable.

7.8 Persistence of Efficacy

Not applicable.

7.9 Product-Product Interactions

Not applicable.

7.10 Additional Efficacy Issues/Analyses

Not applicable.

7.11 Efficacy Conclusions

Not applicable.

8. INTEGRATED OVERVIEW OF SAFETY

Although the Sponsor presented the integrated safety summary, since the standards of care varied across the trials, the most important studies are listed separately (not pooled) in this memorandum. The study entitled, protocol 400-08-002 (phase 3 soft tissue surgery study conducted outside the US) has been summarized above. The small phase 1 partial nephrectomy study (10 patients) conducted in Israel is listed in the appendix.

8.1 Safety Assessment Methods

Not applicable.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Not applicable.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Not applicable.

8.2.3 Categorization of Adverse Events

Not applicable.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Not applicable

8.4 Safety Results

8.4.1 Deaths

Not applicable.

8.4.2 Nonfatal Serious Adverse Events

Not applicable.

8.4.3 Dropouts and/or Discontinuations

Not applicable.

8.4.4 Common Adverse Events

Not applicable.

8.4.5 Clinical Test Results

Not applicable.

8.4.6 Systemic Adverse Events

Not applicable.

8.4.7 Local Reactogenicity

Not applicable.

8.4.8 Adverse Events of Special Interest

Not applicable.

8.5 Additional Safety Evaluations

Not applicable.

8.5.1 Dose Dependency for Adverse Events

Not applicable

8.5.2 Time Dependency for Adverse Events

Not applicable.

8.5.3 Product-Demographic Interactions

Not applicable.

8.5.4 Product-Disease Interactions

Not applicable.

8.5.5 *Product-Product Interactions*

Not applicable.

8.5.6 *Human Carcinogenicity*

This has not been studied. However, there was internal discussion regarding the need to request additional preclinical data on carcinogenicity since the Fibrin Pad will be left in situ and remains incompletely absorbed for up to 2 months. Additionally, the CDRH external consultant, Roxolana Horbowyj, MD, noted that CDRH routine requests 5 year follow up safety data on all devices that are implanted. This follow up period includes evaluation of patients for cancer. At this time, the Division of Hematology has not made a determination as to whether long term follow up of patients to evaluate for carcinogenicity is required. Of note, in the clinical trials that Omrix conducted for use of the Fibrin Pad in soft tissue surgery, the majority of patients, presented to surgery because they had an underlying malignancy. It would be expected that many of these patients might not survive up to 5 years post surgery, due to the natural history of the malignancy. Nonetheless, as the Omrix program for the Fibrin Pad progresses to different patient populations, this issue may need to be revisited.

8.5.7 *Overdose, Drug Abuse Potential, Withdrawal, and Rebound*

Not applicable.

8.5.8 *Immunogenicity (Therapeutic Proteins)*

Immunogenicity

Source: Summary Report per sponsor (From the Antibody response to human thrombin and fibrinogen in samples of subjects participating in Hercules Clinical – amendment 1)

SUMMARY

The antibody response to human thrombin and fibrinogen was evaluated in patients treated with Fibrin Pad (FP) or SURGICEL as part of a safety evaluation in the FP clinical trial evaluating the efficacy and safety of FP.

Method: Blood samples of patients were collected on the day of surgery (T0) and 4 and 8 weeks later (T4 and T8 respectively). The levels of specific antibodies to human thrombin and fibrinogen were analyzed by an Enzyme-Linked Immunosorbent Assays (ELISA) for human thrombin and human fibrinogen using -----(b)(4)-----
-----.

The background level of antibodies to thrombin or fibrinogen in the untreated population was used to set a cut-off value. The antibody levels at each time point for each patient were evaluated by two parameters, a categorical parameter (below or above a pre-defined cut-off value) and a relative quantitative parameter (antibody titer). Two types of analysis were done:

- (a) The results at 4 and 8 weeks after procedure of each patient were compared to Time 0 and
- (b) The proportion of positive samples in different groups at different time points were compared.

Sponsor reported results: Samples of 99 patients from FP, and 22 from SURGICEL treated groups were available for analysis. Of the patients treated with FP, 2 out of 99 (2%, CI 95 0.2-7.1%) had converted with anti-thrombin antibodies from a value below cut-off to a higher value. It is worth noting however that a baseline plasma sample of one of these patients was hemolytic with a very low assay values and the other patient had an 8-week sample with a much lower value than the 4-week sample, suggesting a transient antibody response. None of the patients in any treatment group had a significant change in antibody titer to thrombin or fibrinogen.

The proportion of samples with antibodies to thrombin (detection signals above cut-off) in all groups at all time points was similar to the normal population. No significant statistical differences were found neither between treatment groups nor between time points tested.

Conclusions: Results of this study showed that 2% of the FP treated patients demonstrated a slight and mainly transient increase in antibody response to human thrombin. Four weeks after surgery neither of the two patients with increase of anti-human Thrombin antibodies had abnormal coagulation parameters such as Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), or international normalized ratio (INR). There was no detectable response to human fibrinogen.

Reviewer comment: *The 2% rate of change in the detection signal of thrombin antibodies is consistent with the published literature after treatment with human thrombin and below the rate demonstrated after treatment with bovine thrombin (Chapman et. al.2006, Cheng et. al, 2009). It is unknown if patients had prior exposure to human or bovine thrombin during a surgical procedure. This might influence antibody responses.*

8.5.9 Person to Person Transmission, Shedding

Not applicable.

8.6 Safety Conclusions

The safety of the Fibrin Pad cannot be adequately assessed based on the primary study submitted for licensure (i.e protocol 400-07-002).

The primary efficacy endpoint was met. FDA has previously advised the sponsor that the study on soft tissue surgery is a phase 2 study. An additional study, either in soft tissue surgery or other surgical setting, whereby the FP is used as an adjunct to hemostasis for “mild or moderate” bleeding should be conducted. This soft tissue phase 2 study does not meet the standard for licensure of a biologic (21 CFR 600.3) in that there are some safety

concerns: potential safety signals of thromboembolic, infection and adhesions/ obstructions. The sponsor states the following in regarding the US soft tissue surgery study: “No safety concerns were identified by the study. The AE and SAE and mortality profiles are those that would be expected following long major surgical procedures in the populations treated. The incidence of clinically meaningful AEs was similar in the two treatment groups and the events were of the types that are expected following these major surgical procedures.” (Study synopsis page 9/177). FDA review and analysis of the US soft tissue surgery study does not agree with this conclusion. There were more fatal events in the FP arm compared to the Surgicel arm and the adverse events in several AE categories were not similar between the FP and Surgicel arms. 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). Furthermore, the baseline demographics do 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. Review of case report forms and operative records suggest that monitoring for adverse events may not have been optimal. Design deficiencies to include unknown safety monitoring for thrombotic events. Furthermore, upon review of study 400-07-002 safety monitoring and perhaps stopping rules for a future study should address the potential for infections, adhesions/ obstructions. This is important because ORC based implanted devices are known to potentially lead to infections, adhesions/ obstructions. Finally, lack of stratification based on known covariates limits the use of the supportive studies to bolster the safety information contained in the primary licensing trial (protocol 400-07-002 US soft tissue surgery study).

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

Only adult populations (ages 18 and older) were studied in the clinical trials used to support initial licensure in this BLA. Based on review of the available data there do not appear to be any age specific differences in safety or efficacy for the Fibrin pad in adult populations. No pediatric age groups were included in US soft tissue surgery study (protocol 40-07-002).

9.1.1 Human Reproduction and Pregnancy Data

Not applicable at this time.

9.1.2 Use During Lactation

Not addressed by the sponsor

9.1.3 Pediatric Use and PREA Considerations

Under section 505B (a) (3) of the Pediatric Research Equity Act, the sponsor requested a deferral for conducting pediatric studies citing the following reasons:

“(a) The study serving as the basis for licensure (study 400-07-002) included a predominantly middle-aged to elderly cohort of subjects which reflected the nature of the surgical procedures the subjects were undergoing (i.e., major surgical operations predominantly for malignant conditions). Recruitment of pediatric subjects to a study involving these types of surgical procedures would have been difficult.

(b) The sponsor intends to delay pediatric assessments until additional safety or effectiveness data have been collected.

(c) Agreement has not been reached between FDA and the Sponsor as to the strategy for collection of data to support the use of Fibrin Pad in the pediatric population.

Reviewer comment: Reviewer is in agreement with deferral of pediatric studies.

9.1.4 Immunocompromised Patients

The study did not prospectively plan to analyze this patient population. The numbers in the study are too small to draw any conclusions.

9.1.5 Geriatric Use

The study did not prospectively plan to analyze this patient population. The numbers in the study are too small to draw any conclusions.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

10. CONCLUSIONS

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.

The sponsor states the following regarding this soft tissue surgery study: “No safety concerns were identified by the study. The incidence of clinically meaningful AEs (adverse events) was similar in the two treatment groups and the events were of the types that were expected following these major surgical procedures.” (Study synopsis page 9/177). Review and analysis of the US soft tissue surgery study does not agree with this conclusion. 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.

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 do 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 fact that patients enrolled in this trial were at high risk for venous thromboembolic events (VTE) makes it difficult to detect a real VTE safety signal. A trial design in which subjects are at low risk for VTE or stratified based on VTE risk is worth considering. It is also the case that the majority of the adverse events can be traced to common product lots and a specific time frame (last quarter of 2008 to January 2009). According to the sponsor, “The observation of a cluster of thrombotic/thromboembolic events during study 400-07-002 was extensively investigated. The events occurred mainly during the non-randomized phase of the study when Fibrin Pad Lot M06F164 was in use. Extensive biochemical characterization of Lot M06F164 in comparison to the other lots used in clinical studies revealed no differences that were considered likely to have any relevance to the safety of the product. Analysis of the events by center and by operative procedure/anatomic location did not suggest an association. Half of the events occurred within 14 days of surgery.

The overall incidence was consistent with published data on VTEs and does not suggest an increased risk for thrombotic event in Fibrin Pad treated subjects, although from the available data, this risk cannot be completely ruled out.” (Section 2.7.4 ISS conclusions 2.2.5.3.7 page 30.)

The sponsor claims to have thoroughly investigated the manufacturing and use of these lots. They were not able to find manufacturing or investigator use of the products as explanations for the adverse events. FDA CMC inspectional findings did not find that lot manufacturing differences could reasonably account for the thrombotic adverse event observations.

A review of the operative reports and case report forms indicates that one cannot be certain where the FP or Surgicel was applied (other than in general terms such as thoracic muscle). It is important to note that additional FP or Surgicel (according to assigned treatment) could be used if additional bleeding sites were in need of adjunctive hemostats. These additional sites were often not described in the dictated operative report or noted on the case report forms. Thus, it is difficult to know for certain if the product might have been placed in a location that predisposed to thrombotic or other adverse events.

Overall this phase 2 study design comports with a preliminary safety and effectiveness assessment for two ill defined categories of bleeding. While CBER currently does not make a distinction between mild and moderate bleeding for the purpose of adjuncts to

hemostasis, it is important to note that a lack of validated bleeding severity scale limits assessment of product performance, outcome reproducibility and repeatability, as well as data poolability.

Additional issues identified from this phase 2 study include the following: (See review memo for Roxolana Horbowyj, MD)

- Sample size per anatomic site were too small for independent assessment per anatomic site;
- Outcomes of device use (hemostasis) and. adverse events may not be poolable across anatomic sites, e.g. pneumothorax;
- There are notably higher incidence of abscess (all types) and pneumothorax in the investigational arm;
- As currently marketed products, vicryl and oxidized regenerated cellulose (ORC) devices are not explicitly indicated for use at anatomic sites of cancer resection. The use of these materials in patients with active oncologic disease should be studied independently to assess influence of local recurrence and progression of oncologic disease, as well as survival.
- Short length of follow up (30 days) should be extended to 60 days since the product is expected to fully resorb in 60 days.

11. BENEFIT-RISK CONSIDERATIONS AND RECOMMENDATIONS

11.1 Benefit-Risk Considerations:

Since there are other adjuncts to hemostasis currently marketed for use in general surgery, the risks of potential thrombosis, infection, adhesions require careful consideration. In the overall clinical program, the sponsor seeks to market the FP for use in “more than mild to moderate” bleeding. In this situation, there are less acceptable alternatives, especially for so called severe surgical or traumatic bleeding. The risks verses benefits of the FP may prove to be quite different in the severe bleeding situation. Since this application focused on mild-moderate bleeding (which is understood to be the type of bleeding that traditional adjuncts to hemostasis addresses) another clinical trial either in soft tissue surgery or other surgical setting with appropriate clinical monitoring for adverse events of concerns should be submitted or undertaken. In addition, it may be necessary to evaluate the FP in a patient population that is at low risk for thromboembolic events to sort out the possible thrombosis safety signal.

11.2 Benefit-Risk Summary and Assessment

See discussion above (11.1)

11.3 Discussion of Regulatory Options

The regulatory option is to send a complete response and request 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, the sponsor may submit safety data from an adequate and well controlled study with the Fibrin Pad in a different surgical population.

On September 15, 2011 the letter ready comments in the original final review memo were revised per discussions with Nisha Jain and Basil Golding.

The following clinical letter ready comments should be conveyed to the sponsor:

CR letter ready comments:

Clinical:

1. The review of the submitted data shows an unfavorable trend towards the investigational product (FP) with regard to thrombotic events (TEs). Specifically, our review indicates the following:
 - a. In the non randomized part of the study 400-07-002 a total of nine TEs were reported in seven subjects out of 51 subjects enrolled in the study. As the cluster of TEs were 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 do not adequately address FDA's concern 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 is unclear if the patients were adequately monitored to capture thromboembolic events, infections, abscesses, adhesions/ obstructions.
 - a. Therefore, in order to support licensure of FP 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.
 - b. Alternatively, you may submit safety data from an adequate and well controlled study with the Fibrin Pad in a different surgical population.

BIMO inspections:

FDA inspections and monitoring reports reveal issues with regard to conduct of the trial.

- Please submit detailed information on how the investigators and sub-investigators were trained to comply with the study requirements.
- Failure to prepare or maintain case histories with respect to observations and data pertinent to the investigation. Specifically the protocol requires that certain Inclusion and Exclusion criteria be determined by the Clinical Investigator during surgery, where study specific procedures, such as randomization and the application of the study drug, are to be performed. Operative Reports for subjects 11104, 11106, 11108, 11109, 11113, 11114, 11115, and 11203, which constitute more than a third of the study subjects, do not mention the use of the study drug during surgery, yet this data was submitted to the sponsor, as stated in the *Soft Tissue Study Worksheets* (found in the subject's records) and in the data listings provided by the sponsor. Please identify and submit the source of the above missing information in the operative reports that was submitted to the FDA.
- Failure to comply with 21 CFR 312.61: Study drug was administered to subjects not under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator. Specifically, the Operative Report for subject 11112, dictated by ---(b)(6)--- (not listed in the Statement of Investigator, Form FDA 1572), describes the use of the study drug during his surgery but does not mention the Clinical Investigator or Sub-Investigator as being present at any point during the procedure. The Nurse Intraoperative Report also does not list the Clinical Investigator or Sub-Investigator as being present during the surgery. Please explain.
- An investigation was not conducted in accordance with the investigational plan. Specifically,
 - i. The protocol states that: "Prior to participation, the study procedures and any known or likely risks will be explained to the subjects by the investigator or other medically qualified co-investigator." In 4 of 18 instances, the study procedures and any known or likely risks were explained to potential subjects (who were eventually enrolled into the study) by Study Coordinators who also signed the Informed Consent Form, when the Clinical Investigator or Sub-Investigator were not available to do so. Except for a letter from the Sponsor dated 03/10/2011, provided to FDA during the inspection by Dr. Bochicchio, a Co-Investigator is not defined anywhere in the protocol as a Study Coordinator or any other study staff member. This letter states that the term "medically qualified co-investigator" should have been edited as "or designee", yet this was not an edit reviewed and approved by the IRB. Study Coordinators listed in the "Delegation of Authority" for protocol 400-07-002, which was signed by Dr. Bochicchio, are not qualified to practice medicine.
 - ii. There is no evidence that five members from the research study staff, listed in the "Delegation of Authority" as being Study Coordinators, authorized to

obtain Informed Consent, complete Case Report Forms, obtain Medical History and conduct subject follow-up, were qualified and trained on the specifics of the protocol to do so. Please explain.

The “Site Initiation Training” attendance log, dated April 10,2008, provided by -----(b)(4)-----, at the University of Maryland Medical Center, does not list the following individuals as being present during the site initiation training, yet they are listed in the “Delegation of Authority” (Exhibit 3) for this study: -----(b)(6)----, Sub-Investigator (attended protocol-specific training on 06/24/2008, but was not present at the site initiation), -----(b)(6)-----, Study Coordinator, -----(b)(6)-----, Study Coordinator, -----(b)(6)-----, Study Coordinator, -----(b)(6)-----, Study Coordinator, and -----(b)(6)-----, Study Coordinator. Please submit all training documentations at this site. Also, please submit documentation to confirm that the above mentioned investigators underwent training.

Sixteen of thirty two subjects were enrolled in another investigational study while participating in Protocol 400-07-002 at University of Alabama, Birmingham, Alabama site and there was no documented evidence of sponsor and/or IRB notification and/or approval to enroll the subjects in concurrent studies. Please submit detailed information on the sponsor/IRB notification and subject consents to participate in another investigational study.

11.4 Recommendations on Regulatory Actions

Based on my review of the clinical data, I recommend a complete response to this submission.

11.5 Labeling Recommendations

Since I am recommending a complete response, there are no labeling recommendations for this submission.

11.6 Recommendations on Postmarketing Actions

Since I am recommending a complete response, there are no recommendations on postmarketing actions.