Application Type	**Efficacy Supplement**
STN	**103980/5601**
CBER Received Date	**April 1, 2011**
PDUFA Goal Date	**January 30, 2012**
Division / Office	**DH /OBRR**
Priority Review	**No**
Reviewer Name(s)	**Kimberly Lindsey**
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	**Baxter Healthcare Corporation**
Established Name	**Fibrin Sealant**
(Proposed) Trade Name	**TISSEEL**
Pharmacologic Class	**Fibrin Sealant**
Formulation(s), including Adjuvants, etc	**Sealer Protein Solution** • **Total protein: 96 – 125 mg/mL** **Fibrinogen:** • **Fibrinogen: 67 – 106 mg/mL** • **Fibrinolysis Inhibitor (Aprotinin [Synthetic]): 2250 – 3750 KIU/mL** **Thrombin Solution** • **Thrombin (Human):400-625 units/mL** • **Calcium Chloride: 36 – 44 µmol/mL**
Dosage Form(s) and Route(s) of Administration	**a freeze-dried kit or prefilled frozen syringes** **Both the freeze-dried and frozen forms are supplied as 2 mL, 4 mL or 10 mL (total volume) pack sizes.**
Dosing Regimen	**Dosed by area**
Indication(s) and Intended Population(s)	**Hemostasis:** **as an adjunct to hemostasis in patients undergoing surgery when control of bleeding by conventional surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. TISSEEL is effective in fully heparinized patients undergoing cardiopulmonary bypass.** **Sealant:** **an adjunct to standard surgical techniques (such as suture, and ligature) to prevent leakage from colonic anastomoses following the reversal of temporary colostomies.**

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GLOSSARY OF ACRONYMS

AE	adverse event
BLA	biologics license application
CMC	chemistry, manufacturing, and controls
eCTD	electronic Common Technical Document
ePFTE	expanded polytetrafluoroethylene graft
FDAAA	Food and Drug Administration Amendments Act of 2007
FS*	Fibrin sealant (i.e. TISSEEL)
FS 60	Fibrin sealant (i.e. TISSEEL) polymerization time of 60 seconds
FS 120	Fibrin sealant (i.e. TISSEEL) polymerization time of 120 seconds
FS VH/SD s apr	Fibrin sealant vapor heated, solvent detergent treated, synthetic aprotinin(i.e.TISSEEL)
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IND	Investigational new drug application
ISE	integrated summary of efficacy
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NAI	no action indicated
PD	pharmacodynamics
PeRC	Pediatric Review Committee
PI	package insert
PK	pharmacokinetics
PP	per protocol
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
sBLA	supplemental biologics license application
VAI	voluntary action indicated

1. EXECUTIVE SUMMARY

TISSEEL received approval from the US Food and Drug Administration (FDA) on May 1, 1998 as an adjunct to hemostasis in surgeries in cardiopulmonary bypass (CPB) and treatment of blunt or penetrating splenic injuries, when control of bleeding by conventional surgical techniques, including suture, ligature, and cautery, is ineffective or impractical. It is also indicated as an adjunct to standard surgical techniques (such as suture and ligature) to prevent leakage from colonic anastomoses following the reversal of temporary colostomies. (BLA103980, US license number 140).
The Applicant is submitting this efficacy supplement to present data from the two vascular surgery studies conducted under BBIND -(b)(4)-. These data from these trials are intended to support TISSEEL as a general adjunct to hemostasis.

Subsequent to the initial approval of TISSEEL in 1998, in addition to the vapor heat (VH) treatment used for TISSEEL a second virus inactivation step, solvent/detergent (S/D) treatment, was incorporated into the manufacture of TISSEEL to further improve its viral safety profile. The bovine-derived aprotinin previously used as a fibrinolysis inhibitor was replaced with synthetic aprotinin, thereby eliminating the risk of infection with bovine spongiform encephalopathy (BSE) and other bovine pathogens. In July 2006, TISSEEL with bovine aprotinin received licensure in the US for the indications stated above, and was subsequently replaced by the new generation TISSEEL with synthetic aprotinin in 2007.
Since changes to previous generations of Baxter's fibrin sealant were made to enhance the safety profile only, the different generations of product are herein uniformly referred to as TISSEEL. These modifications to the formulation have been reviewed and approved since the initial approval.

TISSEEL is available as a freeze-dried kit or prefilled frozen syringes. The 2 active ingredients, fibrinogen (human) and thrombin (human), are contained within the 2 separate components of TISSEEL: sealer protein (human) and thrombin (human). Sealer protein (human) is provided as a freeze-dried powder [Sealer Protein Concentrate (Human)] for reconstitution with fibrinolysis inhibitor solution (synthetic aprotinin), or as a finished frozen solution prefilled into one side of a dual-chambered syringe. The main active ingredient in sealer protein (human) is fibrinogen. Aprotinin (synthetic), a fibrinolysis inhibitor, is included in the sealer protein (human) component to delay fibrinolysis, which might cause rebleeding or detachment of sealed or glued tissue parts. Thrombin (human) is provided either as a freeze-dried powder for reconstitution with calcium chloride solution or as a finished frozen solution prefilled into one side of a dual-chambered syringe. The 2 components are mixed together in equal proportions as they are administered to the treatment site, forming a clot within seconds.
The sealer protein and thrombin solutions are manufactured from pooled human plasma. All plasma complies with requirements as published in the US Code of Federal Regulations (US CFR) and the recommendations and guidelines published FDA.

TISSEEL is manufactured using Vapor Heat treatment and S/D treatment as 2 independent/ validated virus clearance steps.

Baxter conducted two clinical trials, Studies 550602 and 550801, to evaluate the use of TISSEEL as an adjunct to hemostasis in peripheral vascular surgery. Both studies used standard labeled dosing of TISSEEL applied to a vascular anastomosis after standard suturing with measurement of time to hemostasis at the site of product application. The control method for establishing hemostasis was manual compression with gauze pads in both studies.

Study 550602 was a phase 2 prospective, randomized, controlled, subject-blinded, multicenter study designed to evaluate the efficacy and safety of TISSEEL for hemostasis in subjects receiving peripheral vascular ePTFE conduits, compared to a control group treated by manual compression with surgical gauze pads. The intent to treat (ITT) populations comprised all 73 randomized and treated subjects: 26 subjects treated

with FS-60 (TISSEEL polymerization time of 60 seconds, 24 subjects with FS-120 (TISSEEL polymerization time of 120 seconds), and 23 subjects with manual compression. In this surgical population the primary efficacy endpoint was time to hemostasis in 4 minutes (4 minutes from time of product application to the suture line, therefore including the polymerization time). Hemostasis had to be maintained until closure of the surgical wound.

Randomization was stratified by protocol defined bleeding severities to keep the balance between the 3 treatment groups. The enrolled subjects who fulfilled the entry criteria were randomized and treated in 3 equal-sized groups. Two treatment groups (FS-60 and FS-120), which differed in polymerization/setting time (60 seconds versus 120 seconds) prior to opening the cross clamps, were treated with TISSEEL. In both TISSEEL groups, TISSEEL was applied onto the bleeding suture lines, while the treatment of the control group consisted of manual compression.

For the intent-to-treat (ITT) population, the highest proportion of subjects that achieved hemostasis at 4 minutes and maintained it until surgical closure was 62.5% (15/24) for the FS-120 subjects, followed by 46.2% (12/26) for the FS-60 subjects and 34.8% (8/23) for control subjects. These proportions are not significantly different. The overall two-sided p-value from the likelihood ratio chi-square test indicated that there was no statistically significant difference at the 10% level in the comparison of hemostasis rates between the 3 treatment groups for the ITT population (P=0.1564) and the PP population (P=0.1944).

Study 550801 was a phase 3 prospective, randomized, controlled, subject-blinded, multicenter study designed to evaluate the efficacy and safety of TISSEEL for hemostasis in subjects receiving peripheral vascular ePTFE conduits, compared to a control group treated by manual compression with surgical gauze pads.
Similar to the phase 2 study, the primary efficacy endpoint is the proportion of subjects achieving hemostasis at the study suture line of the ePTFE graft at 4 minutes. Hemostasis had to be maintained until closure of the surgical wound. The statistical approach was also similar to the phase 2 study except a one-sided significance level of 0.025 was used.

The sample size derivation was based on results of the Phase 2 study (study 550602), 60% and 35% of hemostasis for TISSEEL and manual compression, respectively. A total of 176 subjects were enrolled (i.e., signed informed consent) at 24 study sites and screened for eligibility according to the inclusion/exclusion criteria described in the protocol. The number of subjects randomized and treated at each study site ranged from 0 to 13. Of the 176 subjects enrolled, 140 subjects were randomized and treated, and included in the ITT population; 132 subjects were included in the PP population. A total of 70 subjects were treated with FS, and 70 subjects were treated with manual compression (control). Baseline characteristics (age, weight, height, gender, race, and ethnicity were comparable between the two groups. A total of 140 evaluable subjects (70 subjects per treatment arm) undergoing ePTFE graft placement including arterio-arterial bypasses and arteriovenous (AV) shunts were comparable across the treatment groups.

For the ITT population, the proportion of subjects that achieved hemostasis at the study suture line at 4 minutes and maintained it until surgical closure was 62.9% (44/70 subjects, 95% CI = 51.2% to 73.6%) in the FS-120 group and 31.4% (22/70 subjects; 95% CI = 21.4% to 42.8%) in the control group. The one-sided p-value from the likelihood ratio chi-square test indicated that there was a statistically significant difference at the one-sided 2.5% level in the comparison of hemostasis rates between the two treatment groups (P<0.0001).

The safety evaluation did not raise any concern demonstrated comparable adverse events between the fibrin sealant and control groups.
In conclusion, the study results demonstrated a statistically significant difference between the treatment groups in the proportion of patients who achieved hemostasis 4 minutes post suture line closure after surgery and there were no safety issues identified to preclude a recommendation for approval.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Vascular graft placement to bypass, replace, or patch arteriosclerotic vessels and to establish arteriovenous (AV) shunts in dialysis patients is a clinical situation associated with significant and often difficult to control blood loss. A frequently used graft material is expanded polytetrafluoroethylene (ePTFE). The low thrombogenicity, porosity, and limited elasticity of ePTFE vascular grafts, while beneficial, can lead to prolonged suture line bleeding. The problem is exacerbated by the intraoperative use of heparin, which has become routine in vascular surgery in order to prevent intra- and post-operative thrombosis. In dialysis patients, the underlying disease compromises the coagulation system and dialysis itself may lead to increased fibrinolysis. Use of adjunctive methods, such as topical hemostats, to control bleeding often proves to be useful in these surgical situations.

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

Surgical techniques have improved achieving and maintaining hemostasis in vascular surgery, but this has not completely solved the problem of bleeding that is difficult to control using primary hemostatic methods. The application of topical hemostats and sealants, including different forms of collagen, oxidized cellulose or gelatin alone or in combination with thrombin polyethylene glycol based glues, gelatin, and cyanoacrylate glue have been used with varying success. Typically, suture-hole bleeding is managed by manual compression with surgical swabs and reversal of heparin, which is still the generally accepted standard of care.
Fibrin sealants have shown beneficial results with respect to time to hemostasis and blood loss in various preclinical and clinical studies provided the impetus for the initiation of prospective controlled clinical studies investigating the safety and efficacy of TISSEEL for use as an adjunct to hemostasis in the placement of ePTFE vascular grafts, including arterio-arterial bypasses and AV shunting for dialysis access

2.3 Safety and Efficacy of Pharmacologically Related Products

Management of hemostasis during surgery begins with good surgical technique. In addition to primary methods such as suture, cautery and ligature, to achieve and maintain hemostasis, adjunctive or secondary hemostatic agents have been used widely for yeast and they have a long history for effective and safe use in a variety of surgical procedures. The types of surgical procedures and bleeding influence the choice of topical hemostatic agent that is used by the surgeon.
Topical hemostatic agents can be collagen, cellulose gelatin or thrombin based. Topical sealants and adhesives include fibrin sealants which are regulated as biologics and synthetic glues, which are regulated as devices.

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

TISSEEL is marketed under the trade name TISSEEL/TISSUCOL Duo-500 outside of the US, where it has the following indications: achieve hemostasis, to seal or to glue tissue, and to support wound healing.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

A pre BLA meeting was held in October 2010 to discuss the Applicant's plans to submit a BLA supplement for the vascular surgery studies evaluating TISSEEL as an adjunct to hemostasis. The data from the completed phase 2 and 3 vascular surgery studies together with the splenic and cardiovascular surgery studies for which TISSEEL use is approved, were planned to form the basis for a broad general adjunct to hemostasis in general surgery indication. The studies conducted to support this application are consistent with the designs of previously approved indications for this product and the "Guidance for Industry: Efficacy Studies to Support Marketing of Fibrin Sealant Products Manufactured for Commercial Use."

2.6 Other Relevant Background Information

Not applicable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The efficacy supplement includes sections of modules 1 (Administrative information and prescribing information) 2 (clinical overview and clinical summary) and 5 (clinical study reports for the vascular indication – Clinical Study Reports 550602 and 550801).
Modules 3 (Quality) and 4 (nonclinical) are not applicable as there have been not changes to these portions of the approved BLA (STN 103980).
The submission is adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Biomedical research monitoring observations were conducted for 3 clinical investigators as the findings are as follows:

NAI: September 14, 2011 Kevin Nolan, MD, Providence Hospital and Medical Center in Southfield, Michigan. The inspection revealed no deviations from applicable regulations.

VAI: October 5, 2011. A Form 483 Inspectional Observations was issued and discussed with James Dennis, MD, Department of Surgery Jacksonville, FL,

- Clinical Laboratory assessments at the day-14 post-operative follow-up visit were not performed for 8 of 13 subjects. The study protocol requires clinical laboratory assessments at the pre-operative screening visit and the day-14 post-operative follow-up visit. In addition, the protocol-required rate of respiration was not measured at various study visits for 7 of 13 subjects.
- The intra-operative assessment dated 3/19/10, and the dictated operative report dated 3/19/10 document that Subject --(b)(6)-- was randomized to the moderate bleeding arm of the study. The protocol-required source documentation maintained to show the randomization assignment for Subject --(b)(6)-- includes an opened severe bleeding randomization envelope and an unopened moderate bleeding randomization envelope, indicating that Subject --(b)(6)-- was actually randomized to the Severe Bleeding arm of the study.
- At the end of the inspection, the FDA Investigator discussed with you and your study staff a number of issues including untimely review of study records to determine subject eligibility, study visits that were conducted outside of protocol-specific timeframes, and the incorrect dose of heparin administered to some subjects during surgery.

VAI: October 4, 2011 Mark Sarfati, MD, Salt Lake City, Utah

- Subject --------(b)(6)------- was screened on 4/6/2010 and subsequently enrolled into the study despite having met the study specific exclusion criteria # 7, which states "known severe congenital or acquired immunodeficiency, e.g. HIV infection or long-term treatment with immunosuppressive drugs." Concomitant medication source documents describe Subject --------(b)(6)-------- as having documented use of the study prohibited medications cyclophosphamide with a start date of 1/27/2010 and prednisone with a start date of 3/10/2010.

- Source documents contained at least ten unexplained changes and/or additions to observations made from one to six months after the data were originally captured. Specifically, for several subjects, changes were made by an investigator or the study coordinator to assessment reports which were completed one to six months prior to the corrections being made and without adequate documentation of the reasons for the change/modification of the original data. In at least three cases the original assessment was made by an investigator, and there is no indication that you reviewed the changes which were made by the study coordinator

Reviewer comment: These inspectional observations are not expected to impact the safety and efficacy of TISSEEL. Both VAI recipients responded to the VAI letters with corrective action plans that appear to adequate.

3.3 Financial Disclosures

Financial certification and disclosure information (Form 3454) were submitted. The applicant certifies that there have been no arrangements where the value of the compensation could have been affected by the outcome of the study. A list of Investigators for Study 550602 and 550801 are included in the Financial Information folder of the submission.

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

4.1 Chemistry, Manufacturing, and Controls

TISSEEL is a licensed product. No manufacturing changes were made during the conduct of the trials serving as the basis for this efficacy supplement.
TISSEEL [Fibrin Sealant], Vapor Heated, Solvent Detergent Treated, (TISSEEL) is a two-component fibrin sealant made from pooled human plasma. When combined, the two components, Sealer Protein (Human) and Thrombin (Human), mimic the final stage of the blood coagulation cascade.

Sealer Protein (Human)
Sealer Protein (Human) is a sterile, non-pyrogenic, vapor-heated and solvent/detergent treated preparation made from pooled human plasma. Sealer Protein (Human) is provided either as a freeze-dried powder [Sealer Protein Concentrate (Human)] for reconstitution with Fibrinolysis Inhibitor Solution (Synthetic) or as a finished frozen solution pre-filled into one side of a dual-chambered syringe (1). The active ingredient in Sealer Protein (Human) is fibrinogen. A Fibrinolysis Inhibitor, Aprotinin (Synthetic) is included in the Sealer Protein (Human) component to delay fibrinolysis. Aprotinin (Synthetic) is manufactured by solid phase synthesis from materials completely of non-human/non-animal origin.

Thrombin (Human)
Thrombin (Human) is a sterile, non-pyrogenic, vapor-heated and solvent/detergent treated preparation made from pooled human plasma. Thrombin (Human) is also provided either as a freeze-dried powder for reconstitution with Calcium Chloride Solution or as a finished frozen solution pre-filled into one side of a dual-chambered syringe (2).

The reconstituted solution or pre-filled syringe contains:
Sealer Protein Solution

Total protein: 96 – 125 mg/mL
Fibrinogen: 67 – 106 mg/mL
Fibrinolysis Inhibitor (Synthetic): 2250 – 3750 KIU/mL
Other ingredients include: human albumin, tri-sodium citrate, histidine, niacinamide, polysorbate 80 and water for injection.

Thrombin Solution

Thrombin (Human): 400 – 625 units/mL*
Calcium Chloride: 36 – 44 µmol/mL
Other ingredients include: human albumin, sodium chloride and water for injection.

4.2 Assay Validation

Not applicable.

4.3 Nonclinical Pharmacology/Toxicology

There are no new pharmacology/ toxicology data for review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Upon mixing Sealer Protein (Human) and Thrombin (Human), soluble fibrinogen is transformed into fibrin, forming a rubber-like mass that adheres to the wound surface and achieves hemostasis and sealing or gluing of tissues.

4.4.2 Human Pharmacodynamics (PD)

Thrombin is a highly specific protease that transforms the fibrinogen contained in Sealer Protein (Human) into fibrin. Fibrinolysis Inhibitor, Aprotinin (Synthetic), is a polyvalent protease inhibitor that prevents premature degradation of fibrin. Preclinical studies with different fibrin sealant preparations simulating the fibrinolytic activity generated by extracorporeal circulation in patients during cardiovascular surgery have shown that incorporation of aprotinin in the product formulation increases resistance of the fibrin sealant clot to degradation in a fibrinolytic environment

4.4.3 Human Pharmacokinetics (PK)

Not applicable

4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses cited by the applicant were supported by the submitted data.

4.6 Pharmacovigilance

TISSEEL has been on the US market since 1998. Worldwide, the Applicant has an ongoing active pharmacovigilance program for TISSEEL.

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

Study synopses for recent clinical studies of TISSEEL evaluating the safety and efficacy of TISSEEL for use as an adjunct to hemostasis in vascular surgery under BB-IND -(b)(4)-:
Study 550602 (phase 2)
Study 550801 (phase 3)
These studies are intended to support an adjunct to hemostasis in peripheral vascular surgery indication.

In accordance with the "Guidance for Industry: Efficacy Studies to Support marketing of Fibrin Sealant Products Manufactured for Commercial Use", the compilation of the cardiovascular, splenic salvage indications in combination with a peripheral vascular indication are sufficient to form the basis for a general adjunct to hemostasis indication. Therefore, summary information from the following studies was also briefly reviewed:

- **Study 55003** (Aug 9, 2005): a prospective, parallel group, randomized (1:1), double-blind, multicenter Phase 3 study confirming the equivalence of the efficacy of TISSEEL to TISSEEL VH for use as a hemostatic agent in subjects undergoing cardiovascular surgery requiring CPB (STN 103980/5121; approved July 2006) (n= 317 treated with TISSEEL).

- **Study 550602** (April 14, 2009)

- **Study 020** Final evaluation: a pivotal, confirmatory, historically controlled, prospective study evaluating the efficacy of TISSEEL as a hemostatic agent in subjects who underwent laparotomy for injuries to the spleen and/or liver (STN BL 103980/0; approved May 1998) (n= 119 treated with TISSEEL).

- **Study 014/016** Final evaluation: a pivotal, prospective, randomized Phase 3 study evaluating the efficacy of TISSEEL as a hemostatic agent in subjects undergoing cardiovascular surgery requiring CPB (STN BL 103980/0; approved May 1998) (n= 289 treated with TISSEEL).

- Pediatric pharmacovigilance data submitted by the Applicant at the request of the review team.

- Guidance for Industry: Efficacy Studies to Support Marketing of Fibrin Sealant Products Manufactured for Commercial Use

5.1 Review Strategy

Given that the Applicant seeks a general adjunct to hemostasis indication based on cardiovascular, splenic trauma and vascular surgery, the data from these pivotal trials was considered for overall safety and efficacy in a variety of clinical settings.

The review strategy for the vascular indication was to evaluate the pooled results of phase 2 and 3 vascular surgery studies for safety. The phase 3 (pivotal) vascular surgery trial was the primary basis for efficacy evaluation for the vascular surgery indication. The safety results will be presented individually for the vascular phase 2 and 3 studies as well as pooled data.

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

Documents in eCTD modules 1, 2, and 5. Specifically,

1. Labeling
2. Clinical Summary
3. Clinical study reports
    a. Study 550602
    b. Study 550801
    c. Study 020
    d. Study 014/016
    e. Study 550003
    f. Publications
    g. Case report forms for studies 550602 and 550801
    h. Debarment certification
    i. Financial disclosure information
    j. Request for waiver of pediatric studies

5.3 Table of Studies/Clinical Trials

Table of Studies/Clinical Trials for TISSEEL related to the claimed indication (adjunct to hemostasis for peripheral vascular surgery)
(Adapted from Original sBLA 103980/5601; table 2.5-11 model 2 section 5 clinical overview, p.59-60)

Clinical Studies in TISSEEL Clinical Development Program								
Study Number	**Objective**	**Design**	**Treatment**		**N**	**(Treated)**	**1° Efficacy Endpoint**	**Safety endpoints**
			***IP**	**Control**	**IP**	**Control**		
550602	Hemostasis in subjects receiving peripheral vascular ePTFE conduits, as compared to manual compression with surgical gauze pads	A Phase 2, prospective, randomized, controlled, subject-blinded, multi-center study with 3 parallel, equal sized groups	TISSEEL	Manual compression with surgical gauze pads	50	23	* proportion of subjects achieving hemostasis at the study suture line of the ePTFE graft at 4 minutes	* AEs * vital signs * laboratory values

IP= investigational product

Clinical Studies in TISSEEL Clinical Development Program								
Study Number	**Objective**	**Design**	**Treatment**		**N**	**(Treated)**	**1° Efficacy Endpoint(s)**	**Safety endpoints**
			IP	**Control**	**IP**	**Control**		
550801	Hemostasis in subjects receiving peripheral vascular ePTFE conduits, as compared to manual compression with surgical gauze pads	A Phase 3, prospective, randomized, controlled, subject-blinded, multi-center study	TISSEEL	Manual compression with surgical gauze pads	70	70	* proportion of subjects achieving hemostasis at the study suture line of the ePTFE graft at 4 minutes	* AEs * incidence of infections at surgical site * incidence of graft occlusion

5.4 Consultations

Not applicable.

5.4.1 Advisory Committee Meeting (if applicable)

Not applicable.

5.4.2 External Consults/Collaborations

Not applicable.

5.5 Literature Reviewed (if applicable)

Not applicable.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

The study design is similar for the phase 2 (study 550602) and 3 (study 550801) vascular studies, however, the phase 2 study was used to select the time for set up of TISSEEL 60 seconds vs. 120 seconds for safety and efficacy. The efficacy and safety results from the phase 3 study are presented in detailed in section 6.1. This review summarizes the study design of the phase 2 study in section 6.2. The phase 2 and 3 studies will be pooled for safety.

Studies to support the peripheral vascular indication include (study 550602- phase 2 and study 550801-phase 3)

6.1 Trial #1

Study 550801 (phase 3 peripheral vascular bypass surgery study)

6.1.1 Objectives (Primary, Secondary, etc)

The primary objective of the study was to evaluate the efficacy of TISSEEL for hemostasis in subjects receiving peripheral vascular ePTFE conduits, as compared to a control arm treated with manual compression with surgical gauze pads. The secondary objectives of the study were to evaluate efficacy in terms of the incidence of rebleeding at the study suture line and to evaluate safety in terms of the incidences of AEs, infections of the surgical site, and graft occlusions.

6.1.2 Design Overview

The study was a Phase 3, prospective, controlled, randomized, subject-blinded, multicenter study in two parallel, equal-sized treatment arms to compare the efficacy and safety of TISSEEL versus manual compression with surgical gauze pads. TISSEEL was applied onto the bleeding suture lines for a total of 140 evaluable subjects (70 subjects per treatment arm) undergoing prosthetic ePTFE graft placement.

6.1.3 Population

Subjects were eligible for study inclusion if the met all of the following inclusion criteria:

Inclusion Criteria:
1. Male or female of all ages
2. Subjects undergoing vascular surgery (i.e., conduit placement with an ePTFE graft), including the following:
    a. Arterio-arterial bypasses
        - Axillo-femoral bypass
        - Ilio-femoral bypass
        - Femoro-femoral bypass
        - Ilio-popliteal bypass
        - Femoro-popliteal (including below knee) bypass
        - Femoro-tibial vessel bypass

    b. Arteriovenous shunting for dialysis access in the upper or lower extremity
3. Signed informed consent
4. Suture line bleeding eligible for study treatment is present after surgical hemostasis.

Exclusion Criteria:
1. Concurrent participation in another clinical study treatment with another investigational drug or device within the last 30 days
2. Other vascular procedures during the same surgical session
3. Arterio-arterial bypasses with more than 2 anastomoses
4. Pregnant or lactating women
5. Congenital coagulation disorders
6. Prior kidney transplantation
7. Heparin-induced thrombocytopenia
8. Known prior exposure to aprotinin within the last 12 months
9. Known hypersensitivity to aprotinin or other components of the product
10. Known severe congenital or acquired immunodeficiency
11. Prior radiation therapy to the operating field
12. Severe local inflammation at the operating field
13. Major intraoperative complications that required resuscitation or deviation
14. from the planned surgical procedure
15. Intraoperative change in planned surgical procedure, which resulted in subject no longer meeting preoperative inclusion and/or exclusion criteria.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects randomized to the TISSEEL group were treated once intraoperatively with TISSEEL at the study suture line and once intraoperatively with FS VH S/D 500 s-apr at the non-study suture line (if there was bleeding that required treatment). If additional treatment was required to achieve hemostasis, the choice of the alternative treatment was at the discretion of the investigator; however, no fibrin sealant other than FS VH S/D 500 s-apr was to be used.
Subjects randomized to the control group were treated once intraoperatively with manual compression using surgical gauze pads at the study suture line and non-study suture line. If additional treatment was required to achieve hemostasis, the choice of the alternative treatment was at the discretion of the investigator; however, neither TISSEEL nor any other fibrin sealant was to be used.

6.1.5 Directions for Use

TISSEEL is applied to a bleeding site only after primary methods to control bleeding have been employed. TISSEEL is applied by drip or spray methods as a thin layer to the bleeding surface.

6.1.6 Sites and Centers

Site No.	**Address**	**Investigators**
01	Harbor View Medical Center Vascular Surgery, Box 359796, 325 Ninth Avenue, Seattle, WA 98104	Nam Tran, MD
02	University of Kentucky Dept. of Surgery, Division of Cardiovascular & Thoracic Surgery, Charles Wethington Building, 900 South Limestone St., Suite 407 Lexington, KY 40536	Saha Sibu, MD
03	Kaleida Health – Buffalo General Hospital, Department of Surgery, 100 High Street Buffalo, NY 14203	Gregory Cherr, MD
04	Saint Joseph Hospital,350 N. Wilmot Tucson, AZ 85710	Ronald Kline, MD
05	Allegheny General Hospital,320 E. North Avenue,14th Floor, South Tower Pittsburgh, PA 15212	Satish Muluk, MD,
06	University of Utah, Dept. of Surgery,30 North 1900 East Room 3C344, School of Medicine, Salt Lake City, UT 84132	Mark Sarfati, MD
07	St. Vincent's East, 50 Medical Park East Drive,Birmingham,	

	AL 35235	Stanley Lochridge, MD
08	Holmes Regional Medical Center, 1350 So. Harbor City Blvd., Melbourne, FL 32901	Joseph Wasselle, MD
09	Surgical Therapeutic Advancement Center, University of Virginia Health System Hospital Drive, 4th Floor Barringer Rm. 4361, Charlottesville, VA 22908	Worthington Schenk, III, MD
10	Hackensack University Medical Center, 30 Prospect Avenue, Hackensack, NJ 07601	Gregory Simonian, MD
11	St. Joseph Hospital, 1100 W. Stewart Drive, Orange, CA 92868	Jeffrey Ballard, MD
13	Good Samaritan Hospital, 2222 Philadelphia Drive, Dayton, OH 45406	Eugene Simoni, MD
14	Baton Rouge General Hospital – Bluebonnet Campus, 8585 Picardy Ave., Baton Rouge, LA 70809	Albert Sam, II, MD
15	Wheaton Franciscan Healthcare, 5150 N. Port Washington Rd., Milwaukee, WI 53217	Allan Pasch, MD
16	St. Luke's Baptist Hospital, 7930 Floyd Curl Drive, San Antonio, TX 78229	Patrick Hartsell, MD,
18	College of Medicine, Jacksonville, 653 West 8th Street, Jacksonville, FL 32209	James Dennis, MD
19	UCSF Fresno – Community Regional Medical Center, 2823 Fresno St., Fresno, CA 93721	Eric Ladenheim, MD
20	Montefiore Medical Center, 3219 E. Tremont Avenue, Bronx, NY 10461	Francis Porreca, MD
23	Washington Hospital Center-Medstar, 110 Irving Street, NW, Washington, D.C. 20010	Sean O'Donnell, MD
24	Providence Hospital & Medical Centers, 16001 W. Nine Mile Road, Southfield, MI 48075	Kevin Nolan, MD
26	Trinity Medical Center, 800 Montclair Rd., Ste. 955, Birmingham, AL 35213	Parvez Sultan, MD
27	Lutheran Hospital,7950 W. Jefferson Blvd., Fort Wayne, IN 46804	Vincent Scavo, MD

28	St. Mary's of Michigan, 800 South Washington Ave., Saginaw, MI 48601	Norbert Baumgartner, MD
29	Overlake Hospital, 1035 116th Avenue, NE, Bellevue, WA 98004	Kathleen Gibson, MD

6.1.7 Surveillance/Monitoring

Schedule of Efficacy and Safety Measurements (Source: Original sBLA 103980/5601; Clinical Study Report 550801, p.29)

Table 9.5-1
Schedule of Study Procedures and Assessments

Procedures / Assessments	**PreOp Baseline Visit Within 14 Days Prior to Surgery**	**Interval Study Visits**			**End of Study Visit**
		Intra-op Day 0	**Post- op Discharge/ Day 1**	**Post-op Day 14± 4**	**Post –op Day 30 ± 5**
Informed consent [a]	X				
Inclusion/Exclusion	X	X			
Medical history	X				
Physical Exam	X			X	
Respiratory Rate	X		X	X	
Systolic and diastolic blood pressure, heart rate	X	X[b]	X	X	
Clinical Laboratory Tests [c]	X				
Study Product Treatment		**X**			
Time to hemostasis		**X**			
Type of Anesthesia		X			
Intraoperative complications		X			
Intraoperative rebleeding		X			
Postoperative rebleeding			X	X	X
Infections of the surgical site			X	X	X
Graft occlusion			X	X	X
Medications	X[d]	X	X	X	X
Non-drug therapy	X[d]	X	X	X	X
Adverse events	X	X	X	X	X

a. Occurs at enrollment (before screening).
b. Immediately prior to first opening of clamps.
c. For clinical laboratory assessments, see Table 9.5-2 Clinical Laboratory Assessments.
d. Starting with enrollment or 7 days prior to surgery, whatever occurs earlier.

(Source: Sponsor table page 30, Full study report 550801)

Table 9.5-2 **Clinical Laboratory Assessments**					
Assessments	**PreOp Baseline Visit Within 14 Days Prior to Surgery**	**Interval Study Visits**			**End of Study Visit**
		Intra-op Day 0	**Post- op Discharge/ Day 1**	**Post-op Day 14± 4**	**Post –op Day 30 ± 5**
Hematology[a]	X			X	
Clinical Chemistry[b]	X			X	
Coagulation tests[c]	X			X	
Pregnancy test [d]	X				

a. Hematology assessments include: hemoglobin (Hgb), hematocrit (Hct), red blood cell (RBC) count, white blood cell (WBC) count, differential, and platelet count.
b. Clinical chemistry assessments include: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, blood urea nitrogen (BUN), and creatinine.
c. Coagulation tests include INR and aPTT.
d. Within 72 hours before surgery.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint of the study was the proportion of subjects who achieved hemostasis at the study suture line at 4 minutes

The secondary efficacy endpoints were:

- The proportion of subjects having achieved hemostasis at 6 minutes which is maintained until closure of the surgical wound
- The proportion of subjects having achieved hemostasis at 10 minutes, which is maintained until closure of the surgical wound
- Intraoperative rebleeding at the study suture line after occurrence of hemostasis
- Postoperative rebleeding at the study suture line, defined as any rebleeding requiring surgical re-exploration.

Safety assessments included assessment of AEs, clinical laboratory tests, and vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate). AEs were assessed for relationship to treatment by the investigator at each study site.

In addition to clinical laboratory parameters, surgical site infections and graft occlusions were monitored.

Infections were to be recorded according to the following scale:
Grade I: Only dermis affected

Grade II: Infection invades subcutaneous region but not the arterial implant
Grade III: The arterial implant is infected

Graft occlusion, determined clinically and defined as absence of blood flow through the graft

Apart from pregnancy testing performed locally, all other laboratory test mandated by the protocol were performed in a central laboratory.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The intent to treat analysis set consisted of all subjects who were randomized. A sensitivity analysis was to be performed on the intent to treat population as a secondary analysis to assess the influence of missing data on the primary results

Sample size:
The calculation of the sample size for the pivotal study was based upon data collected during the phase 2 study. As noted in the statistical review by Stan Lin, PhD, the sample size of 75 for the phase 2 was based on the assumptions from the results of a previous pilot study. The proportion of subjects with hemostasis at 4 minutes for both TISSEEL (60 and 120 second's polymerization time) was assumed to be 60%; and for manual compression, 25%.The likelihood ratio chi-square test was carried out. If the overall test showed a statistically significant difference at a 10% two-sided level, then pair-wise comparisons between FS-60, FS-120 and manual compression were performed by the chi-square tests. The significance level was set to 10% two-sided for these pair-wise comparisons

Results for the intent-to-treat (ITT) population on the primary efficacy endpoint demonstrated that the highest proportion of subjects that achieved hemostasis at 4 minutes and maintained it until surgical closure was 62.5% (15/24) for FS-120 subjects, followed by 46.2% (12/26) for FS-60 subjects and 34.8% (8/23) for control subjects. However, these proportions are not statistically significantly different. The overall two-sided p-value from the likelihood ratio chi-square test indicated that there was no statistically significant difference at the 10% level in the comparison of hemostasis rates between the 3 treatment groups for the ITT population (P=0.1564) and the PP population (P=0.1944). A phase 3 study using the 120 second polymerization time was designed.

Similar to the phase 2 study, the primary efficacy endpoint for the phase 3 study was the proportion of subjects achieving hemostasis at the study suture line of the ePTFE graft at 4 minutes. If hemostasis was not achieved at minute 4, or if additional hemostatic treatment other than study treatment was required, or if intraoperative rebleeding occurred, the primary endpoint was deemed a "treatment failure."

The objective of the phase 3 study was to evaluate whether TISSEEL (allowed to polymerize for 120 seconds) was superior to manual compression. Hemostasis was to be maintained until closure of the surgical wound. The statistical approach was also similar to the phase 2 study except a one-sided significance level of 0.025 was used.

Proportions and corresponding 95% two-sided confidence intervals (based on the likelihood-ratio chi square test) were to be calculated for each study arm for the following secondary efficacy endpoints:

- Number of subjects who achieved hemostasis at 6 minutes which had been maintained until closure of the surgical wound (If hemostasis was not achieved at minute 6, or if additional hemostatic treatment was required, or if intraoperative rebleeding occurred, this secondary endpoint was set to "hemostasis at 6 minutes not achieved")
- Number of subjects who achieved hemostasis at 10 minutes which had been maintained until closure of the surgical wound (If hemostasis was not achieved at minute 10, or if additional hemostatic treatment was required, or if intraoperative rebleeding occurred, this secondary endpoint was set to "hemostasis at 10 minutes not achieved")
- Intraoperative rebleeding at the study suture line after hemostasis occurred
- Postoperative rebleeding at the study suture line, defined as any rebleeding that required surgical re-exploration

In addition, the rate of subjects who achieved hemostasis at 6 and 10 minutes after application, the rate of subjects with intraoperative rebleedings, as well as the rate of subjects with postoperative rebleedings, were to be analyzed by the likelihood ratio chi square test for proportions, comparing TISSEEL versus the manual compression arm. The p-values were to be interpreted in a descriptive manner.

Safety evaluation:
There was no pre-specified statistical analyses plan for safety of this product.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The intent to treat (ITT) and safety populations comprised all 140 randomized and treated subjects.

The per protocol (PP) population defined as subjects who met all exclusion /inclusion criteria and were randomized and treated according to the protocol with no major protocol violations, consisted of the 66 subjects in both the FS and control treatment groups.

6.1.10.1.1 Demographics
(Source: sBLA 130980/5801 Full Clinical Study Report 550801 pages 100-108, Intent to treat set Demographic and Baseline Characteristics)

Parameter	**Category**	**FS 120** N=70	**Control** N=70
Gender			
	Male	30 (42.9%)	37 (52.9%)
	Female	(57.1%)	33 (47.1%)
	Mean(SD)	62.5	66.3
	Median	63.5	68.0
	Min, Max	33, 88	43,90
Height (cm)			
	Mean (SD)	166.31	167.55
	Median	167.50	167.65
	Min, Max	112.9, 187.8	139.6, 187.8
Race			
	White	40 (57.1%)	41 (58.6%)
	Black or African American	28 (40.0%)	27 (38.6%)
	Asian	1 (1.4%)	0 (0.0%)
	American Indian or Alaska Native	1 (1.4%)	2 (2.9%)
	Native Hawaiian or other Pacific Islander	0 (0.0%)	0 (0.0%)
Ethnicity			
	Hispanic or Latino	4 (5.7%)	6 (8.6%)
	Non-Hispanic or Latino	66 (94.3%)	64 (91.4%)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Summary of Planned Surgical Procedure for ITT (Source: sBLA 103980/5601 Full Clinical Study Report 550801 pages 109, Table 14.11)

Planned surgical n of N (%)	**Type/ Location n or N (%)**	**Control**	**FS 120**
Arterio-arterial bypass			
	Axillo-femoral	2 of 70 (2.9%)	1 of 70 (1.4%)
	Axillo-bifemoral	1 of 70 (1.4%)	0 of 70 (0.0%)
	Aorto-bifemoral	5 of 70 (7.1%)	5 of 70 (7.1%)
	Ilio-femoral	0 of 70 (0.0%)	1 of 70 (1.4%)
	Femoro-femoral	4 of 70 (5.7%)	2 of 70 (2.9%)
	Ilio-popliteal	2 of 70 (2.9%)	0 of 70 (0.0%)
	Femoro-popliteal	24 of 70 (34.3%)	17 of 70 (24.3%)
	Femoro-tibial vessel	1 of 70 (1.4%)	2 of 70 (2.9%)
Arterio-venous dialysis access shunt	Upper extremity	31 of 70 (44.3%)	40 of 70 (57.1%)
	Lower extremity	0 of 70 (0.0%)	2 of 70 (2.9%)
Body Side	Right Side	27 of 70 (38.6%)	24 of 70 (34.3%)
	Left Side	35 of 70 (50.0%)	39 of 70 (55.7%)
	Both	8 of 70 (11.4%)	7 of 70 (10.0%)

Reviewer comment: The types of procedures are typical for US vascular surgery practices and were comparable across the treatment groups.

6.1.10.1.3 Subject Disposition
Seventy (70) subjects were included in both the FS and control treatment groups.
Of the 176 subjects enrolled, 140 subjects were randomized and treated, and included in the ITT population; 132 subjects were included in the PP population.

A total of 70 subjects were treated with FS, and 70 subjects were treated with manual compression (control) were analyzed as part of the safety population.

Of the 8 randomized and treated subjects who were excluded from the PP population, 8 had major protocol deviations due to eligibility, randomization, or protocol schedule reasons. Specifically,

- Subject 040007 had an eligibility protocol deviation. The subject had other vascular procedures done during the same surgical session (other than stenting and/or endarterectomy of the same artery, which were allowed).
- Subject 060004 had a randomization protocol deviation. Randomization occurred for this subject before the bleeding severity analysis of the study suture line was performed.
- Subject 060008 had an eligibility protocol deviation. The subject had long-term use of an immunosuppressive drug.
- Subject 100002 had an eligibility protocol deviation. The subject had other vascular procedures done during the same surgical session.
- Subject 200002 had a protocol schedule deviation. The manual compression check time at 4 minutes for the subject occurred more than 10 seconds from the planned check time.
- Subject 200005 had a protocol schedule deviation. The 4-minute manual compression check time for the subject occurred 14 seconds late.
- Subject 240008 had an eligibility protocol deviation. The subject had lupus and had long-term treatment with prednisone.
- Subject 260003 had a protocol schedule deviation. The 4-minute manual compression check time for the subject was done over 1 minute late.

In addition, a total of 19 protocol deviations occurring in 17 subjects were categorized as "other;" none of these were considered to be major protocol deviations. The majority (13) of deviations were due to the administration of heparin outside of the protocol-required dose. "Other" protocol deviations included the types of sutures and needles used in arterio-arterial bypass procedures and AV shunt placements did not meet the requirements of the study protocol (3 subjects); enrollment was out of sequence for 1 subject; the use of commercial TISSEEL for another vascular procedure in 1 subject; signing the incorrect consent form before blood was drawn in 1 subject.

The number of subjects randomized and treated at each study site ranged from 0 to 13.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary endpoint chosen was in accordance with the Guidance Document, "Efficacy Studies to Support marketing of Fibrin Sealant Products Manufactured for Commercial Use." This endpoint was also selected for the previous approved indications for TISSEEL.

(Source: sBLA 103980/5601 Full clinical study report 550801 p. 124)

Summary of Hemostasis at 4 Minutes After Treatment Application at the Study Suture Line
(Study 550801: Intent-to-Treat Analysis Set)

Treatment Group	Primary Hemostasis Achieved at 4 Minutes n of N (%)	Additional Treatment Required to Achieve Hemostasis n of N (%)	Intraoperative Rebleeding After Primary Hemostasis n of N (%)	Hemostasis at 4 Minutes n of N (%)
FS-120	47 of 70 (67.1%)	13 of 70 (18.6%)	4 of 70 (5.7%)	44 of 70 (62.9%)
Control	22 of 70 (31.4%)	28 of 70 (40.0%)	1 of 70 (1.4%)	22 of 70 (31.4%)

Reviewer comment:
The study results demonstrated a difference between the treatment groups in the proportion of patients who achieved hemostasis 4 minutes post suture line closure after surgery.
As referenced in Dr. Lin 's statistical review memo: "The proportion of subjects that achieved hemostasis at the study suture line at 4 minutes and maintained it until surgical closure was 62.9% (44/70 subjects, 95% CI = 51.2% to 73.6%) in the FS-120 group and 31.4% (22/70 subjects; 95% CI = 21.4% to 42.8%) in the control group. The one-sided p-value from the likelihood ratio chi-square test indicated that there was a statistically significant difference at the one-sided 2.5% level in the comparison of hemostasis rates between the two treatment groups (P<0.0001). A sensitivity analysis (worst outcome analysis, i.e., all missing data were to be considered treatment failures) was performed on the ITT population as a secondary analysis to assess the influence of missing data on the primary results. Since there were no missing values for subjects who were included in the ITT population, the results of the sensitivity analysis were the same."

6.1.11.4 Dropouts and/or Discontinuations

Thirty six subjects were enrolled but not treated: 32 were screen failures and the remaining 4 subjects for account for Dropouts/discontinuations for the following reasons:
Subject 040004 was withdrawn by the investigator for non-study product-related reasons (a study coordinator was not available to collect data);
Subjects 040006 and 190004 requested to be withdrawn from the study; and

Subject 190007 died from coronary artery disease prior to receiving study treatment (the

Summary of Adverse Events That Occurred During or After Treatment Application in >5% of Subjects in at Least One of the Study Groups (Study 550801: Safety Analysis Set) Source: Applicant Table 14.3-7 p 153-155 Clinical study report 55801

subject signed the informed consent form, but screening was not performed)

6.1.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety analyses for adverse events consist of pooled data from the phase 2 (study 550602) and phase 3 (study 550801) clinical trials.

6.1.12.2 Overview of Adverse Events

No differences were observed in the risk of AEs by preferred term that occurred in >5% of subjects during or after treatment application between the FS and control treatment groups. Most of the adverse events reported are known complications resulting from peripheral vascular surgery or general surgical procedures (e.g. nausea, pain, constipation) and are unrelated to the study treatments.

		Number of Subjects		Number of Events	
System Organ Class	Preferred Term[a]	FS-120 N=70 N(%)[b]	Control N=70 N(%)[b]	FS-120 n[c]	Control n[c]
Gastrointestinal Disorders	Constipation	4 (5.7%)	0 (0.0%)	4	0
General disorders and administration site conditions	Peripheral Edema	7 (10.0%)	4 (5.7%)	8	5
Injury, poisoning and Procedural complications	Operative hemorrhage	4 (5.7%)	1 (1.4%)	5	2
	Vascular graft thrombosis	3 (4.3%)	5 (7.1%)	5	6
Metabolism and nutrition Disorders	Hyponatremia	4 (5.7%)	0 (0.0%)	4	0
Vascular disorders	Hypotension	4 (5.7%)	2 (2.9%)	5	3

a. If the percentage of subjects within a specific preferred term is ≤5% in both treatment groups, then that preferred term will not be shown.
b. Number of subjects.
c. Number of adverse events

6.1.12.3 Deaths

A total of three treated subjects experienced SAEs during or after treatment application that resulted in outcomes of death during the study:

Fibrin sealant (TISSEEL group)

Subject 110002: Died from congestive heart failure. The patient was a 74 year old female who had a long standing history of diabetes, end stage renal disease, coronary artery disease, hypertension. She underwent a right forearm arteriovenous shunt placement and uneventfully. On post of day 2 she presented for her regularly scheduled dialysis treatment but was noted to be hypotensive. She was diagnosed with exacerbation of congestive heart failure. After treatment for her congestive heart failure, she continued to be dialyzed despite initial reports of a possible cellulitis at the AV graft site. According to the medical reports the final diagnosis for the graft site was hematoma with skin necrosis

after a cellulitis had been ruled out. She died on post op day 12 at an outside facility from a cardiac arrest. While it is possible that the subject did have a mild cellulitis she did receive antibiotic treatment and continued to be dialyzed. The cause of death is not likely to be related to TISSEEL.

Manual compression (CONTROL group)
Subject 080001 Died from cardio-respiratory arrest and aspiration pneumonia and had a medical history significant for distal Aorta and bifemoral common iliac artery occlusions, hyperlipidemia, hypertension, and COPD.

Subject 180003 Died from multi-organ failure and had a medical history significant for severe peripheral vascular disease, hypertension and chronic obstructive pulmonary disease.
The causes of the deaths are not likely to be related to treatment (i.e. manual compression)

One subject (190007) died due to coronary artery disease prior to receiving study treatment (the subject signed the informed consent form, but screening was not performed).

6.1.12.4 Nonfatal Serious Adverse Events

The subjects enrolled in the clinical trial had multiple co- morbidities in addition to their peripheral vascular disease. There were nonfatal serious adverse events reported for many subjects undergoing the vascular bypass procedures, but the majority of these adverse events were not related to the study treatment or surgical procedure.
A total of 2 non serious AE's occurred during the study that were reported as possibly related to fibrin sealant (TISSEEL) or control (manual compression with gauze). Specifically,

Subject 040011 (FS group) underwent a femoro-popliteal bypass procedure and experienced bleeding at the study suture line. TISSEEL was applied, resulting in the achievement of primary hemostasis at 6 minutes. During closure of the wound, the investigator noticed an area of blood welling up and seeping from under the application of FS at the study suture line that was assessed as operative hemorrhage. TISSEEL was removed, additional sutures were placed, and 2 mL of TISSEEL, as well as Gelfoam and thrombin, were applied to the study suture line as additional treatments to achieve hemostasis. The event was recorded as mild in severity and considered by the investigator to be possibly related to FS. The event resolved the same day.

Subject 180006 (control group) underwent a femoro-femoral bypass procedure and experienced severe bleeding at the study suture line. Manual compression was applied, resulting in the achievement of primary hemostasis at 10 minutes. Surgicel was applied as additional treatment to achieve hemostasis. On postoperative Day 15, the subject experienced a 3cm right groin hematoma that was assessed as incision site hematoma.

The event was reported as moderate in severity and considered by the investigator to be possibly related to control. The event resolved after 9 days.

Reviewer comment: Hemostatic failure is known to occur following fibrin sealant or adjunctive hemostatic treatment and is often because the primary method to achieve hemostasis was inadequate. Success of adjunctive hemostats such as fibrin sealants or manual compression relies on good control of bleeding from primary hemostatic measures and meticulous surgical technique.

Tabular listing of Nonfatal Serious Adverse Events Adapted from Applicant Tables Original sBLA full Clinical Study Report 550801 Listings 16.2.7-1 p.1307-1314
Fibrin sealant group (FS 120)

6.1.12.5 Adverse Events of Special Interest (AESI)

Medical events of special interest for TISSEEL in this surgical setting include graft thrombosis and surgical site infections. There was no difference in the rate of these events between the control and test arms.

Several factors may influence the rate of graft occlusions and infections, including the subject's underlying disease and their progression, co-morbidities, surgical technique, history of previous graft placement, graft materials used, anatomical features, antibiotic prophylaxis, and wound management. Graft thrombosis is a known potential complication of fibrin sealant use. The fibrin sealant is intended to be applied to the suture line only after satisfactory primary sure or stapling on a vascular anastomosis. When there is residual oozing from the suture line, fibrin sealant can be applied as a secondary hemostatic treatment. Inadvertent intravascular administration is a potential complication in this surgical situation. As noted in a contraindication portion of the current TISSEEL label, intravascular administration of fibrin sealants can lead to thrombosis. It is also not uncommon for patients undergoing peripheral vascular bypass procedures to have thrombotic complications due to progression of their underlying peripheral vascular disease and/or technical complications resulting from construction of the vascular anastomosis, co-morbidities, sub-therapeutic anticoagulation and smoking that can predispose to a pro thrombotic state.

Graft occlusions and surgical site infections in the fibrin sealant group were similar to the control group:

Graft Occlusions:

Fibrin Sealant (120 sec)	Control	P value of FS 120 vs control[1]
5/70 (7.1%)	8/70 (11.4 %)	0.380

Infections at surgical site:

Fibrin Sealant (120 sec)	Control	P value of FS 120 vs control[1]
7/70 (10%)	5/70 (7.1%)	0.545

[1] based on likelihood ratio chi –square test

Reviewer comment: These results were reported by the Applicant and confirmed by the reviewer.

6.1.12.7 Dropouts and/or Discontinuations

Three subjects were discontinued from the study due to adverse events resulting in deaths. These deaths and adverse events are not deemed to be related to manual compression or fibrin sealant treatments (See sections 6.1.10.4 Dropouts and/or Discontinuations for full description and 8.4.3 Study Dropouts/Discontinuations for pooled safety results in this review)

6.2 Trial Study 550602 phase 2

6.2.1 Objectives (Primary, Secondary, etc)

The primary efficacy endpoint was the proportion of subjects achieving hemostasis at the study suture line of the ePTFE graft at 4 minutes. Hemostasis must be maintained until closure of the surgical wound.

Safety endpoints were:

- Adverse events (AEs), specifically infections of the surgical site and graft occlusions
- Vital signs
- Hematology, clinical chemistry, and coagulation laboratory values

6.2.2 Design Overview

Study 550602 was a proof-of-concept study in the clinical development program for TISSEEL. This study was a Phase 2, prospective, randomized, controlled, subject-blinded, multicenter study that was designed to evaluate the efficacy and safety of TISSEEL for hemostasis in subjects receiving peripheral vascular ePTFE conduits, as compared to a control group treated by manual compression with surgical gauze pads. The enrolled subjects who fulfilled the entry criteria were randomized and treated in 3 equal-sized groups. Two treatment groups, which differed in polymerization/setting time (60 seconds versus 120 seconds) prior to opening the cross clamps, were treated with TISSEEL. In both TISSEEL groups, TISSEEL was applied onto the bleeding suture lines, while the treatment of the control group consisted of manual compression. Time to hemostasis was calculated from the time of product application. Although the surgeon was free to decide the amount of TISSEEL needed, the cumulative dose was limited to 4-mL TISSEEL per treated suture line.

For the comparison of the hemostasis rates in the 3 treatment groups, the likelihood ratio chi-square test was carried out. If this overall test showed a statistically significant difference at a 10% two-sided level, then pair-wise comparisons between FS VH S/D 500 s-apr (FS-60 and FS-120) and manual compression were performed by likelihood ratio chi-square tests. The significance level was set to 10% two-sided for these pair-wise comparisons.

Efficacy: For the intent-to-treat (ITT) population, the highest proportion of subjects that achieved hemostasis at 4 minutes and maintained it until surgical closure was 62.5% (15/24) for FS-120 subjects, followed by 46.2% (12/26) for FS-60 subjects and 34.8%

(8/23) for control subjects. The 90% CI for the difference in the success rates between FS-120 and control was 4.7 to 50.8. The data suggested superiority of FS VH S/D 500 s-apr (with a 120-second polymerization time) rather than 60 second polymerization time could be demonstrated to be superior to manual compression in a confirmatory trial. The safety results of this study are discussed in section 8 (integrated overview of safety) of this memo.

7. INTEGRATED OVERVIEW OF EFFICACY

Efficacy results were not pooled. See Section 5 "Review Strategy" for details on the overall approach to the review.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Duration of exposure was typical of what would be expected for use in the target population. A follow up of 30 days is reasonable to assess postoperative complications that could potentially be temporally related to use of the product. Thus, all tests reasonably applicable were conducted to asses the safety of the product.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

See Section 5.3, Tables of Studies/Clinical Trials, specifically studies 550602 and 550801. The other studies formed the basis for the currently approved indications for TISSEEL, namely adjunct to hemostasis during cardiovascular and splenic surgeries.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

(Source: original s BLA module 2 section 2.7 p.163-164)

Tables 2.7.4-33,34
Demographic and Baseline Characteristics- Continuous Data
(Studies 550602 and 550801: Safety Analysis Set)

Parameter	**Statistics**	**550602 FS**	**550801 FS**	**550602+550801 FS**	**550602+550801 Control**
Age (years)	N	50	70	120	93
	mean	63.5	62.5	63.0	65.5
	Median	64.5	63.5	64.0	66.0
	Min. max	24,85	33,88	12.9,88	38,90
Weight (kg)	N	50	70	120	93
	mean	82.30	81.49	81.83	79.75

	Median	77.00	81.80	80.60	77.60
	Min. max	53.2,137.5	39.0,141.0	39.0,141.0	43.6,155.5
Height (cm)	N	50	70	120	93
	mean	170.62	166.31	168.10	167.99
	Median	172.60	167.50	170.10	170.00
	Min. max	137.1, 192.9	112.9, 187.8	112.9,192.9	139.6, 187.8
Gender	Male	33 (66.0%)	30 (42.9%)	63 (52.5%)	48 (51.6%)
	Female	17 (34.0%)	40 (57.1%)	57 (47.5%)	45 (48.4%)
Race	White	31 (62.0%)	40 (57.1%)	71 (59.2%)	52 (55.9%)
	Black or African American	15 (30.0%)	28 (40.0%)	43 (35.8%)	37 (39.8%)
	Asian	0 (0.0%)	1 (1.4%)	1 (0.8%)	1 (1.1%)
	American Indian or Alaska Native	2 (4.0%)	1 (1.4%)	3 (2.5%)	2 (2.2%)
	Native Hawaiian or Other Pacific Islander	2 (4.0%)	0 (0.0%)	2 (1.7%)	1 (1.1%)
Ethnicity	Hispanic or Latino	2 (4.0%)	4 (5.7%)	6 (5.0%)	6 (6.5%)
	Not Hispanic or Latino	48 (96.0%)	66 (94.3%)	114 (95.0%)	87 (93.5%)

8 Reviewer concurs with Applicant tabulations of demographic characteristics

8.2.3 Categorization of Adverse Events

Adverse events were categorized appropriately.

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

Overall the two study populations are similar, as were the two trials. Therefore, there are no caveats pertaining to pooling the safety data.

8.4 Safety Results

8.4.1 Deaths

Summary of Deaths peripheral vascular studies 550602 and 550801
(Adapted from Applicant Table 2.7-4-9 page 21 Clinical Summary section 2.7.4.2.1.2)

Study Number	**N**	**Number of Deaths**		**Number of deaths Possible or probably related to test product (fibrin sealant or manual compression)- Reviewer assessment**
		TISSEEL	Control	
550602	73	0	1	None
550801	140	1	2	None
Total				None

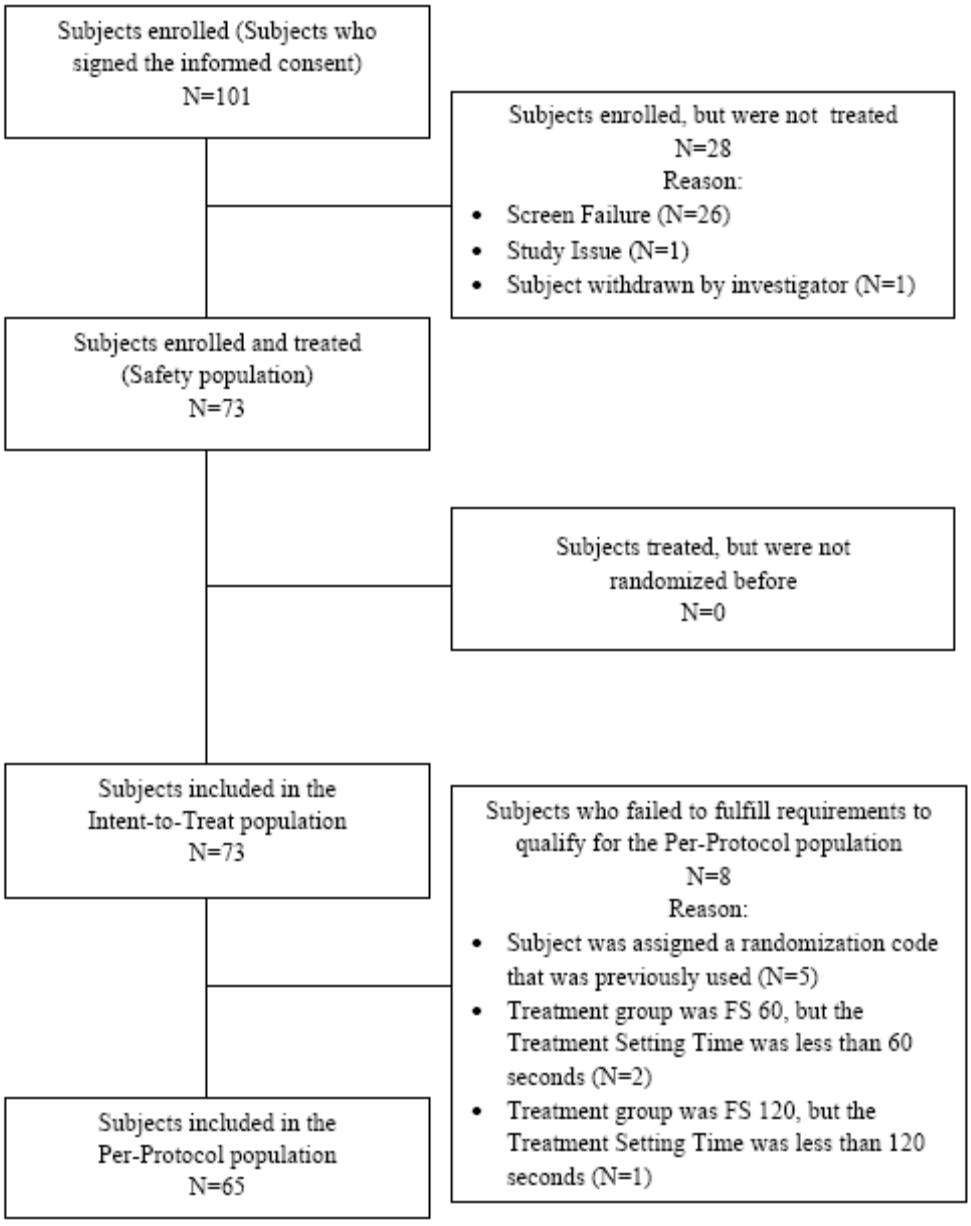
8.4.2 Pooled Nonfatal Serious Adverse Events: graft thrombosis and infections.

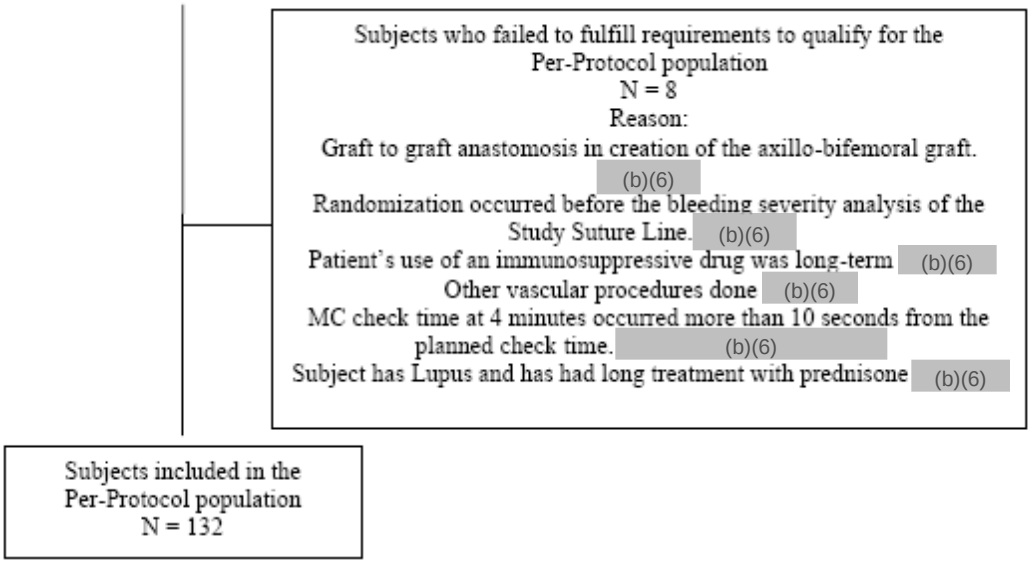
Adverse event	Study 550602				Study 550801		Study 550602		Study 550801	
	FS 60		FS 120		FS 120		Control		Control	
	Subjects (N) Subject numbers	Events (N) Subject numbers	Subjects (N) Subject numbers	Events (N) Subject numbers	Subjects (N) Subject numbers	Events (N) Subject numbers	Subjects (N) Subject numbers	Events (N) Subject numbers	Subjects (N) Subject numbers	Events (N) Subject numbers
Graft thrombosis	2	3	1	1	5	8	0	0	8	9
Infection at graft site (surgical site infection)	1	1	2	2	7	7	0	0	5	5

Reviewer comment: These complications are not uncommon to peripheral vascular surgical procedures and there are no significant differences between the fibrin sealant and control groups.

8.4.3 Study Dropouts/Discontinuations

Table 14.1-2
Flowchart – Subject Disposition
(Study 550602)





8.4.4 Common Adverse Events

Summary of Common serious adverse events occurring during the peripheral vascular surgery procedure

(Source: Original sBLA, Clinical Summary section 2.7.4.2.1.3, Page 23, Study 550602 Table 2.7.4-10)

SAEs Occurring in the TISSEEL Group versus SAEs Occurring in the Control Group (by Preferred Term) (Study 550602)	
SAEs Occurring in the TISSEEL Group	SAEs Occurring in the Control Group
Graft thrombosis (n=1)	Myocardial infarction (n=1)
Incision site hematomas (n=2)	Gastrointestinal hemorrhage (n=1)
Hyperglycemia (n=1)	Dehydration (n=1)
Metabolic acidosis (n=1)	Pulmonary Edema (n=1)
Vascular graft complication (n=1)	Peripheral vascular disease (n=1)
Vascular graft occlusion (n=1)	
Wound (n=1) reported as right groin wound separation	

(Source: Original sBLA, Clinical Summary section 2.7.4.2.1.3, Page 24, Study 550801 Table 2.7.4-10)

SAEs by Preferred Term Study 550801 in order of frequency			
TISSEEL	N	CONTROL	N
Non cardiac chest pain	2	Vascular graft occlusion	2
Vascular graft thrombosis	2	Vascular graft thrombosis	2
Atrial fibrillation	1	Respiratory failure	2
Cardiac failure (congestive)	1	Cardio-respiratory arrest	1
Constipation	1	Small intestinal obstruction	1
Hematemesis	1	Small intestinal perforation	1
Thrombosis in device	1	Multiorgan failure (resulted in death)	1
Appendicitis perforated	1	Sepsis • n=1 sepsis not otherwise specified and • n=1 staphylococcal sepsis	2
Staphyloccocal sepsis	1	Urinary tract infection	1
Wound infection staphylococcal	1	Drug toxicity **Non study drug	1
Femoral neck fracture	1	Graft thrombosis	1
Postoperative wound infection	1	Incision site cellulitis	1
Spinal compression fracture	1	International normalized ratio (INR) increase	1
Vascular graft occlusion	1	Hypovolemia	1
Hyponatremia	1	Arthralgia	1
Ischemic neuropathy	1	Ischemic neuropathy	1
Acute pulmonary edema	1	Dyspnea	1
Respiratory distress	1	Aspiration pneumonia	1
Respiratory failure	1		
Arterial thrombosis limb	1		
Hematoma	1		
Steal syndrome	1		

In these two peripheral vascular studies, there were 3 adverse events that the sponsor considered to be possibly or probably related to study treatment:
550602-

- N=1 suture related complication- intraoperative rebleeding at the study suture line control group

- N= 1 incision site complication (left arm venous stenosis) possibly related TISSEEL 120 sec group

This complication occurred 32 days after exposure to TISSEEL (FS 120 seconds). The PI raised concerns about a possible graft occlusion. However, an angiogram indicated venous stenosis in the area of the venous anastomosis. The principal investigator (PI) considered that a causal relationship to the investigational product was unlikely but could not be completely ruled out.

- 550801-N=1 Operative hemorrhage possibly TISSEEL

Reviewer comment: Agree with Applicant's assessment. It is not possible from the information presented to completely exclude the possibility that the fibrin sealant contributed to some stricturing as part of the healing process. However, in vascular bypass surgery, strictures are not uncommon and often related to surgical technique and patient factors.

8.4.8 Adverse Events of Special Interest

(See section 8.4.2 for adverse events of concern related to the surgical procedure)

8.5.1 Dose Dependency for Adverse Events

There are no expected dose dependent adverse events.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.5.8 Immunogenicity (Safety)

TISSEEL is a licensed product and the current package insert notes that there have been reports of hypersensitivity or anaphylactic reactions with its use postmarketing. TISSEEL contains synthetic aprotinin and should not be used in individuals with a known

8.6 Safety Conclusions

TISSEEL has been on the US market since 1998 and has an acceptable safety profile when used within the scope of its labeled indications. The thrombotic complications seen in the peripheral vascular studies are not unexpected from the surgical procedures and co-morbid conditions of the subjects. The number of graft complications and thrombotic complications were not elevated beyond what would be expected for the population with peripheral vascular disease undergoing a surgical vascular bypass procedure.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

TISSEEL has a pregnancy category C designation. Animal reproduction studies have not been conducted with TISSEEL. It is also not known whether TISSEEL can cause fetal

harm when administered to a pregnant woman or can affect reproduction capacity. Some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus B19 most seriously affects pregnant women (fetal infection). TISSEEL should be given to a pregnant woman only if clearly needed.

9.1.2 Use During Lactation

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TISSEEL is administered to nursing mothers.

9.1.3 Pediatric Use and PREA Considerations

Limited clinical study data are available with regard to the use of TISSEEL in children. Of 365 patients undergoing repeated cardiac surgery or emergency resternotomy in a clinical trial of TISSEEL, 27 pediatric patients aged 16 years or younger were treated with TISSEEL. Of these, 2 patients were less than 6 months, 2 patients were between the ages of 6 months and 2 years, 15 patients were between 3-11 years of age, and 8 patients were between 12-16 years of age. There were no differences in safety observed between these subjects and the overall population.

9.1.5 Geriatric Use

Clinical studies included 218 patients aged 65 years of age or older treated with TISSEEL (159 undergoing cardiac surgery and 59 undergoing vascular surgery). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10. CONCLUSIONS

In conclusion, Study 550801 met its pre-specified primary endpoint in that use of TISSEEL to treat residual bleeding at the vascular anastomosis reduced the time to hemostasis compared to use of manual compression with gauze pads. There were no safety concerns suggested by the phase 2 and 3 peripheral vascular surgery studies to preclude a recommendation for approval.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Peripheral vascular disease is a common disease.	• Incomplete hemostasis can lead to surgical complications such as hematomas, infection, wound dehiscence.
Unmet Medical Need	• There is a need for adjunctive hemostatic treatments where use of cautery, ligature and suture (i.e. primary hemostasis methods) are impractical or impractical because the areas of bleeding are inaccessible or use of the primary hemostat may injury tissue or produce suboptimal hemostasis.	• There are currently approved biologics and combination products for adjunctive hemostatic treatment in a variety of surgical settings. There are also devices cleared for this indication as well.
Clinical Benefit	• The review standard for demonstration of clinical benefit is similar to that used by the Center for Devices and Radiological Health, in clearing a number of devices as adjuncts to hemostasis on the basis of clinical studies in which the primary endpoint was control of hemostasis within a specific time in a variety of clinical settings. AS per the Guidance for Industry: Efficacy Studies to Support Marketing of Commercial Fibrin Sealant Products Manufactured for Commercial Use."http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm077071.htm.,A reduction in time to hemostasis is an acceptable primary endpoint for studies intended to support an adjunct to hemostasis indication has been accepted as a clinically meaningful endpoint. •	• The evidence appears to indicate a clinical benefit for use of TISSEEL as an adjunct to hemostasis during a variety of surgical procedures.
Risk	• There is no added local risk demonstrated with the use of TISSEEL.	• TISSEEL appears to be safe for the proposed surgical settings.
Risk Management	• If TISSEEL's indication was expanded to include all general surgery procedures, routine measures, such as the package insert and the current pharmacovigilance plan would be adequate to manage the risks.	• No additional risk management procedures are recommended.

11.2 Risk-Benefit Summary and Assessment

Data submitted to the BLA supplement establish an acceptable benefit –risk profile for the intended target population.

11.3 Discussion of Regulatory Options

The Applicant submitted adequately designed and well controlled studies with an acceptable clinically meaningful primary endpoint of time to hemostasis. The safety profile is acceptable. The study populations throughout the clinical program are representative of the target population. The recommendation is to choose the regulatory option for approval with no postmarketing requirements or approvals.

11.4 Recommendations on Regulatory Actions

According to my review of the clinical data, it is recommended that TISSEEL be approved for the indication, "for use as an adjunct to hemostasis in patients undergoing surgery when control of bleeding by conventional surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. TISSEEL is effective in heparinized patients and in patients medicated with anti-platelet drugs.

11.5 Labeling Review and Recommendations

Major changes recommended for the Applicant's proposed labeling are as follows:

- Revise section 6 ADVERSE REACTIONS so that it starts with a summary of the entire safety database, then followed by subsection 6.1 Clinical Trials Experience and subsection 6.2 Postmarketing Experience.

- Present adverse reactions in decreasing order of frequency or severity

- Revise the thawing and warming instructions. The information provided with the current instructions, including the information from Tables 1, 2, and 3, are confusing.

- The viral clearance information (currently subsection 12.4 Other Clinical Pharmacology Information) should be presented in section 11 DESCRIPTION.

11.6 Recommendations on Postmarketing Actions

There are no recommendations for postmarketing actions.