SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Hemostatic agent

Device Trade Name: HEMOBLAST™ Bellows

Device Procode: PMX

Applicant's Name and Address: Biom'Up SA
8, Allée Irène Joliot-Curie
69800 Saint Priest France

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P170012

Date of FDA Notice of Approval: December 15, 2017

II. INDICATIONS FOR USEC

The HEMOBLAST™ Bellows is indicated in surgical procedures as an adjunct to hemostasis when control of minimal, mild, and moderate bleeding by conventional procedures is ineffective or impractical, except in neurosurgical, ophthalmic, and urological procedures.

III. CONTRAINDICATIONS

Do not inject HEMOBLAST™ Bellows into a vessel or tissue. There is a risk of allergic-anaphylactoid reaction and/or thromboembolic events, which may be life-threatening.

Do not apply HEMOBLAST™ Bellows in the absence of active blood flow, e.g., while the vessel is clamped or bypassed. Extensive intravascular clotting and even death may result.

Do not use the HEMOBLAST™ Bellows for treatment of severe or extreme bleeding.

Do not administer to patients with known allergies or hypersensitivity to materials of porcine or bovine origin.

Do not use in the closure of skin incisions because it may interfere with the healing of the skin edges due to mechanical interposition of the powder.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the HEMOBLAST™ Bellows labeling.

V. DEVICE DESCRIPTION

The HEMOBLAST™ Bellows consists of the hemostatic powder (HEMOBLAST™ Bellows Hemostatic Powder) supplied in an applicator system incorporating a bellows design. The HEMOBLAST™ Bellows Hemostatic Powder is dry, sterilized, biocompatible, and non-pyrogenic. No intraoperative preparation, mixing, or heating is required. It absorbs *in vivo* over a 4-week period.

HEMOBLAST™ Bellows Hemostatic Powder is composed predominantly of highly purified porcine collagen (with glucose) with smaller amounts of bovine chondroitin sulfate (CS) and human pooled plasma derived thrombin. These components, all of which are supplied in powder form, are shown in **Table 1** below.

Table 1: HEMOBLAST™ Bellows Hemostatic Powder Composition

HEMOBLAST™ Bellows Hemostatic	Source
Collagen Powder (with glucose)	Porcine
Chondroitin Sulfate	Bovine
Thrombin	Human pooled plasma

The HEMOBLAST™ Bellows Applicator contains 1.65 ± 0.05 g of HEMOBLAST™ Bellows Hemostatic Powder. The product is sterilized using gamma-sterilization and provided in double- packaging.

Figure 1: HEMOBLAST™ Bellows Applicator

The HEMOBLAST™ Bellows 10 cm Nozzle Extension, which is made of polycarbonate tubing, serves to assist in the delivery of the HEMOBLAST™ Bellows Hemostatic Powder, during surgery. The HEMOBLAST™ Bellows 10 cm Nozzle Extension can be used to assist with the application of the powder to active bleeding sites where a slightly longer tip is desired by the surgeon. It has not been tested or designed for laparoscopic

application or for application at locations where the surgeon cannot clearly visualize the site of active bleeding.

Figure 2: HEMOBLAST™ Bellows 10 cm Nozzle Extension

Principles of Operation

The HEMOBLAST™ Bellows applies the hemostatic agent to the source of the bleeding *via* manual squeezing of the bellows. The implant material is applied to cover the entire target bleeding site. The hemostatic agent absorbs excess blood and helps in achieving hemostasis. The hemostatic effect of the HEMOBLAST™ Bellows Hemostatic Powder is due to its collagen composition, which activates the coagulation process by absorbing blood, concentrating coagulation factors and platelets and providing a surface for coagulation to initiate.

Thrombin from pooled human plasma, as an ancillary blood derivative, is added to the formulation to aid the effect of the hemostatic agent. The powder thrombin facilitates the conversion of fibrinogen to fibrin. In addition, CS, in powder form, is included in the HEMOBLAST™ Bellows Hemostatic Powder formulation in order to provide cohesion between the hemostatic wound and the surrounding tissue.

Once applied to the target bleeding site, the powder must remain in contact with the source of bleeding to ensure hemostasis. A wet laparotomy pad, temporarily applied to the treated bleeding site, keeps the powder in contact with the bleeding area.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives to control bleeding. Conventional procedures include the use of direct pressure, sutures, and/or electrocautery. Other commercially available devices are hemostats, sealants, and adhesives. These devices include: hemostats composed of gelatin, bovine collagen, cellulose, polysaccharide spheres, thrombin, gelatin and thrombin, and thrombin and fibrinogen; sealants composed of fibrinogen and thrombin, polyethylene glycol polymers with or without albumin, albumin and aldehyde, and cyanoacrylate; and adhesives composed of cyanoacrylate, albumin and aldehyde, and thrombin and fibrinogen. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets their expectations and lifestyle.

VII. MARKETING HISTORY

HEMOBLAST™ Bellows was approved for marketing and sale in the European Union in 2016, and the product is currently marketed in France and Germany. HEMOBLAST™ has never been removed from any market for any reason. The HEMOBLAST™ Bellows has not been marketed in the United States.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Adhesion formation;
- Allergy or anaphylaxis;
- Blockage of cardiopulmonary bypass system and cell saver devices;
- Compromised attachment of orthopedic implants;
- Creutzfeldt-Jakob disease (CJD) agent;
- Increased infection;
- Lack of effectiveness;
- Nerve compression;
- Thrombosis or thromboembolism;
- Transmissible Spongiform Encephalopathies (TSE); and
- Viral disease transmission.

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

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Biocompatibility testing of HEMOBLAST™ Bellows has been performed according to GLP regulations and pursuant to ISO 10993 and FDA's guidance document entitled "*Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process*" (June 16, 2016). Cytotoxicity, Sensitization, and Intradermal Irritation testing were completed on the HEMOBLAST™ Bellows Applicator and HEMOBLAST™ Bellows 10 cm Nozzle Extension; and Cytotoxicity, Sensitization, Intradermal Irritation, Systemic Toxicity, Genotoxicity, and Implantation testing were completed on the HEMOBLAST™ Bellows Hemostatic Powder. The testing demonstrated that the HEMOBLAST™ Bellows is biocompatible as summarized in the tables below.

Table 2: HEMOBLAST™ Bellows Applicator (With Powder) - Biocompatibility

Test	Test Article	Results
Qualitative Cytotoxicity Study on Extract [According to ISO 10993-5 (2009) / GLP (21 CFR 58 - 2002)]	Hemostatic powder in a bellows	PASS
ISO Intracutaneous Study in Rabbits [According to ISO 10993-10 (2010) / GLP (21 CFR 58 - 2002)]	Hemostatic powder in a bellows	PASS
ISO Guinea Pig Maximization Sensitization [According to ISO 10993-10 (2010) / GLP (21 CFR 58 - 2002)]	Hemostatic powder in a bellows	PASS
ISO Acute Systemic Toxicity Study in Mice [According to ISO 10993-11 (2006) / GLP (21 CFR 58 - 2002)]	Hemostatic powder in a bellows	PASS
Mouse Peripheral Blood Micronucleus Study [According to ISO 10993-3 (2003) / GLP (21 CFR 58 - 2002)]	Hemostatic powder in a bellows	PASS
Genotoxicity: Mouse Lymphoma Assay [According to ISO-10993-3 (2003) / ISO 10993-12 (2012) / GLP (21 CFR 58 - 2002)]	Hemostatic powder in a bellows	PASS
Genotoxicity: Bacterial Reverse Mutation Study [According to ISO-10993-3 (2003) / GLP (21 CFR 58 - 2002)	Hemostatic powder in a bellows	PASS
Qualitative Cytotoxicity Study on Extract [According to ISO 10993 Part5 / GLP (21 CFR 58– 2002)]	Hemostatic powder in a bellows	PASS

Table 3: HEMOBLAST™ Bellows Applicator (Without Powder) - Biocompatibility

Test	Test Article	Results
ISO MTS Cytotoxicity Test [According to ISO 10993-5 (2009) / GLP (21 CFR 58 - 2002)]	Bellows	PASS
ISO Intracutaneous in Rabbits [According to ISO 10993-10 (2010) / GLP (21 CFR 58 - 2002)]	Bellows	PASS
ISO Guinea Pig Maximization Sensitization Test [According ISO 10993-10 (2010) / GLP (21 CFR 58 - 2002)]	Bellows	PASS
4-Week Systemic Toxicity Study in Rats Following Subcutaneous Implantation [According to ISO 10993-6 (2007) and -11 (2006) / GLP (21 CFR 58 - 2002)]	Bellows	PASS

Table 4: HEMOBLAST™ Bellows 10 cm Nozzle Extension - Biocompatibility

Test	Test Article	Results
ISO MTS Cytotoxicity Test according to ISO 10993-5 [According to ISO 10993-5 (2009) / GLP (21 CFR 58 - 2002)]	Plastic cannula	PASS
ISO Intracutaneous Study in Rabbits [According to ISO 10993-10 (2010) / GLP (21 CFR 58 - 2002)]	Plastic cannula	PASS
ISO Guinea Pig Maximization Sensitization Test [According to ISO 10993-10 (2010) / (21 CFR 58 - 2002)]	Plastic cannula	PASS

The additional non-clinical tests were conducted to provide additional device characterization. This testing is summarized in the tables below.

Applicator System Testing

Table 5: Applicator System Testing Studies Overview

Test	Test Purpose	Results
Bench Testing on the HEMOBLAST™ Bellows Applicator: Coverage Test of Target Disks by the Hemostatic Powder Delivered by the Bellows	Evaluated: -Delivery accuracy and performance.	PASS
Handling Performance Evaluation of a Bellows (HEMOBLAST™ Bellows) Delivering Powdered Hemostat	Evaluated: Leakage; Delivery.	PASS
HEMOBLAST™ Bellows Applicator Verification Program	Evaluated: Mechanical performance of the HEMOBLAST Bellows Applicator; The effects of ageing, acute temperature and gamma irradiation on HEMOBLASTTM Bellows Applicator.	PASS

Nozzle Extension Testing

Table 6: Applicator System Testing Studies Overview

Test	Test Purpose	Results
Powder Leak Evaluation of HEMOBLAST™ Bellows Without or With Applicator in a Bench Top Model	Evaluated: -Usability, handling and delivery characteristics.	PASS
Delivery Performance Evaluation of HEMOBLAST™ Bellows Without or With Applicator in a Bench Top Model	Evaluated: -Delivery performance.	PASS
Coverage of Target Disks by HEMOBLAST Bellows Without or With Cannula in a Bench Top Model	Evaluated: -Delivery performance.	PASS
HEMOBLAST Bellows Applicator Verification Program	Evaluated: -Mechanical performance characteristics.	PASS

Viral inactivation for the collagen and CS was validated.

Stability testing for the product was conducted and the results were acceptable.

The device is packaged in a double-tray (*i.e.*, blister) configuration and sterilized using gamma-irradiation per ISO 11137. Validation of the packaging, including sealing of the inner and outer trays, has been performed. Real-time stability and shelf-life of the finished sterilized product is ongoing. The testing completed to date supports the labeled shelf-life.

The non-clinical tests of the HEMOBLAST™ Bellows demonstrated that HEMOBLAST™ Bellows is safe for use in surgical procedures as an adjunct to hemostasis when control of minimal, mild, and moderate bleeding by conventional procedures is ineffective or impractical, except in neurosurgical, ophthalmic, and urological procedures.

B. Animal Studies

Nine (9) porcine and three (3) rabbit non-clinical studies of the safety and effectiveness of the HEMOBLAST™ Bellows were performed. This testing is summarized in the table below.

Table 7: Non-clinical Animal Studies Overview

Study Name	Purpose	Study Design	Study Results
Resorption, local tissue effects, and performance in a rabbit orthopedic model	This study was conducted to assess resorption, local tissue effects, and hemostatic performance of the device in comparison to a control device. Cortico-trabecular defects in the femoral condyle and periosteal defects in the tibia were evaluated.	Rabbit = 7 Time points = day 0, 4 weeks, 6 weeks Cortico-trabecular defect in each medial femoral condyle (2 per rabbit for 6 rabbits and 1 per rabbit for T0 rabbit). Periosteal defect in the diaphysis of each tibia (2 per rabbit for 6 rabbits and 1 per rabbit for T0). Hemoblast Bellows: 14 defects Control Device: 12 defects	100% of sites tested achieved hemostasis 3 minutes after a single application. Femoral sites: Device: Bone/cartilage outgrowth identified at test sites in 2 of 4 animals at 4 weeks and 1 of 2 rabbits at 6 weeks Control: Bone/cartilage outgrowth identified in 3 of 4 animals at 4 weeks and in 1 of 2 rabbits at 6 weeks. Tibial sites: Device: Bone/cartilage outgrowth identified at test sites in 2 of 4 rabbits at 4 weeks and 1 of 2 rabbits at 6 weeks Control: Similar swellings were observed in 2 of 4 rabbits at 6 weeks. The tibial sites were not fully healed at 4 weeks.

Study Name	Purpose	Study Design	Study Results
Hemoblast Bellow Hemostatic Agent GLP Safety and Efficacy Study in a Swine Vascular Model	The safety and efficacy of Hemoblast Bellows was evaluated in a swine vascular surgery model using procedural data, adverse events, and histopathology in comparison to a control.	Swine = 12 Time points = 72 hours, 30 days Carotid arteriotomy (simple closure or patch closure) Femoral arteriotomy (simple closure or patch closure) Hemoblast Bellows: 18 sites (9 simple closure, 9 patch) Control: 18 sites (9 simple closure, 9 patch)	<u>Hemostasis:</u> <u>Carotid artery:</u> Hemoblast Bellows: 6 minutes: 50% of sites 10 minutes: 83.3% of sites Control: 6 minutes: 100% of sites 10 minutes: 100% of sites <u>Femoral artery:</u> Hemoblast Bellows: 6 minutes: 83.3% of sites 10 minutes: 100% of sites Control: 6 minutes: 100% of sites 10 minutes: 100% of sites <u>Simple Closure:</u> Hemoblast Bellows: 6 minutes: 88.9% of sites 10 minutes: 99.9% of sites Control: 6 minutes: 100% of sites 10 minutes: 99.9% of sites <u>Patch Closure:</u> Hemoblast Bellows: 6 minutes: 33.3% of sites 10 minutes: 82.1% of sites Control: 6 minutes: 100% of sites 10 minutes: 99.9% of sites All treated vessels were observed angiographically at day 0, 72 hours, and day 30 post-treatment. All vessels were observed to be patent at these time points. No thrombi were seen in any of the systemic tissues evaluated at either time point. There was no histologic evidence of the article at the 30 day time point.

Study Name	Purpose	Study Design	Study Results
Resorption, Local Tissue Effects and Performance of a Hemostatic Device Following Application on Liver Wounds in Pigs	Resorption, hemostatic performance, and local tissue effects were evaluated in a pig liver model with post-treatment follow-up at 4 weeks.	Swine = 2 Time points: 3, 6, and 10 minutes, 4 weeks Liver: Defects (8 mm in diameter 2 to 3 mm deep) Hemoblast Bellows: 10 defects Sham: 6 defects	<u>Hemostasis</u> Hemoblast Bellows: 3 minutes: 50% (5 of 10) 6 minutes: 90% (9 of 10) 10 minutes: 100% (10 of 10) Sham: 3 minutes: 0%(0 of 0) 6 minutes: 0% (0 of 0) 10 minutes: 0% (0 of 0) Histopathological analysis classified the device as a non-irritant in comparison to a sham procedure site. The device was not macroscopically or microscopically detected at the 4 week time point.

Study Name	Purpose	Study Design	Study Results
Resorption, Local Tissue Effects, and Performance of a Hemostatic Device Following Application on Bone Defects in Rabbits	Resorption, local tissue effects and hemostatic performance were evaluated in a rabbit orthopedic surgical model.	Rabbits = 10 Time points: day 0 and 4 weeks Cortico-trabecular defect in the medial femoral condyle. Hemoblast Bellows: 8 defects Sham: 7 defects	<u>Hemostasis:</u> 3 minutes: 100% (8 of 8) 6 minutes: 100% (8 of 8) 10 minutes: 100% (8 of 8)) Sham: 3 minutes: 1 of 6 (14%) 6 minutes: 1 of 6 (14%) 10 minutes: 1 of 6 (14%) Histopathological analysis classified the device as a slight irritant in comparison to a sham procedure site. The device was not macroscopically or microscopically detected at the 4 week time point. 2 of 9 device treated defects were not healed at the 4 week time point.

Study Name	Purpose	Study Design	Study Results
Hemoblast Bellows Hemostatic Agent Acute GLP Efficacy Study in Swine Model	Hemostatic efficacy was assessed in a swine vascular, orthopedic, and hepatic injury model.	Swine = 5 Time points: 3, 6, and 10 minutes Vascular: Arteriotomies with simple closure (5 to 12 mm in length) Hemoblast Bellows: 13 defects Control Device 1: 13 defects Control Device 2: 13 defects Liver: Defects (8 mm in diameter and 2-7 mm deep) Hemoblast Bellows: 18 defects Control Device 1: 18 defects Control Device 2: 18 defects Orthopedic: Femoral condyle defects (1.5 to 4.2 cm^2) Hemoblast Bellows: 12 defects Control Device 1: 12 defects Control Device 2: 12 defects	<u>Hemostasis:</u> Hemoblast Bellows: 3 minutes: 63.9% of sites 6 minutes: 92% of sites 10 minutes: 100% of sites Control Device 1: 3 minutes: 41.0% of sites 6 minutes: 53.8% of sites 10 minutes: 100% of sites Control Device 2: 3 minutes: 61.4% of sites 6 minutes: 76.3% of sites 10 minutes: 100% of sites

Study Name	Purpose	Study Design	Study Results
Hemostasis Maintenance at 24 hours and Performance of a Hemostatic Device Following Application on Liver Wounds in Pigs	Acute hemostasis and maintenance of hemostasis at 24 hours was evaluated in a swine hepatic model using two versions of the hemostatic device (Test article 1: Subject device, Test article 2: 7% chondroitin sulfate).	Swine = 3 Time points: 3, 6, and 10 minutes, 24 hours Liver: Defects (8mm in diameter and 2 to 3 mm deep) Test Article 1: 12 defects Test Article 2: 12 defects	<u>Hemostasis</u> Test Article 1: 3 minutes: 67% (8 of 12) 6 minutes: 100% (12 of 12) 10 minutes: 100% (12 of 12) 24 hours: 100% (12 of 12) Test Article 2: 3 minutes: 58% (7 of 12) 6 minutes: 83% (10 of 12) 10 minutes: 92% (11 of 12) 24 hours: 92% (11 of 12)
Hemostasis Maintenance at 24 hours and Performance of a Hemostatic Device Following Application on Bone Defects in Rabbits	Acute hemostasis and maintenance of hemostasis at 24 hours was evaluated in a rabbit orthopedic model using two versions of the hemostatic device (Test article 1: Subject Device, Test article 2: 7% chondroitin sulfate).	Rabbits = 10 Time points: 3, 6, and 10 minutes, 24 hours Femoral condyle defects Test Article 1: 10 defects Test Article 2: 10 defects	<u>Hemostasis</u> Test Article 1: 3 minutes: 100% (10 of 10) 6 minutes: 100% (10 of 10) 10 minutes: 100% (10 of 10) 24 hours: 100% (10 of 10) Test Article 2: 3 minutes: 100% (10 of 10) 6 minutes: 100% (10 of 10) 10 minutes: 100% (10 of 10) 24 hours: 100% (10 of 10)

Study Name	Purpose	Study Design	Study Results
Performance, resorption, and local tissue effects in a porcine liver model	Hemostatic performance, local tissue effects, and preparation time were evaluated for two methods of hemostatic powder delivery: bellows and prototype	Swine = 1 Time points: 3, 6, and 10 minutes, 24 hours Liver defect (2 cm^2 and 2 to 3 cm in depth) Bellows: 4 sites Prototype: 4 sites	<u>Hemostasis:</u> Hemoblast Bellows: 3 minutes: 0% (0 of 4) 6 minutes: 75% (3 of 4) 10 minutes: 100% (4 of 4) Prototype: 3 minutes: 50% (2 of 4) 6 minutes: 50% (2 of 4) 10 minutes: 100% (4 of 4) No delayed bleeding was observed 24 hours after product application for both delivery devices.
Study of the Efficacy and Tolerance of a New Hemostatic Device in a Swine Model	Hemostatic performance, adhesion formation, risk of air embolism, and local tissue reaction was assessed in a swine hepatic injury model where the hemostatic powder was applied with a prototype device with a short applicator (10 cm) and a long applicator (30 cm).	Swine = 8 Time points: 3, 6, and 10 minutes Liver defect (12 mm in diameter and 3 to 4 mm deep) Short applicator: 6 sites Long applicator: 6 sites Control: 4 sites	<u>Hemostasis:</u> Prototype: 6 minutes: 67% (8 of 12) 10 minutes: 92% (11 of 12) Control: 6 minutes: 100% (4 of 4) 10 minutes: 110% (4 of 4) Tissue attachments/adhesions were present at 100% of treated sites (prototype and control at 1 week and 4 weeks. No significant difference in tenacity was observed. No device was visible at the 4 week endpoint.

Study Name	Purpose	Study Design	Study Results
Acute Hemostatic Performance Study in a Pig Hepatic Bleeding Model	Hemostatic performance was evaluated for two methods of hemostatic powder delivery.	Swine = 1 Time points: 3, 6, and 10 minutes Liver defect (8 mm in diameter and 1 mm deep) 10 sites per article.	Hemostasis: 3 minute: 70% (7 of 10) 6 minute: 90% (9 of 10) 10 minute: 100% (10 of 10)
Acute Hemostatic Performance in a Pig Bony Tissue Bleeding Model	Hemostatic performance was evaluated in a pig orthopedic bleeding model for two methods of hemostatic powder delivery.	Swine = 2 Time points: 3, 6, and 10 minutes Femoral condyle defect (3 to 5 cm^2) 10 sites per article. 2 sites for negative control.	Hemostasis: 3 minutes: 70% (7 of 10) 6 minutes: 100% (10 of 10) 10 minutes: no evaluation performed
Study of the Efficacy of a Hemostatic Device in an Acute Anticoagulated Swine Model	Hemostatic efficacy of the device when applied with a prototype device was assessed in an open hepatic injury model in pigs undergoing treatment with aspirin.	Swine = 3 Time points: 3, 6, and 10 minutes Liver defect (8 mm in diameter, 3 to 4 mm deep) Prototype device: 48 sites Control: 24 sites Sham: 24 sites	Hemostasis: 3 minutes: 50% (24 of 48) 6 minutes: 85% (41 of 48) 10 minutes: 98% (47 of 48)

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed clinical studies to establish a reasonable assurance of safety and effectiveness of general surgical procedures with Hemoblast Bellows as an adjunct to hemostasis when control of minimal, mild, and moderate bleeding by conventional procedures is ineffective or impractical, except in neurosurgical, ophthalmic, and urological procedures in the US under IDEs G150037 and G160063. Data from these clinical studies were the basis for the PMA approval decision. A summary of the clinical studies is presented below.

Pilot Clinical Study:

A. Study Design

This was a prospective, multicenter, single-arm pilot clinical investigation to collect data to support the use of the Surface Bleeding Severity Scale ("SBSS"), and to collect initial safety and efficacy data on HEMOBLAST™ Bellows in clinical use. The Pilot Study enrolled 31 subjects; 27 subjects were included in the safety population and 24 subjects were included in the effectiveness population. Subjects enrolled into the study were required to have a target bleeding site with SBSS score of 1 (minimal bleeding), 2 (mild bleeding), or 3 (moderate bleeding). This 6-week acute study was a single arm study which included patients undergoing only orthopedic and abdominal surgeries with associated bleeding sites; there was no cardiothoracic arm.

The bleeding scale elements used in the SBSS are provided in the table below.

Table 8: Surface Bleeding Severity Scale

Surface Bleeding severity Scale Score	**0**	**1**	**2**	**3**	**4**	**5**
Verbal Descriptor	None	Minimal	Mild	Moderate	Severe; not immediately life-threatening	Extreme; immediately life-threatening
Visual Descriptor	Dry	Oozing	Pooling	Flowing	Streaming	Gushing
Expected Intervention(s)	None	Manual pressure, cautery, adjuvant hemostat(s)	Manual pressure, cautery, suture, adjuvant hemostat(s)	Manual pressure, cautery, suture, adjuvant hemostat(s)	Manual pressure, cautery, suture, staples, tissue repair	Manual pressure, cautery, suture, staples, tissue repair
Maximum Expected ACS-ATLS Shock Risk Class	1	1	1	2	3	4

ACS-ATLS Shock Risk Class: 1 – involves up to 15% of blood volume; typically no change in vital signs and fluid resuscitation is not usually necessary. Class 2 – involves 15-30% of total blood volume; patient is often tachycardic with a narrowing of the difference between the systolic and diastolic blood pressures; the body attempts to compensate with peripheral vasoconstriction; skin may start to look pale and be cool to the touch; volume resuscitation with crystalloids is all that is typically required; blood transfusion is not typically required. Class 3 – involved loss of 30-40% of circulating blood volume; patient's blood pressure drops; heart rate increases, peripheral hypoperfusion worsens; fluid resuscitation with crystalloid and blood transfusion are usually necessary. Class 4 – involves loss of > 40% of circulating blood volume; the limit of the body's compensation is reached and aggressive resuscitation is required to prevent death.

References:

1. Spotnitz WD, Zielske D, Centis V et al. The SPOT GRADE: a new method for reproducibly quantifying surgical

wound bleeding. Spine (Phila Pa 1976). 2017 Oct 10. doi: 10.1097/BRS.0000000000002447. [Epub ahead of print].

2. Kortbeek JB, Al Turki SA, Ali J et al. Advanced trauma life support. 8th edition, the evidence for change. J Trauma 2008;64:1638-50.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the Pilot Study was limited to subjects who met the following preoperative inclusion criteria:

- Subject is undergoing elective open abdominal or orthopedic lower extremity surgery;
- Subject or an authorized legal representative is willing and able to give prior written informed consent for investigation participation;
- Subject on antiplatelets, including aspirin, will discontinue medication at least 10 days prior to surgery; and
- Subject is 21 years of age or older.

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

- Subject does not have an active or suspected infection at the surgical site;
- Subject in whom the Investigator is able to identify a target bleeding site (TBS) for which any applicable conventional means for achieving hemostasis are ineffective or impractical; and
- Subject has a TBS with an SBSS score of 1, 2, or 3.

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

- Subject is undergoing a laparoscopic, thoracoscopic, or robotic surgical procedure;
- Subject is undergoing a spinal surgical procedure;
- Subject is undergoing a neurologic surgical procedure;
- Subject is undergoing an emergency surgical procedure;
- Subject is pregnant, planning on becoming pregnant during the follow-up period, or actively breast-feeding;
- Subject has a clinically significant coagulation disorder or disease, defined as a platelet count <100,000 per microliter and/or International Normalized Ratio > 1.5 within 4 weeks of surgery;
- Subject had chronic corticosteroid use within 2 weeks prior to surgery;
- Subject receiving intravenous heparin or oral Coumadin within 24 hours of surgery;
- Subject has an active or suspected infection at the surgical site;
- Subject has had or has planned any organ transplantation;

- Subject has a known sensitivity or allergy to bovine and/or porcine substance(s) or any other component(s) of the hemostatic agent;
- Subject has ASA classification of > 4;
- Subject has a life expectancy of less than 3 months;
- Subject has a known psychiatric disorder, which in the opinion of the Principal Investigator, would preclude the subject from completing this clinical study;
- Subject has documented severe congenital or acquired immunodeficiency;
- Subject has religious or other objections to porcine or bovine components;
- Subject in whom the investigational device will be used at the site of a cemented or uncemented porous coated joint implant;
- Subject is currently participating or has participated in another clinical trial within the past 30 days and is receiving/has received an investigational drug, device, or biologic agent; and
- Subject is not appropriate for inclusion in the clinical trial, per the medical opinion of the Principal Investigator.

2. Follow-up Schedule

All enrolled subjects were evaluated in the immediate postoperative period (within 24 hours after surgery) and at 6 weeks postoperatively (visit 4-8 weeks postoperatively).

3. Clinical Endpoints

Primary endpoint:
The primary endpoint of this clinical investigation is the mean paired Kappa statistic for the assignment of SBSS scores by two (2) Investigators.

Secondary endpoints:
Secondary endpoints of this clinical investigation consist of:

- Proportion of subjects achieving hemostasis within 6 minutes of HEMOBLAST™ Bellows application;
- Proportion of subjects achieving hemostasis within 10 minutes of HEMOBLAST™ Bellows application;
- Proportion of subjects achieving hemostasis within 3 minutes of HEMOBLAST™ Bellows application; and
- Incidence of adverse events through final follow-up.

B. Accountability

A total of 31 subjects met preoperative eligibility criteria, including roll-in subjects. Four (4) subjects were excluded from the study intraoperatively due to not meeting intraoperative inclusion criteria, resulting in a total of 27 enrolled subjects, including the roll-in subjects. These 27 subjects are considered the safety analysis population.

There was one roll-in subject at each site and roll-in subjects are not included in the effectiveness analysis. Therefore, 24 subjects enrolled in the study are considered the effectiveness analysis population. The exploratory analysis population includes 25 subjects total (the effectiveness analysis population plus one subject who met pre-operative eligibility requirements but failed intra-operative eligibility criteria). Enrollment was fairly balanced across all three (3) sites, with nine (9) subjects being enrolled at Site 2 and 8, and 10 subjects enrolled at Site 6 and Site 8, respectively. Site 2 had three (3) subjects that were excluded intraoperatively, Site 08 had one (1) subject that was excluded intraoperatively, while no subjects were excluded intraoperatively at Site 6.

Table 9: Number of Subjects per Site

Population	All	Site 2	Site 6	Site 8
Total: Preoperative eligible + roll-in subjects	31	12	8	11
Intraoperative ineligible subjects	4	3	0	1
SAFETY ANALYSIS POPULATION: Preoperative AND Intraoperative eligible (ENROLLED and includes roll-in subjects)	27	9	8	10
Roll-in subjects	3	1	1	1
EFFICACY ANALYSIS POPULATION: Preoperative AND Intraoperative eligible (ENROLLED and EXCLUDES roll-in subjects)	24	8	7	9
EXPLORATORY ANALYSIS POPULATION*: Meet preoperative eligibility criteria but fail intraoperative eligibility criteria due to ineligible SBSS scores PLUS EFFICACY ANALYSIS POPULATION (excludes roll-in subjects)	25	9	7	8

*Four subjects were preoperatively eligible but then did not meet intraoperative criteria 02-04, 02-07, 02-08 and 08-03. Only subject 02-07 was excluded intraoperatively due to an SBSS score. Per the Statistical Analysis Plan, the exploratory analysis population should include the subjects intraoperatively ineligible resulting from one or both investigators providing a baseline SBSS score for the TBS that is in the ineligible range (i.e., SBSS 0, 4, or 5). Therefore, subject 02-07 was the only preoperatively eligible subject included in the exploratory analysis population.

Table 10: Number of Subjects in Each Analysis Population

Population	All	Abdominal	Orthopedic
TOTAL: Preoperative eligible + roll-in subjects	31	12	19
Intraoperative ineligible subjects	4	3	1
SAFETY ANALYSIS POPULATION: Preoperative AND Intraoperative eligible (ENROLLED and includes roll-in subjects)	27	9	18
Roll-in subjects	3	1	2

EFFICACY ANALYSIS POPULATION: Preoperative AND Intraoperative eligible (ENROLLED and EXCLUDES roll-in subjects)	24	8	16
EXPLORATORY ANALYSIS POPULATION: Meet pre-operative eligibility criteria but fail intra-operative eligibility criteria PLUS EFFICACY ANALYSIS POPULATION	25	9	16

C. Study Population Demographics and Baseline Parameters

The average age for all subjects was 62.8 and gender was roughly evenly distributed with 51.9% of all subjects being male and 48.1% female. In terms of race, the majority of subjects self-identified as Caucasian (77.8%) and the remaining subjects self-identified as African-American (22.2%). Self-identified Hispanic subjects were 22.2% of the entire subject pool. There were not any notable differences between sites in terms of demographic characteristics other than Site 2 enrolling all of the Hispanic subjects in the study while Sites 6 and 8 enrolled all of the African–American subjects in the study.

Table 11: Study Population Demographics

Measure	All (n=27)	Abdominal (n=9)	Orthopedic (n=18)
Age	62.8 ± 8.64 63.0 [55.0, 68.0]	60.4 ± 10.70 55.0 [53.0, 66.0]	64.0 ± 7.48 64.5 [62.0, 68.0]
Gender			
Male	14/27 (51.9%)	6/9 (66.7%)	8/18 (44.4%)
Female	13/27 (48.1%)	3/9 (33.3%)	10/18 (55.6%)
Ethnicity			
Hispanic or Latino	6/27 (22.2%)	6/9 (66.7%)	0/18 (0.0%)
Not Hispanic or Latino	21/27 (77.8%)	3/9 (33.3%)	18/18 (100.0%)
Race			
Caucasian	21/27 (77.8%)	9/9 (100.0%)	12/18 (66.7%)
African American	6/27 (22.2%)	0/9 (0.0%)	6/18 (33.3%)
American Indian or Alaska Native	0/27 (0.0%)	0/9 (0.0%)	0/18 (0.0%)
Asian	0/27 (0.0%)	0/9 (0.0%)	0/18 (0.0%)
Native Hawaiian or other Pacific Islander	0/27 (0.0%)	0/9 (0.0%)	0/18 (0.0%)
Other	0/27 (0.0%)	0/9 (0.0%)	0/18 (0.0%)

Numbers are mean ± Standard Deviation/ median.

Table 12: Study Population Baseline Parameters

Measure	All	Abdominal	Orthopedic
Liver cell carcinoma	1/27 (3.7%)	1/9 (11.1%)	0/18 (0.0%)
Metastatic colon cancer to the liver	1/27 (3.7%)	1/9 (11.1%)	0/18 (0.0%)
Metastatic gastroesophageal junction cancer	1/27 (3.7%)	1/9 (11.1%)	0/18 (0.0%)

Metastatic rectal cancer	1/27 (3.7%)	1/9 (11.1%)	0/18 (0.0%)
Osteoarthritis of knee	10/27 (37.0%)	0/9 (0.0%)	10/18 (55.6%)
Pancreatic cancer	2/27 (7.4%)	2/9 (22.2%)	0/18 (0.0%)
Concomitant illnesses	20/27 (74.1%)	4/9 (44.4%)	16/18 (88.9%)
Surgical history related to the surgical area	9/27 (33.3%)	4/9 (44.4%)	5/18 (27.8%)
Diabetes			
Type I	0/27 (0.0%)	0/9 (0.0%)	0/18 (0.0%)
Type II	7/27 (25.9%)	4/9 (44.4%)	3/18 (16.7%)
Smoking history			
Never	15/27 (55.6%)	4/9 (44.4%)	11/18 (61.1%)
Former smoker	9/27 (33.3%)	4/9 (44.4%)	5/18 (27.8%)
Occasionally or socially	0/27 (0.0%)	0/9 (0.0%)	0/18 (0.0%)
Less than half a pack a day	0/27 (0.0%)	0/9 (0.0%)	0/18 (0.0%)
Between half a pack and one pack a day	3/27 (11.1%)	1/9 (11.1%)	2/18 (11.1%)
More than one pack a day	0/27 (0.0%)	0/9 (0.0%)	0/18 (0.0%)
Malignancies and prior therapies	10/27 (37.0%)	6/9 (66.7%)	4/18 (22.2%)
Hepatic Disease	3/27 (11.1%)	3/9 (33.3%)	0/18 (0.0%)

Numbers are n/N (percent).

Table 13: Study Population Surgical Baseline Parameters

Measure	All	Site 2	Site 6	Site 8	Abdominal	Orthopedic
Surgical Indication						
Abdominal	9/27 (33.3%)	9/9 (100.0%)	0/8 (0.0%)	0/10 (0.0%)	9/9 (100.0%)	0/18 (0.0%)
Orthopedic	18/27 (66.7%)	0/9 (0.0%)	8/8 (100.0%)	10/10 (100.0%)	0/9 (0.0%)	18/18 (100.0%)
Location						
Medial Retinaculum	1/27 (3.7%)	0/9 (0.0%)	0/8 (0.0%)	1/10 (10.0%)	0/9 (0.0%)	1/18 (5.6%)
Quad	3/27 (11.1%)	0/9 (0.0%)	0/8 (0.0%)	3/10 (30.0%)	0/9 (0.0%)	3/18 (16.7%)
Quad Tendon	3/27 (11.1%)	0/9 (0.0%)	0/8 (0.0%)	3/10 (30.0%)	0/9 (0.0%)	3/18 (16.7%)
Segment 2	1/27 (3.7%)	1/9 (11.1%)	0/8 (0.0%)	0/10 (0.0%)	1/9 (11.1%)	0/18 (0.0%)
Segment 3	3/27 (11.1%)	3/9 (33.3%)	0/8 (0.0%)	0/10 (0.0%)	3/9 (33.3%)	0/18 (0.0%)
Segment 4	2/27 (7.4%)	2/9 (22.2%)	0/8 (0.0%)	0/10 (0.0%)	2/9 (22.2%)	0/18 (0.0%)

Measure	All	Site 2	Site 6	Site 8	Abdominal	Orthopedic
Segment 5	2/27 (7.4%)	2/9 (22.2%)	0/8 (0.0%)	0/10 (0.0%)	2/9 (22.2%)	0/18 (0.0%)
Segments 4 & 6	1/27 (3.7%)	1/9 (11.1%)	0/8 (0.0%)	0/10 (0.0%)	1/9 (11.1%)	0/18 (0.0%)
Suprapatellar pouch	10/27 (37.0%)	0/9 (0.0%)	8/8 (100.0%)	2/10 (20.0%)	0/9 (0.0%)	10/18 (55.6%)
Tendon	1/27 (3.7%)	0/9 (0.0%)	0/8 (0.0%)	1/10 (10.0%)	0/9 (0.0%)	1/18 (5.6%)
Tissue type						
Bone	1/27 (3.7%)	0/9 (0.0%)	1/8 (12.5%)	0/10 (0.0%)	0/9 (0.0%)	1/18 (5.6%)
Liver	9/27 (33.3%)	9/9 (100.0%)	0/8 (0.0%)	0/10 (0.0%)	9/9 (100.0%)	0/18 (0.0%)
Muscle And Soft Tissue	3/27 (11.1%)	0/9 (0.0%)	3/8 (37.5%)	0/10 (0.0%)	0/9 (0.0%)	3/18 (16.7%)
Quad/Tendon	1/27 (3.7%)	0/9 (0.0%)	0/8 (0.0%)	1/10 (10.0%)	0/9 (0.0%)	1/18 (5.6%)
Subcutaneous soft tissue	3/27 (11.1%)	0/9 (0.0%)	0/8 (0.0%)	3/10 (30.0%)	0/9 (0.0%)	3/18 (16.7%)
Synovium	2/27 (7.4%)	0/9 (0.0%)	2/8 (25.0%)	0/10 (0.0%)	0/9 (0.0%)	2/18 (11.1%)
Synovium And Muscle Tissue	2/27 (7.4%)	0/9 (0.0%)	2/8 (25.0%)	0/10 (0.0%)	0/9 (0.0%)	2/18 (11.1%)
Tendon	5/27 (18.5%)	0/9 (0.0%)	0/8 (0.0%)	5/10 (50.0%)	0/9 (0.0%)	5/18 (27.8%)
Tendon/Soft Tissue	1/27 (3.7%)	0/9 (0.0%)	0/8 (0.0%)	1/10 (10.0%)	0/9 (0.0%)	1/18 (5.6%)
TBS approximate dimensions (cm^2)	21.1 ± 75.88 (27) 4.0 [4.0, 9.0]	51.0 ± 131.04 (9) 4.0 [4.0, 16.0]	3.7 ± 1.53 (8) 4.0 [3.1, 4.0]	8.1 ± 4.07 (10) 8.3 [4.0, 12.0]	51.0 ± 131.04 (9) 4.0 [4.0, 16.0]	6.1 ± 3.84 (18) 4.0 [4.0, 9.0]
Conventional Procedures for Hemostasis						
Pressure	12/27 (44.4%)	0/9 (0.0%)	2/8 (25.0%)	10/10 (100.0%)	0/9 (0.0%)	12/18 (66.7%)
Suture, ligation	0/27 (0.0%)	0/9 (0.0%)	0/8 (0.0%)	0/10 (0.0%)	0/9 (0.0%)	0/18 (0.0%)
Cautery	2/27 (7.4%)	0/9 (0.0%)	1/8 (12.5%)	1/10 (10.0%)	0/9 (0.0%)	2/18 (11.1%)

Measure	All	Site 2	Site 6	Site 8	Abdominal	Orthopedic
Other	0/27 (0.0%)	0/9 (0.0%)	0/8 (0.0%)	0/10 (0.0%)	0/9 (0.0%)	0/18 (0.0%)
None (impractical)	14/27 (51.9%)	9/9 (100.0%)	5/8 (62.5%)	0/10 (0.0%)	9/9 (100.0%)	5/18 (27.8%)

Numbers are mean ± Standard Deviation/ median.

D. Safety and Effectiveness Results

The mean paired *kappa* across all sites was 0.9301indicative of almost perfect agreement. Given the pre-specified criteria to advance to the pivotal clinical investigation was that the mean paired *kappa* statistic for assignment of SBSS scores was >0.80, this endpoint is deemed successful. These results validated the use of the SBSS for the pivotal study.

There were 41 adverse events not believed to be device related. One serious adverse event, portal vein thrombosis, occurred in a patient who underwent a right hepatic lobectomy for metastatic colon cancer with metastectomy of additional metastases in the left hepatic lobe. This required prolonged operative time and Pringle maneuver all of which more likely contributed to the portal vein thrombosis. This event was not likely caused by embolization of Hemoblast applied to the liver parenchymal edge of resection and resolved with anticoagulation.

Table 14: Adverse Events

Measure	All	Site 2	Site 6	Site 8	Abdominal	Orthopedic
Number of AEs	41	29	3	9	29	12
Number of subjects with AEs	15/27 55.6% (37.3%,72.4%)	8/9 88.9% (56.5%, 98.0%)	2/8 25.0% (7.1%, 59.1%)	5/10 50.0% (23.7%, 76.3%)	8/9 88.9% (56.5%, 98.0%)	7/18 38.9% (20.3%, 61.4%)
Number of AEs by severity						
Mild	16	13	0	3	13	3
Moderate	22	13	3	6	13	9
Severe	3	3	0	0	3	0
Number of subjects with AEs by severity*						

Measure	All	Site 2	Site 6	Site 8	Abdominal	Orthopedic
Mild	5/27 18.5% (8.2%, 36.7%)	4/9 44.4% (18.9%, 73.3%)	0/8 0.0% (0.0%, 32.4%)	1/10 10.0% (1.8%, 40.4%)	4/9 44.4% (18.9%, 73.3%)	1/18 5.6% (1.0%, 25.8%)
Moderate	8/27 29.6% (15.9%, 48.5%)	2/9 22.2% (6.3%, 54.7%)	2/8 25.0% (7.1%, 59.1%)	4/10 40.0% (16.8%, 68.7%)	2/9 22.2% (6.3%, 54.7%)	6/18 33.3% (16.3%, 56.3%)
Severe	2/27 7.4% (2.1%, 23.4%)	2/9 22.2% (6.3%,54.7%)	0/8 0.0% (0.0%, 32.4%)	0/10 0.0% (0.0%, 27.8%)	2/9 22.2% (6.3%, 54.7%)	0/18 0.0% (0.0%, 17.6%)
Number AEs related to device	0	0	0	0	0	0
Number of subjects with AEs related to device	0/27 0.0% (0.0%, 12.5%)	0/9 0.0% (0.0%,29.9%)	0/8 0.0% (0.0%,32.4%)	0/10 0.0% (0.0%, 27.8%)	0/9 0.0% (0.0%,29.9%)	0/18 0.0% (0.0%,17.6%)
Number of SAEs	8	7	1	0	7	1
Number of subjects with SAEs	4/27 14.8% (5.9%, 32.5%)	3/9 33.3% (12.1%, 64.6%)	1/8 12.5% (2.2%, 47.1%)	0/10 0.0% (0.0%, 27.8%)	3/9 33.3% (12.1%, 64.6%)	1/18 5.6% (1.0%, 25.8%)
Number of SADEs	0	0	0	0	0	0
Number of subjects with SADEs	0/27 0.0% (0.0%, 12.5%)	0/9 0.0% (0.0%, 29.9%)	0/8 0.0% (0.0%, 32.4%)	0/10 0.0% (0.0%, 27.8%)	0/9 0.0% (0.0%, 29.9%)	0/18 0.0% (0.0%, 17.6%)
Number of UADEs	0	0	0	0	0	0
Number of subjects with UADEs	0/27 0.0% (0.0%, 12.5%)	0/9 0.0% (0.0%, 29.9%)	0/8 0.0% (0.0%, 32.4%)	0/10 0.0% (0.0%, 27.8%)	0/9 0.0% (0.0%, 29.9%)	0/18 0.0% (0.0%, 17.6%)

Numbers are n/N percent (95% CI).
Wilson confidence limits (score based) are used in the table.
*The most severe AE is counted for each subject.

Table 15: Thromboembolic Events

	Total Thromboembolic Events	Pulmonary Embolism	Deep Venous Thrombosis	Stroke	Thrombosed AV Fistula	Other(portal vein thrombosis)
HEMOBLAST™ US Pilot	**1/27 (3.7%)**	0/27 (0.0%)	0/27 (0.0%)	0/27 (0.0%)	0/27 (0.0%)	1/27 (3.7%)

Hemoblast induced hemostasis at 3 minutes for half of all subjects in the effectiveness analysis population and 79.2% of this group (19/24) achieved hemostasis at 6 minutes. There were 2/24 subjects that did not achieve hemostasis at 10 minutes. Comparing abdominal surgery subjects to orthopedic surgery subjects at the 6-minute time point, it appears the orthopedic group performed better with 93.8% of subjects achieving hemostasis compared to 50.0% of subjects in the abdominal surgery group.

Table 16: Proportion of Subjects Achieving Hemostasis at 3, 6, and 10 Minutes - Efficacy Analysis Population

Time	**All**	**Site 2**	**Site 6**	**Site 8**	**Abdominal**	**Orthopedic**
3 minutes	12/24 50.0% (31.4%, 68.6%)	2/8 25.0% (7.1%, 59.1%)	3/7 42.9% (15.8%, 75.0%)	7/9 77.8% (45.3%, 93.7%)	2/8 25.0% (7.1%, 59.1%)	10/16 62.5% (38.6%, 81.5%)
6 minutes	19/24 79.2% (59.5%, 90.8%)	4/8 50.0% (21.5%, 78.5%)	6/7 85.7% (48.7%, 97.4%)	9/9 100.0% (70.1%, 100.0%)	4/8 50.0% (21.5%, 78.5%)	15/16 93.8% (71.7%, 98.9%)
10 minutes	22/24 91.7% (74.2%, 97.7%)	6/8 75.0% (40.9%, 92.9%)	7/7 100.0% (64.6%, 100.0%)	9/9 100.0% (70.1%, 100.0%)	6/8 75.0% (40.9%, 92.9%)	16/16 100.0% (80.6%, 100.0%)

Numbers are n/N percent (95% CI).
Wilson confidence limits (score based) are used in the table.
Cumulative numbers of subjects achieving hemostasis at each time are counted.

Pediatric Extrapolation

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

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pilot clinical study included nine (9) investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

Pivotal Study:

A. Study Design

This was a prospective, randomized, controlled, multicenter pivotal study to evaluate the safety and effectiveness of the HEMOBLAST™ Bellows ("HEMOBLAST™") in cardiothoracic, abdominal (both soft tissue and organ space), and orthopedic lower extremity surgeries. Subjects were randomized intraoperatively in a 2:1 ratio to HEMOBLAST ™ or the control treatment, an absorbable gelatin sponge, USP and recombinant thrombin ("G+T"). The study also included a lead-in phase, to ensure consistent assessment of bleeding severity using the SBSS scale by study investigators, wherein subjects were not randomized. Lead-in subjects received HEMOBLAST™ and were followed for safety only.

The specific objective of the study was to evaluate the safety and effectiveness of HEMOBLAST™ compared to G+T. The primary hypothesis in this study was that HEMOBLAST™ is non- inferior relative to G+T for success at achieving hemostasis within 6 minutes. A Clinical Events Committee ("CEC") and Independent Data Monitoring Committee ("IDMC") were utilized to review all serious adverse events and safety and effectiveness data, respectively.

1. Clinical Inclusion and Exclusion Criteria

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

   - Subject is undergoing an elective open cardiothoracic, abdominal, or orthopedic lower extremity surgery;
   - Subject or an authorized legal representative is willing and able to give prior written informed consents for investigation participation;
   - Subject undergoing cardiothoracic surgery is not allergic to protamine; and
   - Subject is 21 years of age or older.

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

   - Subject does not have an active or suspected infection at the surgical site;
   - Subject undergoing cardiothoracic surgery with anticoagulation must have anticoagulation reversed prior to Target Bleeding Site (TBS) identification and treatment;
   - Subject in whom the Investigator is able to identify a TBS for which any applicable conventional means for hemostasis are ineffective or impractical; and
   - Subject has a TBS with an SBSS score of 1, 2, or 3.

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

- Subject is undergoing a laparoscopic, thoracoscopic, or robotic surgical procedure;
- Subject is undergoing a neurologic surgical procedure;
- Subject is undergoing a spinal surgical procedure;
- Subject is undergoing an emergency surgical procedure;
- Subject is pregnant, planning on becoming pregnant during the follow-up period, or actively breast-feeding;
- Subject has a clinically significant coagulation disorder or disease, defined as a platelet count < 100,000 per microliter or International Normalized Ratio > 1.5 within 4 weeks of surgery;
- Subject receiving intravenous heparin within 12 hours before surgery or oral Coumadin within 2 days before surgery;
- Subject receiving antiplatelet medications within 5 days prior to surgery;
- Subject undergoing abdominal or orthopedic lower extremity surgery receiving aspirin within 7 days prior to surgery;
- Subject has an active or suspected infection at the surgical site;
- Subject has had or has planned to receive any organ transplantation;
- Subject has a known sensitivity or allergy to bovine and/or porcine substance(s) or any other component(s) of the hemostatic agent;
- Subject has ASA classification of 5;
- Subject has a life expectancy of less than 3 months;
- Subject has a known psychiatric disorder, which in the opinion of the Principal Investigator, would preclude the subject from completing this clinical study;
- Subject has a documented severe congenital or acquired immunodeficiency;
- Subject has religious or other objections to porcine, bovine, or human components;
- Subject in whom the investigational or control device will be used at the site of a valve replacement or repair;
- Subject in whom the investigational or control device will be used at the site of a synthetic graft or patch implant;
- Subject is currently participating or has participated in another clinical trial within the past 30 days and is receiving/has received an investigational drug, device, or biologic agent; and
- Subject is not appropriate for inclusion in the clinical trial, per the medical opinion of the Principal Investigator.

2. Patient Follow-up Schedule

All patients underwent the same intraoperative investigational evaluations. During the surgery, hemostasis was evaluated by the investigator 3, 6, and 10 minutes after application of the investigational or control treatment until hemostasis was achieved. Reapplication of the randomized hemostat was performed at the 3 and 6 minute evaluation time points, as needed. In cases where hemostasis was not achieved by 10 minutes, the Investigator may have used whatever means necessary in order to

control bleeding, except for any hemostatic products containing thrombin or aprotinin. Thrombin should not have been used in subjects randomized to receive HEMOBLAST, but may have been used in subjects randomized to the G+T arm. Investigators were permitted to use any of the remaining randomized hemostat for bleeding sites other than the target bleeding site ("TBS") or any hemostatic product not containing thrombin or aprotinin.

Safety assessments occurred one day and 6 weeks postoperatively. Blood draws for antibody evaluation were performed preoperatively (within 4 weeks of surgery) and 6 weeks postoperatively.

3. Clinical Endpoints

With regards to safety, endpoints were used to characterize the safety profile include the rate of occurrence of all AEs and SAEs, reoperation rate due to bleeding, mean volume of intraoperative transfusions, total operative time, mean duration of hospitalization, intraoperative blood product administration, and post-operative blood product administration:

- The total operative time was measured as the time from entry into surgical suite to time of exit;
- The duration of hospitalization was measured as the time between admission and discharge; and
- The intraoperative and post-operative administration of blood products was tracked and the associated mean volume administered was measured in units. Blood products included red blood cells, platelets, fresh frozen plasma (FFP), and cryoprecipitate.

With regards to effectiveness, the primary effectiveness endpoint of this clinical investigation was non-inferiority of HEMOBLAST™ relative to G+T for success at achieving hemostasis within 6 minutes.

The secondary effectiveness endpoints of this clinical investigation were:

- Superiority of HEMOBLAST™ relative to G+T in mean preparation time from the opening of package to product being ready to use;
- Non-inferiority of HEMOBLAST™ relative to G+T for success at achieving hemostasis within 3 minutes;
- Superiority of HEMOBLAST™ relative to G+T for success at achieving hemostasis within 6 minutes; and
- Superiority of HEMOBLAST™ relative to G+T for success at achieving hemostasis within 3 minutes.

The pivotal study was designed to test the non-inferiority hypothesis of HEMOBLAST™ relative to G+T for success at achieving hemostasis within 6 minutes and within a 10% margin. The study pre-specified a single interim

analysis for early stopping due to futility or effectiveness after outcome data had been observed on 240 treated subjects. If the study were to continue to the final analysis with a decision in favor of comparable effectiveness, it was anticipated that effectiveness data would be available on a maximum of 400 treated subjects (approximately 267 patients treated with HEMOBLAST™ under a 2:1 randomization scheme).

Effectiveness analyses were conducted on the time-to-hemostasis ("TTH") population, defined as all subjects who were randomized, received study intervention, and had a TTH assessment recorded regardless of whether the measurement was censored (defined as the use of an additional hemostatic product or surgical rescue prior to the end of observation time, or failing to achieve and maintain complete hemostasis prior to the end of observation time). Lead-in subjects were not part of the TTH Population. Safety analyses were conducted on the Full Analysis population, defined as all subjects who were randomized into the study and received study intervention and all lead-in subjects.

In the primary analyses, missing TTH values were not imputed. All values right censored prior to 6 minutes were considered treatment failures for the purpose of the primary analysis.

With regard to success/failure criteria, individual subject success will be defined as hemostasis of the target bleeding site within 6 minutes of hemostat application. The proportion of subjects, overall, and in each surgical indication, meeting this success criterion will be estimated and a 95% confidence interval for the true proportion of subjects meeting the success criteria will be presented.

Overall study success will be defined as non-inferiority of HEMOBLAST™ relative to G+T in the proportion of subjects achieving hemostasis within 6 minutes of hemostat application.

B. Accountability of PMA Cohort

The study was stopped early for effectiveness, per the IDMC recommendation, based on the pre-specified stopping rules. At the time of the interim analysis, a total of 258 subjects were enrolled in the study, including 16 lead-in subjects and 242 randomized subjects. The interim analysis on completion of half the intended total number of patients in the pivotal study demonstrated non-inferiority at the 6 minute hemostasis primary endpoint and superiority at the 10-30% superiority at all the secondary endpoints including hemostasis at 6 minutes, 3 minutes, and 10 minutes, as well as, superiority on time to preparation for use. Furthermore, the pivotal study demonstrated non inferiority of Hemoblast for hemostasis at 10 minutes.

Table 17 represents the enrollment for each treatment group and **Table 18** represents the enrollment for each surgical arm. Randomization was stratified by surgical arm.

Table 17: Enrollment Details for Each Treatment Group

Population	All	HEMOBLAST™	G+T
TOTAL: Preoperative eligible + lead-in subjects	260*;;	175	83
Intraoperative ineligible subjects	1	0	0
SAFETY ANALYSIS POPULATION: Preoperative AND Intraoperative eligible (ENROLLED and includes lead-in subjects)	258;;	175	83
Lead-in subjects	16	16	0
EFFICACY ANALYSIS POPULATION: Preoperative AND Intraoperative eligible (ENROLLED and EXCLUDES lead-in subjects)	242;;	159	83

*One subject failed to meet intra-operative eligibility criteria, due to an intraoperative SBSS score of 0, and one subject was withdrawn after randomization/enrollment, but prior to hemostat application.

;;Two (2) subjects were enrolled, that were identified at subsequent monitoring visits, to have not met preoperative eligibility criteria. Because these subjects were enrolled and received HEMOBLAST™ or G+T application, they are considered part of the total, safety analysis and effectiveness analysis populations.

Table 18: Enrollment by Surgical Arm

Population	All	Cardiothoracic	Abdominal	Orthopedic
TOTAL: Preoperative eligible + lead-in subjects	260*;;	64	98	98
Intraoperative ineligible subjects	1	0	0	1
SAFETY ANALYSIS POPULATION: Preoperative AND Intraoperative eligible (ENROLLED and includes lead-in subjects)	258;;	64	97	97
Lead-in subjects	16	6	7	3
EFFICACY ANALYSIS POPULATION: Preoperative AND Intraoperative eligible (ENROLLED and EXCLUDES lead-in subjects)	242;;	58	90	94

* One subject failed to meet intra-operative eligibility criteria, due to an intraoperative SBSS score of 0, and one subject was withdrawn prior to hemostat application due to an intraoperative SBSS score of 0.

;;Two (2) subjects were enrolled, that were identified at subsequent monitoring visits, to have not met preoperative eligibility criteria. Because these subjects were enrolled and received HEMOBLAST™ or G+T application, they are considered part of the total, safety analysis and efficacy analysis populations.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a hemostatic device study performed in the US. **Table 19** presents physical measurement for height, weight, BMI, and blood pressure, which were similar between treatment arms.

Table 19: Physical Measurements by Treatment Group

Measure	All (n=258)	HEMOBLAST™ (n=175)	G+T (n=83)
Height (cm)	167.4 ± 10.19	167.4 ± 10.43	167.3 ± 9.72
	167.0 [160.0, 175.0]	165.0 [160.0, 175.0]	167.0 [160.0, 175.0]
Weight (kg)	83.8 ± 19.121	84.6 ± 19.19	82.1 ± 19.26
	82.5 [70.5, 97.0]	83.0 [71.0, 97.5]	80.9 [69.4, 97.0]
BMI (kg/m^2)	29.9 ± 6.33	30.2 ± 6.14	29.3 ± 6.71
	29.1 [25.5, 33.7]	29.4 [25.6, 34.1]	27.9 [25.1, 33.1]
Systolic Blood pressure (mmHg)	129.0 ± 18.54	128.8 ± 18.28	129.4 ± 19.18
	128.0 [116.0, 138.0]	128.0 [116.0, 138.0]	128.0 [118.0, 141.0]
Diastolic Blood pressure (mmHg)	76.6 ± 12.60	76.5 ± 12.33	76.9 ± 13.24
	78.0 [70.0, 85.0]	78.0 [69.0, 84.0]	76.0 [70.0, 85.0]

Numbers are mean ± SD (N)/ median

Table 20 and **Table 21** present the baseline SBSS score for the TBS by treatment group and surgical arm, respectively.

Table 20: Baseline SBSS Score for Each Treatment Group

Measure	All (N=242)	HEMOBLAST™ (N=159)	G+T (N=83)
Investigator SBSS			
0	0 (0.0%)	0 (0.0%)	0 (0.0%)
1	84 (34.7%)	59 (37.1%)	25 (30.1%)
2	100 (41.3%)	61 (38.4%)	39 (47.0%)
3	58 (24.0%)	39 (24.5%)	19 (22.9%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)
SBSS score 2:2	158 (65.3%)	100 (62.9%)	58 (69.9%)

Numbers are n/N (percent).

Table 21: Baseline SBSS Score for Each Surgical Arm

Measure	All (N=242)	Cardiothoracic (N=58)	Abdominal (N=90)	Orthopedic (N=94)
Investigator SBSS Score				
0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
1	84 (34.7%)	14 (24.1%)	8 (8.9%)	62 (66.0%)
2	100 (41.3%)	24 (41.4%)	46 (51.1%)	30 (31.9%)
3	58 (24.0%)	20 (34.5%)	36 (40.0%)	2 (2.1%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Numbers are n/N (percent).

The orthopedic procedures had a much greater number of patients in the lower SBSS scores. The orthopedic procedures represented a great variety of procedures the largest numbers being in hip and knee replacement and other open surgeries. The abdominal procedure group of patients consisted of 90 patients. The most prevalent abdominal procedures included liver resection surgery for both primary and metastatic cancers with less than 5% of the liver resections performed for biliary cancers and benign hepatic tumors. There were a total of 32 liver resection cases of the 90 patients in the abdominal group. A large portion of the remaining abdominal surgeries included abdominoplasties and abdominal hernia repairs. The cardiothoracic cases comprised the smallest group of patients and consisted of patients requiring application of the subject or control hemostat to the sternal edges, aortotomy sites, saphenous vein graft anastomosis site (proximal or distal not defined), pericardium and myocardial suture lines. Application to synthetic graft bleeding was excluded from this arm of the study.

D. Safety and Effectiveness Results

1. Safety results

The analysis of safety was based on the pivotal study cohort of 175 patients available for the 6 week evaluation. The key safety outcomes and adverse effects for this study are presented below.

In summary, at the time of the interim analysis, the HEMOBLAST™ group had a lower rate of subjects experiencing adverse events, although this did not reach statistical significance (48.0% vs. 56.6%, p=0.1516).

Serious adverse events

The proportion of patients experiencing a serious adverse event was comparable between treatment groups (10.9% for HEMOBLAST™ vs. 13.3% for G+T, p=0.5415). The two (2) groups were found to have a similar number of subjects experiencing an adverse event related to the device.

There were three (3) possible device-related adverse events report in three (3) subjects receiving HEMOBLAST™:

- Subject reported symptoms indicating possible systemic inflammatory response syndrome. This event was classified as possibly related to HEMOBLAST™; the event resolved with no sequelae.
- Subject experienced a generalized skin reaction with hives 11 days postoperatively; the event resolved with no sequelae. This was deemed as possibly related to HEMOBLAST™ and the CEC adjudicated this event as a Serious Adverse Device Effect (SADE).
- Subject was diagnosed with a pulmonary embolus 10 days postoperative; the

event resolved with no sequelae. This was deemed as possibly related to HEMOBLAST™, but probably related to the investigational procedure.

There were four (4) possible device-related adverse events reported in 4 subjects receiving G+T:

- Subject experienced acute blood loss anemia 4 days postoperative and was transfused with packed RBCs; the event resolved with no sequelae. This event was classified as possibly related to G+T.
- Subject developed a period of hypotension following surgery; it resolved with no sequelae after an infusion of albumin. This event was classified as possibly related to G+T.
- Subject had re-bleeding of the target bleeding site treated with G+T prior to surgical closure. The re-bleeding was controlled using a clip. This was deemed possibly related to the use of G+T.
- Subject had a re-bleeding of the target bleeding site treated with G+T prior to surgical closure. The re-bleeding was controlled using cautery. This was deemed possibly related to G+T and definitely related to the investigational procedure.

In summary, there was a single event identified as a SADE (subject who experienced skin reaction, described above).

Table 22: Serious Adverse Events

Adverse Event Type*	All	HEMOBLAST™	G+T
Abnormal Bloodwork	18/258 (7.0%)	13/175 (7.4%)	5/83 (6.0%)
Acute Kidney Injury	6/258 (2.3%)	4/175 (2.3%)	2/83 (2.4%)
Anemia	19/258 (7.4%)	10/175 (5.7%)	9/83 (10.8%)
Anxiety	1/258 (0.4%)	0/175 (0.0%)	1/83 (1.2%)
Arrhythmia	23/258 (8.9%)	16/175 (9.1%)	7/83 (8.3%)
Atelectasis	7/258 (2.7%)	4/175 (2.3%)	3/83 (3.6%)
Bile Leak	1/258 (0.4%)	1/175 (0.6%)	0/83 (0.0%)
Constipation/Ileus	17/258 (6.6%)	12/175 (6.9%)	5/83 (6.0%)
Dehydration	1/258 (0.4%)	0/175 (0.0%)	1/83 (1.2%)
Delirium	2/258 (0.8%)	1/175 (0.6%)	1/83 (1.2%)
Depression	1/258 (0.4%)	1/175 (0.6%)	0/83 (0.0%)
Dislocation	2/258 (0.8%)	1/175 (0.6%)	1/83 (1.2%)
Diarrhea	3/258 (1.2%)	3/175 (1.7%)	0/83 (0.0%)
Dizziness	3/258 (1.2%)	2/175 (1.1%)	1/83 (1.2%)
Epistaxis	1/258 (0.4%)	1/175 (0.6%)	0/83 (0.0%)
Fever	4/258 (1.6%)	2/175 (1.1%)	2/83 (2.4%)
Fluid Overload	13/258 (5.0%)	8/175 (4.6%)	5/83 (6.0%)
Hypervolemia	*1/258 (0.4%)*	*0/175 (0.0%)*	*1/83 (1.2%)*
Edema	*6/258 (2.3%)*	*3/175 (1.7%)*	*3/83 (3.6%)*
Pleural Effusion	*6/258 (2.3%)*	*5/175 (2.9%)*	*1/83 (1.2%)*
Fracture	1/258 (0.4%)	1/175 (0.6%)	0/83 (0.0%)
Hypertension	3/258 (1.2%)	2/175 (1.1%)	1/83 (1.2%)
Hypotension	3/258 (1.2%)	2/175 (1.1%)	1/83 (1.2%)
Infection (Non wound Related)	13/258 (5.0%)	7/175 (4.0%)	6/83 (7.2%)
Bacteremia	*3/258 (1.2%)*	*2/175 (1.1%)*	*1/83 (1.2%)*
Drain	*1/258 (0.4%)*	*1/175 (0.6%)*	*0/83 (0.0%)*
Phlebitis	*1/258 (0.4%)*	*0/175 (0.0%)*	*1/83 (1.2%)*
Respiratory	*3/258 (1.2%)*	*1/175 (0.6%)*	*2/83 (2.4%)*
Urinary Tract	*4/258 (1.6%)*	*1/175 (0.6%)*	*3/83 (3.6%)*
Yeast	*2/258 (0.8%)*	*1/175 (0.6%)*	*1/83 (1.2%)*
Other[1]	*4/258 (1.6%)*	*3/175 (1.7%)*	*1/83 (1.2%)*
Lactic Acidosis	1/258 (0.4%)	1/175 (0.6%)	0/83 (0.0%)
Lethargy	1/258 (0.4%)	0/175 (0.0%)	1/83 (1.2%)
Leukocytosis	3/258 (1.2%)	3/175 (1.7%)	0/83 (0.0%)
Nausea	18/258 (7.0%)	15/175 (8.6%)	3/83 (3.6%)
Orthostasis	1/258 (0.4%)	0/175 (0.0%)	1/83 (1.2%)
Pain	36/258 (14.0%)	25/175 (14.3%)	11/83 (13.3%)
Mouth/Throat	*8/258 (3.1%)*	*5/175 (2.9%)*	*3/83 (3.6%)*

Post Operative	*28/258 (10.9%)*	*21/175 (12.0%)*	*7/83 (8.4%)*
Other[2]	*8/258 (3.1%)*	*5/175 (2.9%)*	*3/83 (3.6)*
Paresthesia	1/258 (0.4%)	1/175 (0.6%)	0/83 (0.0%)
Pericarditis	1/258 (0.4%)	1/175 (0.6%)	0/83 (0.0%)
Pneumothorax	2/258 (0.8%)	0/175 (0.0%)	2/83 (2.4%)
Pruritis	4/258 (1.6%)	3/175 (1.7%)	1/83 (1.2%)
Respiratory Insufficiency	9/258 (3.5%)	6/175 (3.4%)	3/83 (3.6%)
TBS Re-bleed	5/258 (1.9%)	1/175 (0.6%)	4/83 (4.8%)
Thrombocytopenia	2/258 (0.8%)	2/175 (1.1%)	0/83 (0.0%)
Thromboembolic Event	4/258 (1.6%)	4/175 (2.3%)	0/83 (0.0%)
Thrombosed AV Fistula	*1/258 (0.4%)*	*1/175 (0.6%)*	*0/83 (0.0%)*
Deep Vein Thrombosis	*2/258 (0.8%)*	*2/175 (1.1%)*	*0/83 (0.0%)*
Other[3]	*1/258 (0.4%)*	*1/175 (0.6%)*	*0/83 (0.0%)*
Urinary Retention/Oliguria	7/258 (2.7%)	4/175 (2.3%)	3/83 (3.6%)
Vaginal Discharge	1/258 (0.4%)	0/175 (0.0%)	1/83 (1.2%)
Vomiting	5/258 (1.9%)	4/175 (2.3%)	1/83 (1.2%)
Wound Related	16/258 (6.2%)	12/175 (6.9%)	4/83 (4.8%)
Dehiscence	*1/258 (0.4%)*	*1/175 (0.6%)*	*0/83 (0.0%)*
Hematoma	*3/258 (1.2%)*	*2/175 (1.1%)*	*1/83 (1.2%)*
Infection	*4/258 (1.6%)*	*3/175 (1.7%)*	*1/83 (1.2%)*
Non-healing	*2/258 (0.8%)*	*1/175 (0.6%)*	*1/83 (1.2%)*
Seroma	*6/258 (2.3%)*	*6/175 (3.4%)*	*0/83 (0.0%)*
Other[4]	*1/258 (0.4%)*	*0/175 (0.0%)*	*1/83 (1.2%)*
Other[5]	11/258 (4.3%)	9/175 (5.1%)	2/83 (2.4%)

* Open text field, like responses were pooled

[1] HEMOBLAST™: Pancolitis, diarrhea positive for clostridium difficile, dental abscess; G+T: tricuspid valve vegetation

[2] HEMOBLAST™: right leg pain, back pain, right ear pain, left hip pain, right shoulder; G+T: sore shoulder, pain at epidural site and back pain, abdominal pain

[3] Intraoperative TEE demonstrated internal jugular vein clot

[4] Wound irritation from one stitch

[5] HEMOBLAST™: muscle spasm, thoracic aorta dissection, hematoma, vocal cord paralysis, endoleak, pressure ulcer, decreased right ventricular function during cardiopulmonary bypass removal, arthralgia of right leg, recurrent shingles, gout flare, left thumb tenderness, insomnia, right shoulder acute bursitis, right bronchopleural fistula, blisters around tape covering incision; G+T: right atrium lead dislodgment, left arm weakness, femoral artery perforation

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Note: Mortality events only occurred in the G+T control group 3/83 patients or 3.6% and serious adverse events tended to be related to re-bleeding episodes.

Non-serious adverse events

Table 23 lists non-serious AEs occurring in 5% or more of all patients, or in one of the treatment arms.

Table 23: Number of Subjects Experiencing Each Type of Non-serious Adverse Event

Adverse Event Type*	All	HEMOBLAST	G+T
Abnormal Bloodwork	18/258 (7.0%)	13/175 (7.4%)	5/83 (6.0%)
Anemia	19/258 (7.4%)	10/175 (5.7%)	9/83 (10.8%)

Arrhythmia	23/258 (8.9%)	16/175 (9.1%)	7/83 (8.3%)
Constipation/Ileus	17/258 (6.6%)	12/175 (6.9%)	5/83 (6.0%)
Fluid Overload	13/258 (5.0%)	8/175 (4.6%)	5/83 (6.0%)
Infection (Non wound Related)	13/258 (5.0%)	7/175 (4.0%)	6/83 (7.2%)
Nausea	18/258 (7.0%)	15/175 (8.6%)	3/83 (3.6%)
Pain	36/258 (14.0%)	25/175 (14.3%)	11/83 (13.3%)
Wound Related	16/258 (6.2%)	12/175 (6.9%)	4/83 (4.8%)
Other[1]	11/258 (4.3%)	9/175 (5.1%)	2/83 (2.4%)

*Open text field, like responses were pooled.

[1]HEMOBLAST™: muscle spasm, thoracic aorta dissection, hematoma, vocal cord paralysis, endoleak, pressure ulcer, decreased right ventricular function during cardiopulmonary bypass removal, arthralgia of right leg, recurrent shingles, gout flare, left thumb tenderness, insomnia, right shoulder acute bursitis, right bronchopleural fistula, blisters around tape covering incision; G+T: right atrium lead dislodgment, left arm weakness, and femoral artery perforation

Unanticipated Adverse Device Effects

There were no Unanticipated Adverse Device Effects.

The incidence of adverse events and serious adverse events were statistically the same in both experimental and control groups. The three (3) main categories of potential adverse events identified in the pivotal study included thromboembolic events, wound healing complications primarily in the appearance of sternal dehiscence, and porcine collagen antibody titers. Each of these concerns was further assessed as follows.

2. Effectiveness Results

The analysis of effectiveness was based on the 242 evaluable patients at the 6-week time point. Key effectiveness outcomes are presented in Tables 24 to 28.

Primary endpoint

The primary efficacy endpoint of non-inferiority of HEMOBLAST™ relative to G+T for success at achieving hemostasis within 6 minutes was met, with 93.1% of the HEMOBLAST™ group achieving hemostasis at 6 minutes versus 73.5% of the G+T group, a difference of 19.5% (9.5% to 29.5%, $p<0.0001$ for non-inferiority). See **Table 24**. A 95% repeated confidence interval that accounts for the pre-specified stopping rule is calculated to be (7.1%, 31.9%), ruling out the non- inferiority margin of -10%.

Table 24: Primary Efficacy Endpoint with Full Efficacy Population

Time	HEMOBLAST	G+T	Difference (95% CI)	Z-statistic	P-value
6 minutes	148/159 (93.1%)	61/83 (73.5%)	19.5% (9.5%, 29.5%)	5.7926	<0.0001

The confidence interval for the estimated difference in the probability of hemostasis at 6 minutes and the P value are computed using the Cochran-Mantel-Haenszel estimator stratified by surgical arms.

A summary of the proportion of each treatment group that achieved hemostasis at 3, 6, and 10 minutes is shown in **Table 25**. The HEMOBLAST™ group showed a higher proportion of patients achieving hemostasis at each time point assessed.

Table 25: Proportion of Each Treatment Group Achieving Hemostasis at 3, 6, and 10 Minutes

Time	All	HEMOBLAST	G+T
3 minutes	151/242 (62.4%)	113/159 (71.1%)	38/83 (45.8%)
6 minutes	209/242 (86.4%)	148/159 (93.1%)	61/83 (73.5%)
10 minutes	223/238 (93.7%)	154/158 (97.5%)	69/80 (86.3%)

Numbers are n/N (percent).

The study was stopped early for efficacy, per the IDMC recommendation, based on the pre-specified stopping rules.

The proportion of subjects in each treatment group achieving hemostasis at each time point was broken out by surgical arm, see **Tables 26**, **27**, and **28**. The HEMOBLAST™ group showed significantly higher rates of hemostasis at 3 and 6 minutes in the abdominal and orthopedic surgical arms. There was no significant difference between groups in the cardiothoracic arm, as shown in the tables below.

Table 26: Proportion Achieving Hemostasis for Cardiothoracic Surgical Arm

Time	All	HEMOBLAST™	G+T	P-value
3 minutes	31/58 (53.4%)	20/38 (52.6%)	11/20 (55.0%)	>0.9999
6 minutes	46/58 (79.3%)	31/38 (81.6%)	15/20 (75.0%)	0.7343
10 minutes	51/56 (91.1%)	34/37 (91.9%)	17/19 (89.5%)	>0.9999

Table 27: Proportion Achieving Hemostasis for Abdominal Surgical Arm

Time	All	HEMOBLAST™	G+T	P-value
3 minutes	46/90 (51.1%)	39/59 (66.1%)	7/31 (22.6%)	0.0001
6 minutes	74/90 (82.2%)	55/59 (93.2%)	19/31 (61.3%)	0.0003
10 minutes	80/88 (90.9%)	58/59 (98.3%)	22/29 (75.9%)	0.0015

Table 28: Proportion Achieving Hemostasis for Orthopedic Lower Extremity Surgical Arm

Time	All	HEMOBLAST™	G+T	P-value
3 minutes	74/90 (78.7%)	54/64 (87.1%)	20/32 (62.5%)	0.0082
6 minutes	89/90 (94.7%)	62/64 (100.0%)	27/32 (84.4%)	0.0037
10 minutes	92/90 (97.9%)	62/64 (100.0%)	30/32 (93.8%)	0.1135

Secondary endpoints

Mean preparation time

The preparation time for the HEMOBLAST™ group was found to be significantly shorter than the G+T group, with a mean of 0.37 minutes (22 seconds) for the HEMOBLAST™ group and a mean of 2.40 minutes (144 seconds) for the G+T group (-2.03 [-2.10, -1.86], p<0.0001). This shows that HEMOBLAST™ takes 2.03 minutes (122 seconds) less to prepare than the control agent.

Non-inferiority in achieving hemostasis – 3 min

The HEMOBLAST™ group met the secondary endpoint of non-inferiority in success achieving hemostasis at the 3 minute time point, with 71.1% of HEMOBLAST™ subjects achieving hemostasis versus 45.8% in the G+T group; a difference of 27.5% (14.0% to 40.9%, p<0.0001 for non-inferiority).

Superiority in achieving hemostasis – 6 minutes

The secondary endpoint of superiority of HEMOBLAST™ in achieving hemostasis at 6 minutes was met in the overall population. As described in the Primary Endpoint section, the proportion of HEMOBLAST™ subjects achieving hemostasis at 6 minutes was 93.1% versus 73.5% for the G+T group (p=0.0001 for superiority).

Superiority in achieving hemostasis – 3 minutes

The secondary endpoint of superiority of HEMOBLAST™ in achieving hemostasis at 3 minutes was met in the overall population. As described in the Primary Endpoint section, the proportion of HEMOBLAST™ subjects achieving hemostasis at 3 minutes was 71.1% versus 45.8% for the G+T group (p=0.0001 for superiority).

In regard to surgical procedure and baseline TBS, the number of subjects in each surgical arm were found to be similar between the two (2) treatment groups, as were the locations for the surgical procedure, the TBS tissue type, and the conventional procedures for hemostasis. The estimated size of the TBS was also found to be similar between treatment groups, with a mean of 5.4 cm^2 in the HEMOBLAST™ group and 5.8 cm^2 in the G+T group.

3. Pediatric Extrapolation

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

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 39 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Outside United States (OUS) Study

The OUS study was designed to evaluate the efficacy and safety of a HEMOBLAST device prototype in comparison with a control group. The study had three (3) surgical arms cardio-thoracic, abdominal, orthopedic (lower extremity, and spine). This was a prospective comparative randomized, single-blinded, and multicenter, non-inferiority study. The study was prematurely terminated due to changes in device applicator and poolability with the information from the U.S. pivotal study. There were 400 subjects with planned enrollement; however, the actual enrollment consisted of 78 subjects (26 control, 52 HEMOBLAST). All subjects eligible for participation in the study were screened according to pre-defined inclusion/exclusion peri-operative criteria. On the patients assessed prior to study termination, the 6 minutes, hemostatic success was 100% with control devices and 91.5% with Hemoblast; a difference of -8.5% 95% CI: -20.5%, 5.6%. There were 41 minor complications that were not related to Hemoblast. There was one (1) patient with pulmonary emboli in the Hemoblast group in a patient undergoing esophagectomy with application of the hemostat to the diaphragmatic crus. This event occurred with a device prototype and not the Hemoblast Bellows. The second pulmonary emboli (PE) occurred in a patient morbidly obese patient undergoing abdominoplasty with removal of 2400 grams of fat in the pivotal study. The risk of PE from this procedure typically exceeds 7%. The Hemoblast Bellows was used to control bleeding in the right lower quadrant subcutaneous space; 10 days after the patient was discharged and off prophylaxis for Deep Venous Thrombosis (DVT) she developed a symptomatic pulmonary embolism. This event is highly unlikely to be related to embolization of Hemoblast powder placed in the subcutaneous space and much more likely to be related to a pre-existing deep venous thrombosis.

Table 29: Study Population by Surgical Indication

Measure	Control	HEMOBLAST™
Surgical indication		
Cardio-thoracic surgery	23.1% (6/26)	23.1% (12/52)
Orthopedic Lower extremity surgery	23.1% (6/26)	23.1% (12/52)
Spine surgery	23.1% (6/26)	23.1% (12/52)
Abdominal surgery	30.8% (8/26)	30.8% (16/52)

Table 30: Time to Hemostasis

Time	Control	HEMOBLAST™	Estimated Difference (%)
3 Minutes	57.7% (15/26)	64.7% (33/51)	7.6 (-13.4, 28.7)
6 Minutes	100.0% (24/24)	91.5% (43/47)	-8.5 (-20.5, 5.6)
10 Minutes	100.0% (24/24)	100.0% (47/47)	0.0 (-8.4, 14.3)

Table 31: Post-surgery bleeding complications by surgery type

Surgery type Measure	Control	HEMOBLAST™
Cardio-thoracic surgery		
Subject with post-surgery bleeding complication(s)	0.0% (0/6)	8.3% (1/12)
Orthopedic Lower extremity surgery		
Subject with post-surgery bleeding complication(s)	0.0% (0/6)	0.0% (0/12)
Spine surgery		
Subject with post-surgery bleeding complication(s)	0.0% (0/6)	0.0% (0/12)
Abdominal surgery		
Subject with post-surgery bleeding complication(s)	0.0% (0/8)	12.5% (2/16)

Post-surgery bleeding complications before discharge and within 6 week follow up are included.
Numbers are percent (n/N) for categorical measures.

Additional Analyses

Non-inferiority in achieving hemostasis in the Pivotal Study – 10 minutes
An exploratory analysis was completed evaluating the non-inferiority of HEMOBLAST™ in achieving hemostasis at 10 minutes. The proportion of HEMOBLAST™ subjects achieving hemostasis at 10 minutes was 97.5% versus 86.3% in the G+T group, a difference of 10.4% (2.6%, 18.3%, $p<0.001$ for non-inferiority).

Superiority in achieving hemostasis in the Pivotal Study – 10 minutes

An exploratory analysis was completed evaluating the superiority of HEMOBLAST™ in achieving hemostasis at 10 minutes. The proportion of HEMOBLAST™ subjects achieving hemostasis at 10 minutes was 97.5% versus 86.3% in the G+T group, a difference of 10.4% (2.6%, 18.3%, p=0.0092 for superiority).

Analysis of Thromboembolic Events in the OUS, Pilot and Pivotal Studies

There was a predominance of thromboembolic events in the Hemoblast group, particularly in the cardiac surgery and abdominal surgery arms of the study and these are detailed in the tables below.

Table 32: Summary of Thromboembolic Events by Treatment Group

HEMOBLAST™ Clinical Investigations						
Treatment Group	**Total Thromboembolic Events**	Pulmonary Embolism	Deep Venous Thrombosis	Stroke	Thrombosed AV Fistula	Other
G+T	**3/132 (2.3%)**	1/132 (0.8%)	0/132 (0.0%)	2/132 (1.5%)	0/132 (0.0%)	0/132 (0.0%)
HEMOBLAST™ US Pivotal (full cohort)	**8/280 (2.9%)**	1/280 (0.4%)	3/280 (1.1%)	3/280 (1.1%)	1/280 (0.4%)	0/280 (0.0%)
HEMOBLAST™ OUS	**2/52 (3.8%)**	1/52 (1.9%)	0/52 (0.0%)	1/52 (1.9%)	0/52 (0.0%)	0/52 (0.0%)
HEMOBLAST™ OUS, US Pilot, and Pivotal (Full Cohort + Lead-ins)	**11/359 (3.1%)**	2/359 (0.6%)	3/359 (0.8%)	4/359 (1.1%)	1/359 (0.3%)	1/359 (0.3%)

Table 33. Subjects with Thromboembolic Events

Subject	**Event**	**HEMOBLAST™ Application Site**
26-04 (US Pivotal)	Pulmonary embolus (PE)	Abdominal wall – right lower quadrant, right upper quadrant, left upper quadrant
05-007 (OUS Pilot)	Transient embolic ischemic insult	Aortotomy suture line
02-035 (OUS Pilot)	Pulmonary embolus (PE)	Diaphragmatic crura
07-08 (US Pivotal)	Deep venous thrombosis - right internal jugular vein	Liver parenchyma
26-29 (US Pivotal)	Deep venous thrombosis	Fascia of lower right abdominal wall

Overall there were three (3) thromboembolic events in 132 patients in the G+T group in the pivotal study: two (2) strokes and one pulmonary embolism. In the Hemoblast group in all

three (3) studies for a total of 359 patients there were 11 thromboembolic events, this seem a little more prominent than in the control group realizing the Hemoblast patients outnumbered the control patients. Deep venous thrombosis was noted in only three (3) patients and only in the pivotal study none of which had associated pulmonary embolism. All the patients received Hemoblast powder for hemostasis. The first patient was taking estradiol, underwent an abdominoplasty and presented with lower extremity deep venous thrombosis 17 days after surgery. The Hemoblast was applied to the subcutaneous tissue of the abdomen making it unlikely to migrate retrograde to the lower extremity venous system. The second patient with end stage renal failure sustained a right internal jugular vein thrombosis two (2) days after hepatectomy for intrahepatic biliary cystic disease. Hemoblast was applied to the liver parenchymal bleeding. The site of thrombosis was associated with an infected central line catheter which was the most likely cause of the DVT and not the Hemoblast powder which was applied below the diaphragm. The same patient developed thrombosis of her AV fistula intra operatively and likely before application of Hemoblast to the liver parenchyma. Distant migration of Hemoblast powder from liver parenchyma to AV fistula is clinically unlikely. The third DVT event occurred in a 66 year old African American male with type II diabetes and former smoker. Concomitant illnesses at the time of surgery included chronic kidney disease, hypertension, hepatitis C, end-stage renal disease, hyperparathyroidism, and anemia. Medical history includes kidney transplant and stroke. The subject underwent a coronary artery bypass grafting (CABG) procedure. HEMOBLAST™ Bellows was applied to a target bleeding site on the sternum and a secondary site on the mammary anastomosis. During the procedure, surveillance with trans-esophageal echocardiogram indicated clot formation in the right internal jugular vein. The event was identified as non-serious and resolved with no sequelae.

Stroke occurred in two (2) patients in the pivotal study control group and three (3) patients in the Hemoblast pivotal study using the bellows application. All three (3) patients had other clear etiologies of stroke unrelated to the application of Hemoblast. For, example one patient had the subject underwent a prolonged Bentall procedure requiring replacement of the aortic arch and valve with coronary artery bypass and prolonged cardiopulmonary bypass. This patient developed a lacunar stroke after hemostat applied to the sternal edges. It is highly unlikely that the hemostat entered the systemic circulation from the sternum to cause the stroke. Additional information was provided by the sponsor on two (2) additional strokes in the pivotal study. They occurred in patients with known history of stroke in one case and a known history of severe cardiovascular disease in both cases. Hemoblast was applied to the sternum for bleeding in both cases and to the internal mammary coronary anastomosis in one case. In both these scenarios the probability of device embolization into the systemic circulation is remote at best.

Wound Complications:

The adverse event of sternal dehiscence in the cardiovascular arm of the Hemoblast group raised concern that the device may have affected the healing process. The sponsors note that Hemoblast was applied to the sternum in 52 of 58 cardiovascular cases in the pivotal study. There were two (2) episodes of sternal dehiscence in the Hemoblast experimental group and one (1) in the control group. In one case the Hemoblast was applied to the vascular graft

and not the sternum. In the second case, Hemoblast was applied to the sternum; however, the patient had many factors to explain poor wound healing including use of steroids for systemic lupus and diabetes mellitus. The same patient also had dehiscence of a saphenous vein harvest site on the leg. These associated comorbidities made it less likely that Hemoblast was the sole cause of poor wound healing resulting in sternal dehiscence.

Porcine Collagen Antibody Titers:

In review of the pivotal study results it was noted that antibody titers to porcine collagen occurred with five (5) times more frequently compared to base line in patients receiving powdered Hemoblast collagen compared to the gelatin sponge, USP.

Table 34: Comparison of Porcine Antibody Titers in HEMOBLAST and G+T Groups

	HEMOBLAST	G+T	P value
Preoperative			0.6820a
Positive	4/157 (2.5%)	3/73 (4.1%)	
Negative	153/157 (97.5%)	70/73 (95.9%)	
6-wk follow-up			0.2564a
Positive	19/157 (12.1%)	5/73 (6.8%)	
Negative	138/157 (87.9%)	68/73 (93.2%)	

[a]Based on Fisher's exact test.

The presence of these elevated titers did not result in an increased incidence of allergic or anaphylactic reactions and had unknown clinical relevance. The one patient in the pivotal study who may have had a delayed hypersensitivity reaction to Hemoblast had no change in his porcine collagen antibody titer from baseline.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

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

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The HEMOBLAST™ Bellows hemostatic agent has met all pre-specified primary and secondary efficacy endpoints, showing not only statistical non-inferiority, but also superiority in achieving hemostasis at 3 and 6 minutes relative to the G+T group in the overall population. In addition, the mean preparation time for the HEMOBLAST™ product was significantly shorter than the G+T comparator.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies, as well as data collected in clinical studies conducted to support PMA approval as described above. The safety profile of the HEMOBLAST™ hemostatic agent was found to be similar to that of the standard of care (G+T) with regard to the rate and types of AEs and SAEs. In addition, there were no unanticipated adverse device effects.

C. Benefit-Risk Determination

When Hemoblast ™ was used as an adjunct to hemostasis during open cardiothoracic, abdominal, and orthopedic procedures to control minimal, mild, and moderate bleeding in the pivotal study the benefits of HEMOBLAST™ included higher rates of achieving hemostasis within 3 and 6 minutes of application compared to the control group in the overall population. It was non inferior to the G+T group for the primary endpoint of hemostasis at 6 minutes. Hemoblast was almost 20% superior in reaching hemostasis at 6 minutes, 25% superior at 3 minutes and 11% superior at 10 minutes. The secondary endpoint of preparation time for the HEMOBLAST™ was found to be significantly shorter than the control group, with a mean of 0.37 minutes (22 seconds) for the HEMOBLAST™ group and a mean of 2.40 minutes (144 seconds) for the control. HEMOBLAST™ group showed significantly higher rates of hemostasis at 3 and 6 minutes in the abdominal and orthopedic surgery arms; however, there was no significant difference between groups in the cardiothoracic surgery arm. The incidence of failed hemostasis and re-bleeding was lower with use of Hemoblast™ than in the G+T. HEMOBLAST™ had a lower rate of subjects experiencing adverse events compared to G+T (48.0% vs. 56.6%, respectively) and a lower proportion of subjects reporting a serious adverse event (10.9% for HEMOBLAST™ vs. 13.3% for G+T. Further study of the types of adverse events and serious adverse events occurring in the Hemoblast group compared to a matched control revealed no increased mortality, no thromboembolic events or wound healing complications directly attributable Hemoblast™. The increased incidence of collagen antibody titers in patients exposed to Hemoblast does not seem to have any consistent clinical consequences. The potential for sensitization is noted in the label adverse events.

1. Patient Perspectives
   This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for the HEMOBLAST™ Bellows, the benefits outweigh the risk for use in surgical procedures as an adjunct to hemostasis when control of minimal, mild, or moderate bleeding by conventional procedures is ineffective or impractical (excluding neurosurgical, ophthalmic, and urological procedures).

D. Overall Conclusions

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

XIV. CDRH DECISION

CDRH issued an approval order on December 15, 2017.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.